






BMJ Open Effect of non-pharmacological interventions for overweight/obese women with polycystic ovary syndrome on ovulation and pregnancy outcomes: a protocol for a systematic review and network meta-analysis

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To cite: Yang H, Xiao Y, Liu J, *et al.* Effect of non-pharmacological interventions for overweight/obese women with polycystic ovary syndrome on ovulation and pregnancy outcomes: a protocol for a systematic review and network meta-analysis. *BMJ Open* 2022;**12**:e059090. doi:10.1136/bmjopen-2021-059090

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-059090>).

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Received 08 November 2021
Accepted 19 May 2022



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ABSTRACT

Introduction Most overweight/obese women with polycystic ovary syndrome (PCOS) have infertility issues which are difficult to treat. Non-pharmacological interventions used for the management of infertility include lifestyle interventions, acupuncture therapies and nutritional supplements. These interventions have been reported to be beneficial in alleviating infertility among overweight women with PCOS. However, effect and safety of these non-pharmacological interventions vary, and there is no standard method of clinical application. Therefore, it is necessary to conduct a systematic review and network meta-analysis (NMA) to rank these non-pharmacological interventions in terms of effect and determine which one is more effective for clinical application.

Methods and analysis We will retrieve eight databases including Cochrane Library, Medline, Embase, PsycINFO, Chinese National Knowledge Infrastructure, WanFang Data, the Chongqing VIP Database and China Biology Medicine disc from their inceptions onwards. In addition, four clinical trial registries and the related references will be manually retrieved. The primary outcome will be clinical pregnancy. Live birth, ovulation, pregnancy loss, multiple pregnancy and adverse events related to interventions will be considered as the secondary outcomes. STATA software V.15.0 and Aggregate Data Drug Information System V.1.16.8 will be used to conduct pairwise meta-analysis and NMA. The Grading of Recommendations Assessment, Development and Evaluation system will be adopted to evaluate the certainty of evidence.

Ethics and dissemination Ethical approval will not be required because the study will not include the original information of participants. The results will be published in a peer-reviewed journal or disseminated in relevant conferences.

PROSPERO registration number CRD42021283110.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic and

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This will be the first study to comprehensively compare efficacy and evaluate safety of different non-pharmacological interventions for overweight/obese women with polycystic ovary syndrome (PCOS) and their effects on ovulation and pregnancy outcomes using Bayesian network meta-analysis.
- ⇒ The certainty of evidence will be evaluated by the Grading of Recommendations Assessment, Development and Evaluation system.
- ⇒ The study will focus on commonly used non-pharmacological interventions, such as lifestyle interventions, acupuncture therapies and nutritional supplements, which may lead to limitations to application of the findings for clinical guidance.
- ⇒ The population will be restricted to overweight/obese PCOS patients, which may limit the extrapolation of the findings to other populations.
- ⇒ Different protocols of the same intervention will not be compared in this study; the optimal protocol of the intervention remains to be further investigated.

reproductive disorder characterised by anovulation, hyperandrogenism and polycystic ovarian morphology.^{1 2} PCOS affects approximately 5%–20% of women of reproductive age worldwide^{3 4} and is the main cause of infertility.⁵ It was estimated that the economic burden of PCOS was US\$8 billion annually in 2020.⁶ Overweight and obese patients account for a significant proportion of women with PCOS.⁷ For example, approximately 37% of patients diagnosed with PCOS in China are overweight or obese.⁸ Obesity can further aggravate metabolic and reproductive disorder of women with PCOS.⁹ For instance, it can

increase insulin resistance and androgen levels, further impairing ovarian function. Moreover, obesity can increase the incidence of anovulation and menstrual disorders, and lower sensitivity of clomiphene and gonadotropin to ovulation, making treatment more difficult, and imposing a serious burden to the families and the whole society.¹⁰

