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

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1 **Non-pharmacological interventions for overweight/obese women with polycystic**

2 **ovary syndrome on ovulation and pregnancy outcomes: a protocol for systematic**

3 **review and network meta-analysis**

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31 **ABSTRACT**

32 **Introduction** The process of seeking fertility in most overweight/obese women with

33 polycystic ovary syndrome (PCOS) is often difficult. Non-pharmacological

34 interventions, mainly including lifestyle interventions, acupuncture therapies, and

35 nutritional supplements, have been reported to be beneficial. However, the efficacy

36 and safety of these non-pharmacological interventions varies, and the clinical

37 applications are not uniform. Hence, it is necessary to conduct this systematic review

38 (SR) and network meta-analysis (NMA) to provide a ranking of these

39 non-pharmacological interventions to explore the most optimal clinical treatment plan

40 and promote clinical application.

41 **Methods and analysis** We will search the 8 databases: Cochrane Library, MEDLINE,

42 EMbase, PsycINFO, Chinese National Knowledge Infrastructure (CNKI), WanFang

43 Data, the Chongqing VIP Database (VIP), and China Biology Medicine disc

44 (CBM), from inception to December 2021. In addition, 4 clinical trial registries will

45 be searched, the relevant references will be screened, and experts in the field will be

46 consulted. Clinical pregnancy rate will be regarded as the primary outcome. Live birth

47 rate, ovulation rate, and adverse events related to interventions will be considered as

48 the secondary outcomes. STATA software Version.15.0 and ADDIS V.1.16.8 will be

49 chosen to conduct pairwise meta-analysis and network meta-analysis. The Grading of

50 Recommendations Assessment, Development and Evaluation System (GRADE) will

51 be adopted to evaluate the quality of evidence.

52 **Ethics and dissemination** Ethical approval is not necessary because the current study

53 will not include the original information of the individuals. We plan to publish the

54 results in a peer-reviewed journal or disseminated in relevant conferences.

55 **PROSPERO registration number** CRD42021283110

56 **Key word:** Non-pharmacological interventions; Polycystic ovary syndrome; Obesity;

57 Systematic review; Network meta-analysis.

58 **Article summary**

59 **Strengths and limitations of this study**

60 ► It will be the first study to comprehensively evaluate and compare the efficacy and

61 safety of different non-pharmacological interventions for overweight/obese women

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62 with polycystic ovary syndrome (PCOS) on ovulation and pregnancy outcomes by

63 using Bayesian network meta-analysis.

64 ► The quality of evidence of each outcome will be evaluated by the Grading of

65 Recommendations Assessment, Development, and Evaluation system (GRADE).

66 ► The study will be conducted strictly according to the recommendation of updated

67 Cochrane handbook for systematic reviews of interventions.

68 ► Only English and Chinese databases will be searched, which may have a limitation

69 on acquired data and cause bias to some extent.

70 ►The quality of the pooled effects will be influenced by original studies.

71

72 **INTRODUCTION**

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

74 reproductive disorder, featured with anovulation, hyperandrogenism, and polycystic

75 ovarian morphology[1] [2], which affects approximately 5~20% of women of

76 reproductive age all over the world[3] [4] and becomes a main cause to infertility[5]. It was

77 reported that in 2004, the cost associated with treating PCOS was more than \$4 billion

78 in the United States alone, even without taking the extra expenditure of the increased

79 incidence of complications during pregnancy, type 2 diabetes, and other disorders into

80 account[6]. Among women with PCOS, overweight and obese patients account for a

81 significant proportion[7]. For example, in China, it was reported that around 37% of

82 patients diagnosed with PCOS were overweight or obese[8]. Obesity can further

83 aggravate the metabolic and reproductive dysfunction of women with PCOS[9]. For

84 instance, it can increase insulin resistance and androgen levels, further impair ovarian

85 function, and increase the incidence of anovulation and menstrual disorders. At the

86 same time, it can lower the sensitivity of clomiphene and gonadotropin to ovulation,

87 making treatment more difficult, and bringing a serious burden to the families and the

88 whole society[10].

89 Overweight/obese women with PCOS often try various therapies to maximize

90 ovulation and pregnancy outcomes. There are many researches assessing a variety of

91 interventions in overweight/obese women with PCOS, including pharmacotherapy,

92 non-pharmacological interventions, and surgery. In terms of improving ovulation and

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93 pregnancy outcomes, non-pharmacological interventions have been reported to be

94 beneficial[11]. Currently, lifestyle interventions are listed as the first-line of treatment in

95 the guidelines for patients with PCOS, especially for overweight/obese patients with

96 PCOS[12]. It was reported that preconception lifestyle changes had significant benefits

97 in weight loss and improving ovulation rates[13]. There is a growing concern about the

98 efficacy of complementary and alternative therapies, such as acupuncture therapy. In

99 addition, there is growing evidence suggested that nutritional supplements worked in

100 patients with PCOS[14-16]. Nutritional supplementation with inositol or

101 N-acetyl-cysteine, or acupuncture has been proven to have an advantage in improving

102 the ovulation rates of women with PCOS, and that on the basis of ovulation induction

103 drugs, supplementation with N-acetyl-cysteine or acupuncture can improve the

104 clinical pregnancy rate[11]. However, the efficacy and safety of these

105 non-pharmacological interventions are different, and the clinical applications are not

106 uniform, which makes it difficult to draw conclusions about the optimal clinical

107 treatment plan, hindering their clinical application and promotion to a certain extent.

108 It have shown that the network meta-analysis (NMA) can be used to analyze the

109 indirect and direct randomized data to rank the different interventions[17 18]. Hence, it is

110 necessary to conduct this systematic review (SR) and NMA to assess a variety of

111 non-pharmacological interventions comprehensively.

112 **Objective**

113 Our study aims to assess and compare the efficacy and safety of existing

114 non-pharmacological interventions for overweight/obese women with PCOS on

115 improving ovulation and pregnancy outcomes through conducting this SR and NMA.

