Jin *et al. Journal of Ovarian Research (2025) 18:8*
https://doi.org/10.1186/s13048-025-01595-5

Journal of Ovarian Research

REVIEW

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Effects of non-pharmacological interventions on biochemical hyperandrogenism in women with polycystic ovary syndrome: a systematic review and network meta-analysis

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Abstract

Objective To systematically evaluate the effectiveness of non-pharmacological interventions (NPIs), including electroacupuncture, exercise, diet, and lifestyle changes, in reducing androgen levels in women with polycystic ovary syndrome (PCOS) through a systematic review and network meta-analysis.

Methods Comprehensive searches were conducted in PubMed, Embase, Cochrane Library, Web of Science, CNKI, and Wanfang up to June 2024. Randomized controlled trials (RCTs) comparing NPIs with other NPIs or placebo treatments in adult women with PCOS were included. Study selection was independently performed by three authors. Quality assessment followed PRISMA guidelines using the Cochrane RoB2 tool. The confidence of evidence was examined using Confidence in Network Meta-Analysis (CINeMA). Traditional meta-analysis of continuous variables was conducted using Stata 17.0 software with a random-effects model, reporting effect sizes as standardized mean differences (SMD) and weighted mean differences (WMD). Network meta-analysis (NMA) was used to synthesize data, with network diagrams illustrating comparisons between NPIs. We assessed the consistency of the results, performed sensitivity analyses, and examined publication bias to evaluate the influence of individual studies. Furthermore, subgroup analysis and network meta-regression analysis were conducted to explore potential sources of heterogeneity.

Results The review included 21 studies with 1,196 participants, with meta-analysis focusing on 17 studies involving 1,013 participants. NPIs significantly reduced serum testosterone (SMD = -0.57; 95% CI: -0.86 to -0.29, $p < 0.01$), A4 (SMD = -1.37; 95% CI: -2.63 to -0.12, $p = 0.03$), and mFG score (WMD = -0.81; 95% CI: -1.26 to -0.37, $p < 0.01$). Notably, the reduction in testosterone levels achieved with NPIs met the Minimum Clinically Important Difference (MCID) of 12.47 ng/dL (WMD = -12.57; 95% CI: -18.92 to -6.23; $p < 0.01$), affirming the clinical relevance of these reductions. No significant effects were observed on Free Androgen Index (FAI), Sex Hormone-Binding Globulin (SHBG), Dehydroepiandrosterone (DHEA), DHEA Sulfate (DHEAS), Free Testosterone (FT), or Dihydrotestosterone (DHT) levels (all $p > 0.05$). The NMA (18 studies, 1,067 participants) identified electroacupuncture combined with diet and exercise as the most effective intervention for reducing serum testosterone (WMD = -21.75; 95% CI: -49.58 to 6.07; SUCRA 72.3%). Evidence

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certainty for many interventions was low, highlighting the need for higher-quality studies. Sensitivity analysis confirmed the robustness of the findings, and no publication bias was detected.

Conclusions NPIs, particularly electroacupuncture combined with exercise and dietary management, effectively reduce androgen levels in PCOS patients. These findings provide valuable guidance for clinicians and women with PCOS, with multi-component approaches recommended for more substantial clinical benefit.

Trial registration PROSPERO CRD42023426226.

Keywords Polycystic ovary syndrome, Non-pharmacological interventions, Hyperandrogenism, Testosterone

Background

PCOS is a collection of syndromes with intricate and varied causes and diverse clinical presentations affecting 10% to 13% of women [1, 2]. Its primary diagnostic feature is hyperandrogenism, characterized by elevated serum testosterone levels, hirsutism, acne, oligomenorrhea or amenorrhea, and an increased number of preantral follicles [3]. PCOS is associated with increased risks of infertility, type 2 diabetes mellitus (II-DM), and cardiovascular disease (CVD) [4]. The pathogenesis of PCOS is highly complex and is generally believed to be associated with multiple factors, including genetics, environment, lifestyle, obesity, and psychological factors. Dysfunction of the hypothalamic-pituitary axis leads to abnormal gonadotropin secretion, resulting in increased luteinizing hormone (LH) and androgen levels in patients. Elevated androgen levels may contribute to insulin resistance and disturbances in glucose and lipid metabolism [5]. Due to its unclear pathogenesis, there are currently no definitive treatments [6]. The 2023 international guidelines emphasize controlling hyperandrogenism through NPIs such as exercise, diet, and lifestyle management [7]. In recent years, non-pharmacological therapies, including Traditional Chinese Medicine (TCM) practices like acupuncture, massage, Tai Chi, and Qigong, have shown promise in improving PCOS symptoms and biochemical markers [8]. However, high-quality evaluative evidence in this area remains insufficient.