Studies have explored a variety of interventions in overweight/obese women with PCOS to maximise ovulation and pregnancy outcomes, including pharmacotherapy, non-pharmacological interventions and surgery. A previous study reported that non-pharmacological interventions were effective in improving ovulation and pregnancy outcomes.¹¹ Currently, lifestyle interventions have been recommended as the first line of treatment for patients with PCOS, especially for overweight/obese PCOS according to guidelines.¹² Notably, preconception lifestyle changes are beneficial to weight loss and improve ovulation rates.¹³ There is a growing concern on the efficacy of acupuncture therapy. It has been reported that acupuncture could improve recovery of menstrual cycles and decrease the levels of body mass index in women with PCOS.¹⁴ Several studies report that nutritional supplements are able to alleviate infertility in patients with PCOS.^{15–17} A recent study has explored the effect of inositol in improving sex hormone binding globulin, dehydroepiandrosteronesulfate and testosterone levels compared with common pharmacological interventions.¹⁸ However, studies are inconsistent in efficacy and safety of these non-pharmacological interventions. Therefore, it is challenging for decision-makers to choose non-pharmacological interventions.

Network meta-analysis (NMA) can be used for analysis of indirect and direct data to rank different interventions,^{19 20} which realises the possibility of including randomised controlled trials (RCTs) that do not have a non-treatment or minimal treatment control group in the same analysis. The aim of the study is to compare the efficacy and evaluate the safety of common non-pharmacological interventions for overweight/obese women with PCOS and their role in improving ovulation and pregnancy outcomes through systematic review (SR) and NMA.

METHODS

Study registration

This protocol was registered on PROSPERO (CRD42021283110) and was reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement guidelines (online supplemental file 1 for PRISMA-P checklist).²¹ The findings of this study will be presented following the checklist of items to include when reporting a systematic review involving a network meta-analysis (PRISMA-NMA).²²

Inclusion criteria

Types of studies

Only RCTs presented in English or Chinese will be included in the study. Articles on parallel design RCTs and the first stage of cross-over RCTs will be retrieved.

Participants

Participants diagnosed with PCOS and overweight or obese will be included. Women who will either chose to undergo assisted reproductive technology (ART) or conceive naturally will be enrolled. There will be no restrictions on age, race, nationality and education levels.

Types of interventions

Non-pharmacological interventions used as main treatment or main adjuvant treatment will be included. Non-pharmacological interventions will be limited to lifestyle interventions (including dietary intervention, exercise intervention and behavioural intervention), acupuncture therapies and nutritional supplements. Dietary intervention include calorie reduction or diet structure change (carbohydrate counting, fat counting, protein counting).²³ And exercise intervention include resistance or aerobic exercise.²³ Studies used single or multiple non-pharmacological intervention(s) will be considered.

Types of comparator(s)/control

Comparators will be ART, or western medicine, or usual care, or placebo, or sham interventions, or blank control, or other different non-pharmacological interventions.

Types of outcome measures

Primary outcomes

Clinical pregnancy will be considered as the primary outcome in the study. Clinical pregnancy will be defined as a viable intrauterine pregnancy confirmed by ultrasound at greater than 6 weeks gestation.²⁴ As for multiple intrauterine gestational sacs, it will be regarded as one clinical pregnancy.

Secondary outcomes

Live birth, ovulation, pregnancy loss and multiple pregnancy will be regarded as secondary outcomes. Live birth will be defined as live newborns beyond week 24 of gestation.²⁵ Multiple newborns at the same delivery will be counted as one live birth. Ovulation will be monitored by ultrasound or urine luteinising hormone strips. Pregnancy loss will include miscarriage, termination of pregnancy and perinatal mortality, which will be defined as any stillbirth or neonatal death in the first week of life excluding those due to congenital anomalies (chromosomal and/or structural) assessed via death certification.²⁶ Multiple pregnancy will be defined as carrying two or more fetuses in one pregnancy. Adverse events related to interventions will be used to evaluate safety.

Exclusion criteria

1. Design type is non-RCT.
2. Patients with other diseases that affect fertility.

3. Studies that compared different pharmacological interventions or surgeries between groups.
4. Duplicated studies.
5. Studies lacking the full text despite all efforts to obtain it.

Studies that meet any of the criteria above will be excluded.

Search methods for identification of studies

Articles will be retrieved from eight databases including four English databases (Cochrane Library, Medline, Embase and PsycINFO) and four Chinese databases (Chinese National Knowledge Infrastructure, WanFang Data, the Chongqing VIP Database and China Biology Medicine disc). Studies published from inception onwards will be retrieved. The literature search will be conducted using search terms such as “non-pharmacological intervention”, “obesity”, “PCOS” and “RCT” based on the principle of subject words combined with free words. Appropriate adjustments will be made according to different database. A specific searching strategy is presented in [table 1](#) using Medline as example.