116 **METHODS**

117 **Study registration**

118 This protocol have been registered on PROSPERO (CRD42021283110) and is

119 written based on the Preferred Reporting Item for Systematic Review and

120 Meta-analysis (PRISMA-P) statement (Supplementary file 1 for PRISMA-P

121 checklist)[19]. The result of this study will be presented following the Checklist of Items

122 to Include When Reporting a Systematic Review Involving a Network Meta-analysis

123 (PRISMA-NMA)[20]. We plan to start in December 2021 and finish in June 2022.

124 **Inclusion criteria**

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125   Types of studies

126   Only randomized controlled trials (RCTs) presented in English or Chinese will

127   be included, including parallel design RCTs and the first stage of cross-over RCTs.

128   There will be no restriction of region of researches.

129   Types of participants

130   The subjects will be women diagnosed with PCOS who were seeking treatment

131   to solve fertility problems. At the same time, they were diagnosed as overweight or

132   obese. Women either chose to undergo assisted reproductive technology (ART) or

133   conceive naturally will be included. There will be no restrictions on the age, race,

134   nationality, and education background.

135   Types of interventions

136   Non-pharmacological interventions as the main treatment or main adjuvant

137   treatment will be included. We will include the following non-pharmacological

138   interventions: lifestyle interventions (including dietary intervention, exercise

139   intervention, and behavioral intervention), acupuncture therapies, and nutritional

140   supplements. Both single non-pharmacological intervention and combinations of two

141   or several non-pharmacological interventions will be considered.

142   Types of comparator(s)/control

143   The ART, or western medicine, or usual care, or placebo, or sham interventions,

144   or blank control, or a comparison of different non-pharmacological interventions will

145   be included.

146   Types of outcome measures

147   Primary outcomes

148   Clinical pregnancy rate will be regarded as the primary outcome.

149   Secondary outcomes

150   Live birth rate and ovulation rate will be considered to evaluate efficacy.

151   Besides, adverse events related to interventions will be considered to evaluate safety.

152   **Exclusion criteria**

153   1. Design type is non-RCT.

154   2. In addition to PCOS and obesity, the patients also had other diseases that

155   affected fertility.

156   3. In addition to non-pharmacological interventions, different pharmacological

157   interventions or surgeries were compared between the groups.

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158   4. Acupuncture therapy in the intervention group left the acupoints or meridians.

159   5. The intervention group and control group(s) compared different doses or

160 frequency or duration of the same intervention.

161   6. The data is found to be significantly falsified.

162   7. The full text is not available after all efforts.

163 **Search methods for identification of studies**

164   The following 8 databases will be searched: including 4 English databases

165 (Cochrane Library, MEDLINE, EMbase, and PsycINFO) and 4 Chinese databases

166 (Chinese National Knowledge Infrastructure (CNKI), WanFang Data, the Chongqing

167 VIP Database (VIP), and China Biology Medicine disc (CBM)), from inception to

168 December 2021. Based on the principle of subject words combined with free words,

169 the literature search will be constructed around search terms for

170 "non-pharmacological intervention", "obesity", "PCOS", and "RCT". The appropriate

171 adjustments will be made according to the necessity of each database. There will be

172 no restriction of publication date. Taking MEDLINE as an example, the specific

173 searching strategy is listed in Table 1.

174   The following clinical trial registries will be searched for relevant ongoing trials

175 and unpublished trials: the International Clinical Trials Registry Platform

176 (http://www.who.int/ictrp/en/), the National Institutes of Health (NIH) clinical

177 registry ClinicalTrials.gov (https://www.clinicaltrials.gov/), the Australian New

178 Zealand Clinical Trials Registry (http://www.anzctr.org.au/), and the Chinese clinical

179 registry (http://www.chictr.org/en/). The references of all identified publications will

180 be screened. In addition, experts in the field will be consulted for relevant studies.

181 **Data collection and analysis**

182 Selection of studies

183   Firstly, we will import the retrieved studies into Endnote software V.9.1. to

184 manage and remove duplicates. Secondly, two independent researchers (JJL and

185 ZYX) will screen the studies by reading titles and abstracts, according to the

186 pre-designed inclusion and exclusion criteria. Thirdly, second screening will be

187 conducted by reading the full text by the two researchers. During this phase, the

188 reason for exclusion will be recorded detailedly. The final screened results will be

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189   cross-checked. If any dispute occurs, we will discuss to reach an agreement. If

190   disagreement cannot be resolved, the third researcher (FRL) will be consulted. The

191   selection procedure is shown in a PRISMA flow chart (Figure 1).

192   Data extraction and management

193   Two researchers (HY and JZ) will extract data based on the pre-designed form

194   independently, including the 5 main domains: ① basic information (name of the first

195   author, year of publication, country, study type, sample size, number of centers,

196   sources of funds, and conclusion); ② participants (age, diagnostic criteria, and

197   course of disease); ③ interventions (intervention type, details of intervention, and

198   intervention session/ frequency/ duration/ dosage); ④ controls (control type, details

199   of control, and treatment session/ frequency/ duration/ dosage); ⑤ outcomes (data

200   for each measurement, and safety). If there are unclear or missing information, we

201   will try to contact corresponding authors. After completing data extraction, the two

202   researchers will cross-check. If any dispute occurs, we will discuss to reach an

203   agreement. If disagreement cannot be solved, the third researcher (FRL) will be

204   consulted.

205   **Quality assessment**

206   Assessment of risk of bias

207   According to the Cochrane Collaboration's tool for assessing risk of bias (ROB)

208   2.0[21 22], two independent researchers (ZHY and GXX) will assess the included studies'

209   risk of bias. We will evaluate from the following five domains: 1) bias arising from

210   the randomization process, 2) bias due to deviations from intended interventions, 3)

211   bias due to missing outcome data, 4) bias in outcome measurement, and 5) bias in the

212   selection of the reported result. If all domains are marked *low risk*, we will consider

213   the overall bias as *low risk of bias*. If one domain is marked *some concern*, we will

214   consider the overall bias as *some concerns*. If one domain is marked *high risk* or

215   several domains are marked *some concern* that could influence the robustness of the

216   study, we will consider the overall bias as *high risk of bias*. If there is information

217   missing, which influences our assessment, we will take efforts to contact with the

218   relevant corresponding authors. When assessments have been completed, cross-check

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219 will be done by the two researchers. If any dispute occurs, we will discuss to reach an

220 agreement. If disagreement cannot be resolved, the third researcher (FRL) will be

221 consulted.