Data collection and analysis

Selection of studies

Endnote software V.9.1. will be used to manage the retrieved studies and remove duplicates. Two independent researchers (J-jL and Z-yX) will screen the studies by reading the titles and abstracts, according to the eligible criteria. Then, second screening will be conducted by reading the full text. The reasons for exclusion will be recorded. The included studies will be cross-checked. The two researchers will hold a discussion in case of any dispute to reach an agreement. A third researcher (F-rL) will be consulted if the disagreement will not be resolved through discussion. The selection procedure is presented in a PRISMA flow chart ([figure 1](#)).

Data extraction and management

Two researchers (HY and JZ) will independently extract data based on a predesigned form. The extracted data will be as followed: (1) basic information (name of the first author, year of publication, country, study type, sample size, number of centres, sources of funds and conclusion); (2) participants (age, diagnostic criteria and course of disease); (3) interventions (intervention type, details of intervention and intervention session/frequency/duration/dosage); (4) controls (control type, details of control and treatment session/frequency/duration/dosage); (5) outcomes (data for each measurement and safety). The corresponding authors will be contacted for missing information. The two researchers will cross-check the data after completion of data extraction. The disagreements will be solved by the team discussion or consultation with the third researcher (F-rL).

Assessment of risk of bias

Two independent researchers (Y-qX and G-xX) will assess the risk of bias (ROB) of included studies using

Table 1 Search strategy for Medline (through Ovid).

Number	Search items
1	exp Polycystic Ovary Syndrome/
2	polycystic ovar\$.tw.
3	PCOS.tw.
4	PCOD.tw.
5	hirsut\$.tw.
6	exp Amenorrhea/ or exp Oligomenorrhea/ or exp Hirsutism/
7	oligomenorrh\$.tw.
8	amenorrh\$.tw.
9	or/1–8
10	(Obesity or obese or overweight).tw.
11	exp Obesity/ or exp Overweight/ or exp Body Weight/
12	exp Body Composition/ or exp Body Fat Distribution/
13	exp Body Mass Index/
14	(High BMI or BMI above).tw.
15	(BMI adj3 over).tw.
16	Body Mass Index.tw.
17	or/10–16
18	exp Diet Therapy/
19	diet\$.tw.
20	exp Weight Loss/
21	(weight adj2 lose).tw.
22	Weight Loss.tw.
23	(weight adj3 reduc\$.tw.
24	((body mass index adj2 loss) or reduc\$ or decreas\$).tw.
25	((BMI adj2 loss) or (BMI adj2 reduc) or (BMI adj2 decreas\$)).tw.
26	exp Exercise Therapy/
27	(exercise\$ or exercising).tw.
28	exp sports/ or exp bicycling/ or exp running/ or exp swimming/ or exp walking/
29	(run\$ or jog\$).tw.
30	(sport\$ or walk\$).tw.
31	swim\$.tw.
32	train\$.tw.
33	fitness.tw.
34	yoga.tw.
35	exp cognitive therapy/ or exp relaxation techniques/
36	(cognitive adj2 therap\$).tw.
37	exp Psychotherapy/
38	Psychotherapy.tw.
39	psychosocial.tw.
40	exp Behavior Therapy/

Continued

Table 1 Continued

Number	Search items
41	(Behavio?r adj2 therap\$).tw.
42	behavio?r modif\$.tw.
43	(behavio?r adj2 manage\$).tw.
44	CBT.tw.
45	exp life style/ or exp life change events/
46	((life*style adj2 change\$) or intervention\$).tw.
47	counselling.tw.
48	social support/
49	(social adj2 support).tw.
50	relaxation.tw.
51	exp self efficacy/
52	self efficacy.tw.
53	exp Health Promotion/
54	(Health adj2 Promotion).tw.
55	exp Health Education/
56	(Health\$ adj2 Education).tw.
57	(motivation\$ adj2 therap\$).tw.
58	acupuncture.tw.
59	exp Acupuncture/
60	exp acupuncture therapy/ or exp acupuncture, ear/ or exp electroacupuncture/ or exp meridians/ or exp acupuncture points/ or exp moxibustion/
61	electroacupuncture.tw.
62	meridian\$.tw.
63	needling.tw.
64	moxi\$.tw.
65	acup\$ point\$.tw.
66	(shiatsu or tui na).tw.
67	shu.tw.
68	acupressure.tw.
69	(trigger adj3 point\$).tw.
70	oral nutritional supplement.mp.
71	exp *Dietary Supplements/
72	exp *Nutritional Support/
73	or/18–72
74	randomized controlled trial.pt.
75	controlled clinical trial.pt.
76	randomized.ab.
77	randomised.ab.
78	placebo.tw.
79	clinical trials as topic.sh.
80	randomly.ab.
81	trial.ti.
82	(crossover or cross-over or cross over).tw.
83	or/74–82

Continued

Table 1 Continued

Number	Search items
84	exp animals/ not humans.sh.
85	83 not 84
86	9 and 17 and 73 and 85

Moreover, clinical trial registries will be searched for relevant ongoing trials and unpublished trials including the International Clinical Trials Registry Platform (<http://www.who.int/ictrp/en/>), the National Institutes of Health clinical registry ClinicalTrials.gov (<https://www.clinicaltrials.gov/>), the Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au/>) and the Chinese clinical registry <http://www.chictr.org/en/>. References in all identified publications will be searched manually. In addition, experts in this field will be consulted for eligible studies. BMI, body mass index.

the Cochrane Collaboration's tool for assessing ROB V.2.0.^{27,28} The following five domains will be evaluated: (1) bias arising from the randomisation process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in outcome measurement and (5) bias in selection of the reported result. The overall bias will be considered *low ROB* if all domains will be marked *low risk*. The overall bias will be expressed as having *some concerns* if one domain will be denoted as *some concern*. The overall bias will be *high ROB* if one domain will be marked *high risk* or several domains will be denoted as *some concern* and may influence the robustness of the study. Corresponding authors will be contacted if there is any missing information that would affect the assessment. The two researchers will cross-check the data after completion of assessments. The two researchers will

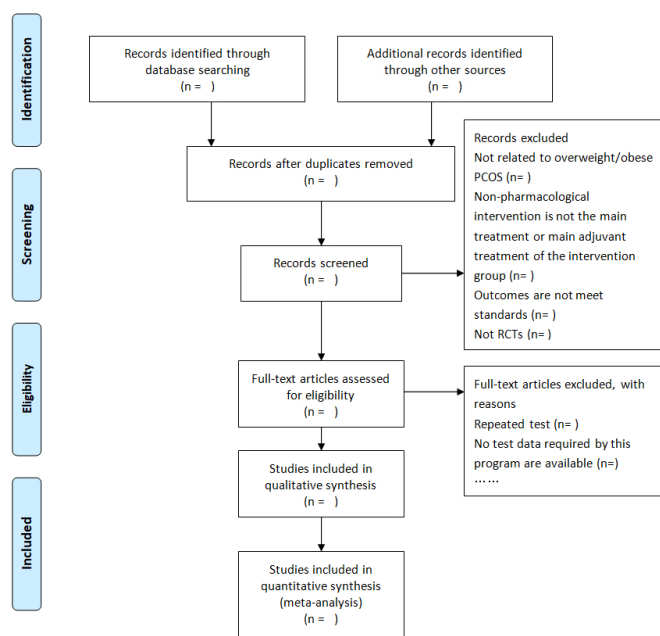


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing the study selection process. PCOS, polycystic ovary syndrome; RCTs, randomised controlled trials.

hold a discussion if any dispute occurs to reach an agreement. A third researcher (F-rL) will be consulted if the two researchers will not reach a consensus.

Evaluation of certainty of evidence

Two independent researchers (JL and ZY) will evaluate the certainty of evidence of each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.²⁹ The certainty of evidence will be rated as *high*, *moderate*, *low* or *very low* based on the rating criteria recommended in GRADE. Two researchers will cross check the results after evaluation of the certainty of evidence. Any dispute will be solved through discussion or a third researcher (F-rL) will be consulted.

Assessment of similarity and consistency

Similarity and consistency will be evaluated to obtain valid and credible results. Similarity will be assessed according to clinical characteristics and methodological characteristics owing to the challenges in clarifying similarity by statistical analysis. Study designs, participant characteristics and interventions will be included in the assessment. Local inconsistency will be evaluated using the node splitting method. $P > 0.05$ indicates no statistical significance implying that it is consistent to the direct and indirect comparison. $P < 0.05$ represents statistical significance indicating inconsistency. A consistency model or inconsistency model will be chosen based on the results. Potential scale reduced factor (PSRF) will be used to determine convergence. PSRF close to 1 indicates successful convergence.