222   Assessment of evidence quality

223   According to the Grading of Recommendations Assessment, Development and

224 Evaluation (GRADE) system[23], two independent researchers (JL and ZY) will

225 evaluate the quality of evidence of each outcome. Based on the rating standards of

226 GRADE, we will rate the quality of evidence as *high*, *moderate*, *low*, or *very low*.

227 **Assessment of similarity and consistency**

228   In order to acquire a valid and credible result, we will evaluate similarity and

229 consistency. Considering the difficulty of clarifying similarity by statistical analysis,

230 we will assess it according to clinical characteristics and methodological

231 characteristics, in which study designs, participant characteristics, and interventions

232 will be taken into consideration. In addition, we will evaluate the local inconsistency

233 by adopting the node splitting method. It will be regarded as no statistical significance

234 when $P > 0.05$, indicating that it is consistent of the direct and indirect

235 comparison. Otherwise, it will be regarded as inconsistent. Then, either consistency

236 model or inconsistency model will be chosen. The model convergence is the potential

237 scale reduced factor (PSRF). It will be suggested as successful convergence if PSRF

238 close to 1.

239 **Pairwise meta-analysis**

240   We will choose the STATA software Version.15.0 (Stata Corp LP, College

241 Station, Texas, USA) to analyze data. For each study we included, we will take the

242 pre-post differences as outcome indicators. Trial with more than two arms will be

243 divided into several trials with two arms as possible combinations for meta-analysis.

244   Through examining the characteristics of the participants, interventions and

245 outcomes of the included studies, we will assess the clinical and methodological

246 heterogeneity. Statistical heterogeneity will be evaluated by calculating the I^2 value.

247 When $I^2 < 50\%$, suggests that heterogeneity is acceptable and the fixed effect model

248 will be adopted, by using the Mantel–Haenszel procedure. If not, we will consider that

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249 the heterogeneity is substantial and the random effect model will be adopted[24], by

250 using the Der Simonian-Laired procedure. In addition, we will explore the source of

251 heterogeneity. If the heterogeneity is substantial to a great extent and the source

252 cannot be identified, descriptive review will be adopted. In our study, which analysis

253 method will be used to evaluate efficacy outcomes (clinical pregnancy rate, live birth

254 rate, and ovulation rate) will be decided on a specific condition, while for safety

255 outcome, only descriptive analysis will be adopted.

256   Considering that the efficacy outcomes which we will include are dichotomous

257 outcomes, we will choose risk ratio (RR) to analyze.

258   **Network meta-analysis**

259   We will choose the Aggregate Data Drug Information System (ADDIS V.1.16.8,

260 Drugis, Groningen, NL) and use the Markov Chain Monte Carlo (MCMC) method to

261 conduct the Bayesian network analysis to synthesis and analyze efficacy data

262 statistically[25]. Besides, we will use the STATA software Version.15.0 to compare

263 different interventions of each outcome by generating forest plots to show the results

264 of NMA. At last, we will generate the rank of the various non-pharmacological

265 interventions. The comparisons between interventions will be reflected by network

266 plot and the contribution of different designs to the final effect size of the NMA will

267 be shown by rank plots. Non-pharmacological interventions will be ranked by P

268 score, which measures the extent of certainty when intervention group is superior to

269 control group. If P score up to 100%, it indicates that the treatment can be regarded as

270 the best; if P value is marked as 0%, it suggests that the treatment is the worst.

271   **Subgroup analysis and sensitivity analysis**

272   If there is sufficient evidence, we will do subgroup analysis based on the

273 duration of PCOS, the degree of obesity, the age of patients, and whether ART has

274 been used. In addition, we will perform sensitivity analysis to verify the robustness of

275 the primary decision made in the review process. The trials with small sample size or

276 high risk of bias will be taken into consideration. In order to acquire reliable results,

277 the above steps will be essential.

278   **Publication bias assessment**

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279   A comparison-adjusted funnel plot will be conducted to examine if there is

280   reporting bias.

Patients and public involvement

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282   Because our study is a SR and NMA based on existing studies, there will be no

283   patients or public involved directly.

DISCUSSION

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285   With the improvement of people's living standard, the increasing pressure of

286   social environment, the change of lifestyle and eating habits, the deterioration of

287   natural environment and some other factors, the incidence of PCOS with obesity has a

288   great increasing trend[26], which have become a global public health problem that

289   cannot be ignored[10]. Many women with PCOS are overweight or obese[27], which in

290   turn can increase the risk of metabolic disorders[28], making pregnancy more difficult.

291   There is more and more evidence suggesting that non-pharmacological interventions

292   benefit overweight or obese women with PCOS[29 30]. However, there are a variety of

293   non-pharmacological interventions, making it tough for clinicians to choose the

294   optimal treatment. Considering that searching for the most suitable

295   non-pharmacological intervention will increase the economic burden and cause the

296   waste of medical resources, NMA is a good analysis which can assist in assessing the

297   comparative efficacy and safety of different non-pharmacological interventions

298   through integrating direct and indirect comparisons across a set of multiple variables

299   [31 32].

300   To our knowledge, our study will be the first SR and NMA to investigate and

301   compare the efficacy and safety of non-pharmacological interventions for

302   overweight/obese women with PCOS on ovulation and pregnancy outcomes,

303   which will be expected to provide a ranking to benefit patients, doctors and policy

304   makers.

Ethics and dissemination

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306   This study does not necessitate ethical approval because this study is an analysis

307   based on existing studies. The results are expected to be published in a peer-reviewed

308   journal or disseminated at relevant conferences to provide more robust evidence of

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309 non-pharmacological interventions for overweight/obese women with PCOS on

310 ovulation and pregnancy outcomes and bring benefits to clinical application and

311 further research.

312 **Acknowledgements**

313 None

314 **Contributions**

315 HY conceived the review protocol and drafted the manuscript. JL, JY, and FRL

316 revised the study design. HY, ZHY, JZ, JJL, ZYX, LYL, and ZY participated in the

317 design of the search strategy and data extraction dataset. ZHY, GXX, LYL, XYZ, and

318 HY formed the data synthesis and analysis plan. In practice, JY and FRL will monitor

319 each procedure of the review and be responsible for quality control. All authors have

320 read and approved the publication of the protocol.

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323 Foundation of China (82174517); the National Natural Science Foundation of China

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325 **Competing interests**

326 None declared.

327 **Patient consent for publication**

328 Not required.

329 **Provenance and peer review**

330 Not commissioned; externally peer reviewed.

331 **Footnote**

332 Data Sharing Statement: Not applicable.

333

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415   combination of Guiluo's Tiao Zhou prescription and acupoint catgut embedding [Master].

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419   of the polycystic ovary syndrome. *Human reproduction (Oxford, England)* 2000;15(4):785-9.

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429   ovary syndrome after behavioural modification intervention-A randomized controlled trial.
430   *Clinical endocrinology* 2019;90(3):468-78. doi: 10.1111/cen.13919 [published Online First:
431   2018/12/20]
432 31. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments
433   meta-analysis: many names, many benefits, many concerns for the next generation evidence
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437   direct and indirect evidence. *BMJ (Clinical research ed)* 2005;331(7521):897-900. doi:
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440   **Supplementary file 1 PRISMA-P checklist**

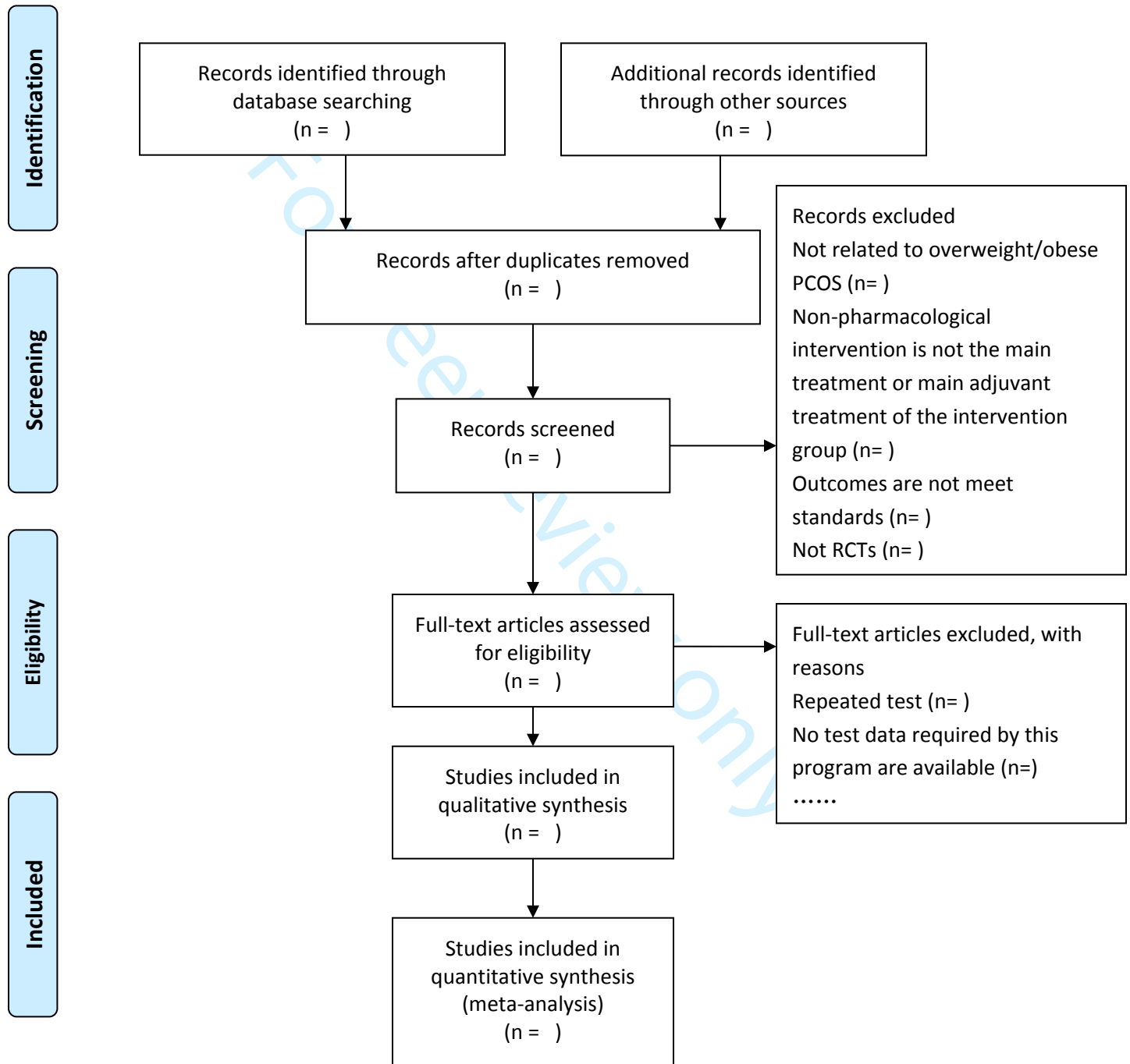441   **Table 1 Search strategy in MEDLINE (via Ovid).**

442   **Figure 1 PRISMA flow diagram of the study selection process.**

14

PRISMA 2009 Flow Diagram

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of the study selection process.

Identification

Records identified through database searching
(n =   )

Additional records identified through other sources
(n =   )

Screening

Records after duplicates removed
(n =   )

Records screened
(n =   )

Records excluded
Not related to overweight/obese PCOS (n=)
Non-pharmacological intervention is not the main treatment or main adjuvant treatment of the intervention group (n=)
Outcomes are not meet standards (n=)
Not RCTs (n=)

Eligibility

Full-text articles assessed for eligibility
(n =   )

Full-text articles excluded, with reasons
Repeated test (n=)
No test data required by this program are available (n=)
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Included

Studies included in qualitative synthesis
(n =   )

Studies included in quantitative synthesis (meta-analysis)
(n =   )

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097*

For more information, visit www.prisma-statement.org.

Table 1 Search strategy in MEDLINE (via 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/
41	(Behavio?r adj2 therap$).tw.