Pairwise meta-analysis

STATA software V.15.0 (Stata Corp LP) will be used for data analysis. Statistical heterogeneity will be evaluated by calculating the I^2 value. $I^2 < 50\%$ indicates that the heterogeneity is acceptable. Otherwise, heterogeneity will be considered as significant. The random-effects model will be chosen in consideration of the suggestion that it is generally a more plausible match.³⁰ Descriptive review will be adopted if the heterogeneity is significant. Since clinical pregnancy, live birth, ovulation, pregnancy loss and multiple pregnancy are dichotomous outcomes, risk ratio will be used to synthesise the pooled data.

Network meta-analysis

Aggregate Data Drug Information System (V.1.16.8, Drugis, Groningen, Netherlands) and Markov Chain Monte Carlo method will be used for Bayesian network analysis to synthesise data.³¹ In addition, STATA software V.15.0 will be used to compare different interventions of each outcome and forest plots will be generated to present the NMA results. The rank of various non-pharmacological interventions will then be generated. Comparisons between interventions will be presented as a network plot and the contribution of different designs to the final effect size of the NMA will be presented as rank plots. Non-pharmacological interventions will be ranked based on the p score, which determined whether the

extent of certainty when the intervention group is superior compared with the control group. A p of 100% indicates that the treatment is better relative to the control whereas p value of 0% indicates that the treatment worse compared with the control.

Subgroup analysis, metaregression analysis and sensitivity analysis

Subgroup analysis and metaregression analysis will be conducted to explore the possible sources of heterogeneity and inconsistency. If data are available, subgroup analysis will be performed based on different types of non-pharmacological interventions and metaregression analysis will be performed based on the duration of PCOS, the degree of obesity, the age of patients, country of origin of patients, whether ART has been used, and dose of intervention. In addition, sensitivity analysis will be conducted by excluding one study by one study to verify the robustness of the results.

Publication bias assessment

A comparison-adjusted funnel plot will be generated to detect the reporting bias if more than 10 studies will be included.

Patients and public involvement

The study will be an SR and NMA based on existing studies; therefore, no patients or public will be involved directly.

DISCUSSION

To the best of our knowledge, this will be the first SR and NMA study to compare the efficacy and safety of non-pharmacological interventions in overweight/obese women with PCOS based on ovulation and pregnancy outcomes. The findings from the study will provide a ranking of non-pharmacological interventions to help patients, doctors and policy-makers for decision-making. In addition, the GRADE will be adopted to evaluate the certainty of evidence. There will be also some limitations of the study. First, non-pharmacological interventions in PCOS are an extensive research field, but we only focus on lifestyle interventions, acupuncture therapies and nutritional supplements,¹¹ which may lead to limitations of clinical practice. Second, considering that overweight/obese patients have an increased risk of metabolic disorders³² and tend to benefit more from non-pharmacological interventions compared with normal weight patients, we will restrict the population to overweight/obese PCOS, which may limit the extrapolation of the conclusion. Third, the efficacy of different protocols of the same non-pharmacological intervention will not be investigated.

Ethics and dissemination

The study will not require ethical approval because it comprises analysis based on existing studies. The results are expected to be published in a peer-reviewed journal

or disseminated at relevant conferences. The findings will provide evidence on use of non-pharmacological interventions for overweight/obese women with PCOS and the effect on ovulation and pregnancy outcomes thus promoting the clinical application of these methods.

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Contributors HY conceived the review protocol and drafted the manuscript. JL, JY and F-rL revised the study design. HY, Y-qX, JZ, J-jL, Z-yX, L-yL and ZY participated in the design of the search strategy and data extraction dataset. Y-qX, G-xX, L-yL, X-yZ and HY formed the data synthesis and analysis plan. In practice, JY and F-rL will monitor each procedure of the review and be responsible for quality control. All authors have read and approved the publication of the protocol.

Funding This study will be supported by grants from the National Natural Science Foundation of China (82174517) and the National Natural Science Foundation of China (82074556).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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