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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

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

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page Number/Line Number	Reported on Section/Paragraph
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Page 1/Line 2-3	Title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2/Line 55	Abstract
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1/Line 4-17	Affiliations
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 11/Line 314-320	Contributions
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A	N/A
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Page 11/Line 321-324	Funding
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A	N/A
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 4/Line 94-111	Introduction
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4/Line 112-115	Introduction
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 6/Line 124-173	Methods /Inclusion criteria

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage		Page 5/Line 163-180	Methods/Search methods for identification of studies
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated		Page 6/Line 168-173	Methods/Search methods for identification of studies
Study records:					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review		Page 6/Line 183-184	Methods/Selection of studies
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)		Page 6-7/Line 181-191	Methods/Selection of studies
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators		Page 7/Line 192-204	Methods/Data extraction and management
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications		Page 7/Line 194-200	Methods/Data extraction and management
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale		Page 5/Line 146-151	Methods/Inclusion criteria
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis		Page 7-8/Line 206-221	Methods/Assessment of risk of bias
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised		Page 8-9/Line 239-257	Methods/Pairwise meta-analysis
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)		Page 8-9/Line 246-252	Methods/Pairwise meta-analysis

	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 9/Line 271-277	Methods/ Subgroup analysis and sensitivity analysis
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 9/Line 251-252	Methods/Pairwise meta-analysis
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 9-10/Line 278-280	Methods/Publication bias assessment
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 8/Line 222-226	Methods/Assessment of evidence quality

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

The effect of non-pharmacological interventions for overweight/obese women with polycystic ovary syndrome on ovulation and pregnancy outcomes: A protocol for systematic review and network meta-analysis

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1 **The effect of non-pharmacological interventions for overweight/obese women**

2 **with polycystic ovary syndrome on ovulation and pregnancy outcomes: A**

3 **protocol for systematic review and network meta-analysis**

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10 Chinese Medicine, Chengdu, China.

11 [d]Medical Information and Engineering School, Chengdu University of Traditional

12 Chinese Medicine, Chengdu, China.

13 [1]Han Yang, Zi-han Yin and Jia-jia Liu contributed equally to this work.

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31   **ABSTRACT**

32   **Introduction:** Most overweight/obese women with polycystic ovary syndrome

33   (PCOS) have infertility issues which are difficult to treat. Non-pharmacological

34   interventions used for the management of infertility include lifestyle interventions,

35   acupuncture therapies, and nutritional supplements. These interventions have been

36   reported to be beneficial in alleviating infertility among overweight women with

37   PCOS. However, effect and safety of these non-pharmacological interventions varies,

38   and there is no standard method of clinical application. Therefore, it is necessary to

39   conduct a systematic review (SR) and network meta-analysis (NMA) to rank these

40   non-pharmacological interventions in terms of effect and determine which one is

41   more effective for clinical application.

42   **Methods and analysis:** We will retrieve 8 databases including Cochrane Library,

43   MEDLINE, EMbase, PsycINFO, Chinese National Knowledge Infrastructure (CNKI),

44   WanFang Data, the Chongqing VIP Database (VIP), and China Biology Medicine

45   disc (CBM) from their inceptions onwards. In addition, 4 clinical trial registries and

46   the related references will be manually retrieved. The primary outcome will be

47   clinical pregnancy. Live birth, ovulation, pregnancy loss, multiple pregnancy and

48   adverse events related to interventions will be considered as the secondary outcomes.

49   STATA software Version.15.0 and ADDIS V.1.16.8 will be used to conduct pairwise

50   meta-analysis and NMA. The Grading of Recommendations Assessment,

51   Development and Evaluation System (GRADE) will be adopted to evaluate the

52   certainty of evidence.

53   **Ethics and dissemination:** Ethical approval will not be required because the study

54   will not include the original information of participants. The results will be published

55   in a peer-reviewed journal or disseminated in relevant conferences.

56   **PROSPERO registration number:** CRD42021283110

59   **Article summary**

60   **Strengths and limitations of this study**

61   ► This will be the first study to comprehensively compare efficacy and evaluate

2

62 safety of different non-pharmacological interventions for overweight/obese women

63 with polycystic ovary syndrome (PCOS) and their effects on ovulation and pregnancy

64 outcomes using Bayesian network meta-analysis.

65 ► The certainty of evidence will be evaluated by the Grading of Recommendations

66   Assessment, Development and Evaluation system (GRADE).

67 ► The study will focus on commonly used non-pharmacological interventions, such

68   as lifestyle interventions, acupuncture therapies, and nutritional supplements, which

69   may lead to limitations to application of the findings for clinical guidance.

70 ► The population will be restricted to overweight/obese PCOS patients, which may

71 limit the extrapolation of the findings to other populations.

72 ► Different protocols of the same intervention will not be compared in this study, the

73 optimal protocol of the intervention remains to be further investigated.

74

75 **INTRODUCTION**

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

77 reproductive disorder characterized by anovulation, hyperandrogenism, and

78 polycystic ovarian morphology[1 2]. PCOS affects approximately 5~20% of women of

79 reproductive age worldwide[3 4] and is the main cause of infertility[5]. It was estimated

80 that the economic burden of PCOS was $8 billion annually in 2020 USD[6].

81 Overweight and obese patients account for a significant proportion of women with

82 PCOS[7]. For example, approximately 37% of patients diagnosed with PCOS in China

83 are overweight or obese[8]. Obesity can further aggravate metabolic and reproductive

84 disorder of women with PCOS[9]. For instance, it can increase insulin resistance and

85 androgen levels, further impairing ovarian function. Moreover, obesity can increase

86 the incidence of anovulation and menstrual disorders, and lower sensitivity of

87 clomiphene and gonadotropin to ovulation, making treatment more difficult, and

88 imposing a serious burden to the families and the whole society[10].

89   Studies have explored a variety of interventions in overweight/obese women

90 with PCOS to maximize ovulation and pregnancy outcomes, including

91 pharmacotherapy, non-pharmacological interventions, and surgery. A previous study

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92   reported that non-pharmacological interventions were effective in improving

93   ovulation and pregnancy outcomes[11]. Currently, lifestyle interventions have been

94   recommended as the first-line of treatment for PCOS patients, especially for

95   overweight/obese PCOS according to guidelines[12]. Notably, preconception lifestyle

96   changes are beneficial to weight loss and improve ovulation rates[13]. There is a

97   growing concern on the efficacy of acupuncture therapy. It has been reported that

98   acupuncture could improve recovery of menstrual cycles and decrease the levels of

99   body mass index (BMI) in women with PCOS[14]. Several studies report that nutritional

100   supplements are able to alleviate infertility in patients with PCOS[15-17]. A recent study

101   has explored the effect of inositol in improving sex hormone binding globulin

102   (SHBG), dehydroepiandrosteronesulfate (DHEAS), and testosterone levels compared

103   with common pharmacological interventions[18]. However, studies are inconsistent in

104   efficacy and safety of these non-pharmacological interventions. Therefore, it is

105   challenging for decision makers to choose non-pharmacological interventions.

106   Network meta-analysis (NMA) can be used for analysis of indirect and direct

107   data to rank different interventions[19 20], which realizes the possibility of including

108   RCTs that do not have a non-treatment or minimal treatment control group in the

109   same analysis. The aim of the study is to compare the efficacy and evaluate the safety

110   of common non-pharmacological interventions for overweight/obese women with

111   PCOS and their role in improving ovulation and pregnancy outcomes through

112   systematic review (SR) and NMA.

113   **METHODS**

114   **Study registration**

115   This protocol was registered on PROSPERO (CRD42021283110) and was

116   reported following the Preferred Reporting Item for Systematic Review and

117   Meta-analysis (PRISMA-P) statement guidelines (Supplementary file 1 for

118   PRISMA-P checklist)[21]. The findings of this study will be presented following the

119   Checklist of Items to Include When Reporting a Systematic Review Involving a

120   Network Meta-analysis (PRISMA-NMA)[22].

121   **Inclusion criteria**

122   Types of studies

123   Only randomized controlled trials (RCTs) presented in English or Chinese will

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124   be included in the study. Articles on parallel design RCTs and the first stage of

125   cross-over RCTs will be retrieved.

126   Participants

127   Participants diagnosed with PCOS and overweight or obese will be included.

128   Women who will either chose to undergo assisted reproductive technology (ART) or

129   conceive naturally will be enrolled. There will be no restrictions on age, race,

130   nationality, and education levels.

131   Types of interventions

132   Non-pharmacological interventions used as main treatment or main adjuvant

133   treatment will be included. Non-pharmacological interventions will be limited to

134   lifestyle interventions (including dietary intervention, exercise intervention, and

135   behavioral intervention), acupuncture therapies, and nutritional supplements. Dietary

136   intervention include calorie reduction or diet structure change (carbohydrate-counting,

137   fat-counting, protein-counting)[23]. And exercise intervention include resistance or

138   aerobic exercise[23]. Studies used single or multiple non-pharmacological

139   intervention(s) will be considered.

140   Types of comparator(s)/control

141   Comparators will be ART, or western medicine, or usual care, or placebo, or

142   sham interventions, or blank control, or other different non-pharmacological

143   interventions.

144   Types of outcome measures

145   Primary outcomes

146   Clinical pregnancy will be considered as the primary outcome in the study.

147   Clinical pregnancy will be defined as a viable intrauterine pregnancy confirmed by

148   ultrasound at greater than 6 weeks gestation[24]. As for multiple intrauterine gestational

149   sacs, it will be regarded as one clinical pregnancy.

150   Secondary outcomes

151   Live birth, ovulation, pregnancy loss, and multiple pregnancy will be regarded as

152   secondary outcomes. Live birth will be defined as live newborns beyond week 24 of

153   gestation[25]. Multiple newborns at the same delivery will be counted as one live birth.

154   Ovulation will be monitored by ultrasound or urine Luteinizing Hormone strips.

155   Pregnancy loss will include miscarriage, termination of pregnancy and perinatal

156   mortality, which will be defined as any stillbirth or neonatal death in the first week of

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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 8 databases including 4 English databases (Cochrane Library, MEDLINE, EMbase, and PsycINFO) and 4 Chinese databases (Chinese National Knowledge Infrastructure (CNKI), WanFang Data, the Chongqing VIP Database (VIP), and China Biology Medicine disc (CBM)). Studies published from inceptions 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.

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/

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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/
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.

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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
84	exp animals/ not humans.sh.
85	83 not 84
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180

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 (NIH) 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

8

188   studies.

Data collection and analysis

190   Selection of studies

191   Endnote software V.9.1. will be used to manage the retrieved studies and remove

192   duplicates. Two independent researchers (JJL and ZYX) will screen the studies by

193   reading the titles and abstracts, according to the eligible criteria. Then, second

194   screening will be conducted by reading the full text. The reasons for exclusion will be

195   recorded. The included studies will be cross-checked. The two researchers will hold a

196   discussion in case of any dispute to reach an agreement. A third researcher (FRL) will

197   be consulted if the disagreement will not be resolved through discussion. The

198   selection procedure is presented in a PRISMA flow chart (Figure 1).

199   Data extraction and management

200   Two researchers (HY and JZ) will independently extract data based on a

201   pre-designed form. The extracted data will be as followed: ① basic information

202   (name of the first author, year of publication, country, study type, sample size,

203   number of centers, sources of funds, and conclusion); ② participants (age,

204   diagnostic criteria, and course of disease); ③ interventions (intervention type, details

205   of intervention, and intervention session/ frequency/ duration/ dosage); ④ controls

206   (control type, details of control, and treatment session/ frequency/ duration/ dosage);

207   ⑤ outcomes (data for each measurement, and safety). The corresponding authors will

208   be contacted for missing information. The two researchers will cross-check the data

209   after completion of data extraction. The disagreements will be solved by the team

210   discussion or consultation with the third researcher (FRL).

Assessment of risk of bias

212   Two independent researchers (ZHY and GXX) will assess the risk of bias of

213   included studies using the Cochrane Collaboration's tool for assessing risk of bias

214   (ROB) 2.0[27 28]. The following five domains will be evaluated: 1) bias arising from the

215   randomization process, 2) bias due to deviations from intended interventions, 3) bias

216   due to missing outcome data, 4) bias in outcome measurement, and 5) bias in

217   selection of the reported result. The overall bias will be considered *low risk of bias* if

9

218 all domains will be marked *low risk*. The overall bias will be expressed as having

219 *some concerns* if one domain will be denoted as *some concern*. The overall bias will

220 be *high risk of bias* if one domain will be marked *high risk* or several domains will be

221 denoted as *some concern* and may influence the robustness of the study.

222 Corresponding authors will be contacted if there is any missing information that

223 would affect the assessment. The two researchers will cross-check the data after

224 completion of assessments. The two researchers will hold a discussion if any dispute

225 occurs to reach an agreement. A third researcher (FRL) will be consulted if the two

226 researchers will not reach a consensus.

227 **Evaluation of certainty of evidence**

228 Two independent researchers (JL and ZY) will evaluate the certainty of evidence

229 of each outcome using the Grading of Recommendations Assessment, Development

230 and Evaluation (GRADE) system[29]. The certainty of evidence will be rated as *high*,

231 *moderate*, *low*, or *very low* based on the rating criteria recommended in GRADE. Two

232 researchers will cross-check the results after evaluation of the certainty of evidence.

233 Any dispute will be solved through discussion or a third researcher (FRL) will be

234 consulted.

235 **Assessment of similarity and consistency**

236 Similarity and consistency will be evaluated to obtain valid and credible results.

237 Similarity will be assessed according to clinical characteristics and methodological

238 characteristics owing to the challenges in clarifying similarity by statistical analysis.

239 Study designs, participant characteristics, and interventions will be included in the

240 assessment. Local inconsistency will be evaluated using the node splitting method.

241 $P > 0.05$ indicates no statistical significance implying that it is consistent to the direct

242 and indirect comparison. $P < 0.05$ represents statistical significance indicating

243 inconsistency. A consistency model or inconsistency model will be chosen based on

244 the results. Potential scale reduced factor (PSRF) will be used to determine

245 convergence. PSRF close to 1 indicates successful convergence.

246 **Pairwise meta-analysis**

247 STATA software Version.15.0 (Stata Corp LP, College Station, Texas, USA)

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248 will be used for data analysis. Statistical heterogeneity will be evaluated by

249 calculating the I^2 value. $I^2 < 50\%$ indicates that the heterogeneity is acceptable.

250 Otherwise, heterogeneity will be considered as significant. The random-effects model

251 will be chosen in consideration of the suggestion that it is generally a more plausible

252 match[30]. Descriptive review will be adopted if the heterogeneity is significant. Since

253 clinical pregnancy, live birth, ovulation, pregnancy loss, and multiple pregnancy are

254 dichotomous outcomes, risk ratio (RR) will be used to synthesize the pooled data.

255 **Network meta-analysis**

256 Aggregate Data Drug Information System (ADDIS V.1.16.8, Drugis, Groningen,

257 NL) and Markov Chain Monte Carlo (MCMC) method will be used for Bayesian

258 network analysis to synthesize data[31]. In addition, STATA software Version.15.0 will

259 be used to compare different interventions of each outcome and forest plots will be

260 generated to present the NMA results. The rank of various non-pharmacological

261 interventions will then be generated. Comparisons between interventions will be

262 presented as a network plot and the contribution of different designs to the final effect

263 size of the NMA will be presented as rank plots. Non-pharmacological interventions

264 will be ranked based on the P score, which determined whether the extent of certainty

265 when the intervention group is superior compared with the control group. A P of

266 100% indicates that the treatment is better relative to the control whereas P value of

267 0% indicates that the treatment worse compared with the control.

268 **Subgroup analysis, meta-regression analysis, and sensitivity analysis**

269 Subgroup analysis and meta-regression analysis will be conducted to explore the

270 possible sources of heterogeneity and inconsistency. If data are available, subgroup

271 analysis will be performed based on different types of non-pharmacological

272 interventions and meta-regression analysis will be performed based on the duration of

273 PCOS, the degree of obesity, the age of patients, country of origin of patients, whether

274 ART has been used, and dose of intervention. In addition, sensitivity analysis will be

275 conducted by excluding one study by one study to verify the robustness of the results.

276 **Publication bias assessment**

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277   A comparison-adjusted funnel plot will be generated to detect the reporting bias

278   if more than 10 studies will be included.

279   **Patients and public involvement**

280   The study will be a SR and NMA based on existing studies, therefore, no patients

281   or public will be involved directly.

282   **DISCUSSION**

283   To the best of our knowledge, this will be the first SR and NMA study to

284   compare the efficacy and safety of non-pharmacological interventions in

285   overweight/obese women with PCOS based on ovulation and pregnancy outcomes.

286   The findings from the study will provide a ranking of non-pharmacological

287   interventions to help patients, doctors and policy makers for decision making. In

288   addition, the Grading of Recommendations Assessment, Development and Evaluation

289   system (GRADE) will be adopted to evaluate the certainty of evidence. There will be

290   also some limitations of the study. Firstly, non-pharmacological interventions in

291   PCOS are an extensive research field, but we only focus on lifestyle

292   interventions, acupuncture therapies, and nutritional supplements[11], which may lead to

293   limitations of clinical practice. Secondly, considering that overweight/ obese patients

294   have an increased risk of metabolic disorders[32] and tend to benefit more from

295   non-pharmacological interventions compared with normal weight patients, we will

296   restrict the population to overweight/obese PCOS, which may limit the extrapolation

297   of the conclusion. Thirdly, the efficacy of different protocols of the same

298   non-pharmacological intervention will not be investigated.

299   **Ethics and dissemination**

300   The study will not require ethical approval because it comprises analysis based

301   on existing studies. The results are expected to be published in a peer-reviewed

302   journal or disseminated at relevant conferences. The findings will provide evidence on

303   use of non-pharmacological interventions for overweight/obese women with PCOS

304   and the effect on ovulation and pregnancy outcomes thus promoting the clinical

305   application of these methods.

306   **Acknowledgements**

12

307   None

308   **Contributions**

309   HY conceived the review protocol and drafted the manuscript. JL, JY, and FRL

310 revised the study design. HY, ZHY, JZ, JJL, ZYX, LYL, and ZY participated in

311 design of the search strategy and development of the data extraction dataset. ZHY,

312 GXX, LYL, XYZ, and HY designed the data synthesis and analysis strategy. JY and

313 FRL will monitor each procedure of the review and be responsible for quality control.

314 All authors have read and approved the manuscript draft.

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317 Foundation of China (82174517) and the National Natural Science Foundation of

318 China (82074556).

319   **Competing interests**

320   None declared.

321   **Patient consent for publication**

322   Not required.

323   **Provenance and peer review**

324   Not commissioned; externally peer reviewed.

325   **Footnote**

326   Data Sharing Statement: Not applicable.

327

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433 **Supplementary file 1. PRISMA-P checklist**

434 **Figure 1. PRISMA flow diagram showing the study selection process.**

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Identification

Records identified through database searching
(n =   )

Additional records identified through other sources
(n =   )

Screening

Records after duplicates removed
(n =   )

Records screened
(n =   )

Records excluded
Not related to overweight/obese PCOS (n=)
Non-pharmacological intervention is not the main treatment or main adjuvant treatment of the intervention group (n=)
Outcomes are not meet standards (n=)
Not RCTs (n=)

Eligibility

Full-text articles assessed for eligibility
(n =   )

Full-text articles excluded, with reasons
Repeated test (n=)
No test data required by this program are available (n=)
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Studies included in qualitative synthesis
(n =   )

Included

Studies included in quantitative synthesis (meta-analysis)
(n =   )
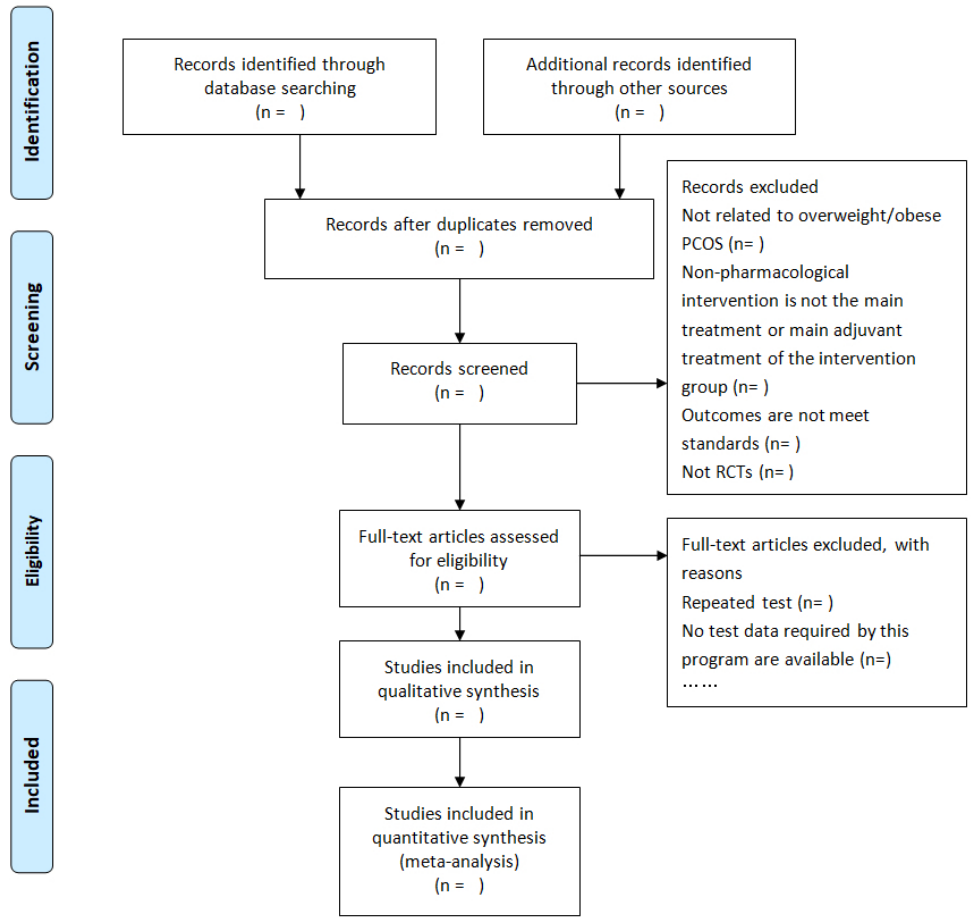
311x291mm (72 x 72 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page Number/Line Number	Reported on Section/Paragraph
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Page 1/Line 2-3	Title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2/Line 56	Abstract
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1/Line 4-17	Affiliations
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 12-13/Line 307-313	Contributions
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A	N/A
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Page 13/Line 314-317	Funding
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A	N/A
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3-4/Line 89-105	Introduction
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4/Line 109-112	Introduction
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 4-6/Line 121-160	Methods/ Inclusion criteria
Information	9	Describe all intended information sources (such as electronic databases, contact with study authors,	Page 6,8/Line 170-	Methods/ Search

sources		trial registers or other grey literature sources) with planned dates of coverage	178-181 90-187	methods for identification of studies
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 6-8/Line 179	Methods/ Table 1
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 9/Line 190-191	Methods/ Data collection and analysis/ Selection of studies
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 9/Line 191-197	Methods/ Data collection and analysis/ Selection of studies
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 9/Line 199-209	Methods/ Data collection and analysis/ Data extraction and management
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 9/Line 200-207	Methods/ Data collection and analysis/ Data extraction and management
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5-6/Line 144-160	Methods/Inclusion criteria/Types of outcome measures
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 9-10/Line 211-225	Methods/ Assessment of risk of bias

Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 10-11/Line 246-253	Methods/ Pairwise meta- analysis
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 10/Line 235-244	Methods/ Assessment of similarity and consistency
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 11/Line 268-274	Methods/ Subgroup analysis, meta-regression analysis, and sensitivity analysis
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 11/Line 251	Methods/ Pairwise meta- analysis
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 11/Line 276-277	Methods/ Publication bias assessment
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 10/Line 227-233	Methods/ Evaluation of certainty of evidence

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.