Previous studies have explored various NPIs for treating PCOS, including acupuncture, exercise, diet, and lifestyle management. Among these, Pundir et al. conducted a comprehensive systematic review assessing NPIs' impact on fertility and non-fertility outcomes in PCOS. Their review found that lifestyle interventions could improve glucose-related outcomes, hyperandrogenism symptoms, and some anthropometric measures, but did not rank the NPIs or evaluate all relevant biomarkers [9]. Other reviews analyzed exercise, acupuncture, and lifestyle interventions, focusing mainly on insulin resistance, BMI, or pregnancy outcomes [10–13].

Given the critical role of biochemical hyperandrogenism in PCOS, there is a need for a thorough evaluation and comparison of NPIs aimed at reducing excessive androgen levels. This study employs NMA to integrate direct and indirect evidence from multiple studies, assessing the effectiveness of various NPIs in lowering androgen biomarkers and providing clinical insights for treatment.

Methods

Protocol registration

The protocol was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. Furthermore, the protocol has been registered on PROSPERO with the registration number CRD42023426226.

Search strategy

We searched the journals published in PubMed, Embase, Cochrane Library, Web of Science, CNKI and Wanfang up to June 2024. The search keywords were focused on 'polycystic ovary syndrome', 'hyperandrogenism', 'androgens', 'acupuncture', 'electroacupuncture', 'auricular acupuncture', 'acupoint catgut embedding', 'mind–body therapies', 'mindfulness', 'meditation', 'yoga', 'tai chi', 'qigong', 'massage', 'tuina', 'physical exercise'. The final search formula was obtained by searching for the subject words, subordinate words, and free words. The reference list of all selected articles will be independently screened to identify additional studies missed in the initial search (Supplementary Files 1: Appendix 1).

Screening and study eligibility

We utilized Endnote X9 as a tool for organizing the studies that were obtained. Two researchers, JQ and YY, conducted a comprehensive literature review, extracting relevant information and cross-verifying their results. Any disagreements were settled by engaging in discussions or negotiations with a third researcher, LL. In literature screening, first read the title of the article. After excluding obviously irrelevant literature, the abstracts and full texts were further read to decide whether to include them. Authors of the original studies were contacted by email or phone to obtain information that had not yet been identified but was important to this study. The data extracted from the included literature include the demographic characteristics of the study population, the types of intervention and control groups, the number of subjects in each group (intervention group plus control group), the follow-up time of the randomized controlled trial, outcome indicators, etc. Information was extracted from androgen biomarker levels at the beginning and end of RCT follow-up or from the difference between the mean values, depending on the data presentation format of the primary study.

Eligibility criteria

Type of studies

Studies included single- or multi-arm randomized controlled trials, full-text journal publications, and any trials conducted in the healthcare field. Abstracts, unpublished academic papers, editorials, clinical observations, case studies, cohort design studies, non-randomized trials, and case–control studies were excluded. We reviewed all existing systematic reviews and meta-analyses to ensure that all appropriate references were included in this process.

Types of participants

Study subjects must be adult women aged 18–40 years, diagnosed with PCOS, with no BMI restrictions. Endpoint assessments must include at least one androgen biomarker evaluated under non-pharmacological interventions.

Types of interventions

Nonpharmacological intervention, as the main treatment method, is limited to the following four aspects of treatment. (1) Psychology: mindfulness, meditation; (2) Physical therapy: massage, tui-na, exercise; (3) Psychosomatic exercise (such as acupuncture, including acupuncture, electroacupuncture, ear acupuncture, acupoint catgut embedding, yoga, Tai Chi, Qigong). Studies using single or multiple complementary alternative medical interventions will be considered. Control groups include conventional treatment, placebo, sham intervention, blank control, or other different NPIs.

Type of outcome measures

The serum T level at the last treatment was used as the primary outcome measure of this study. SHBG, FAI, FT, A4, DHT, DHEAS and mFG score at the last treatment was used as a secondary outcome measure.

Study quality

Two investigators (JQ and YY) independently evaluated the risk of bias using the methods specified by the Cochrane Manual. A third researcher (YP) clarifies any inconsistencies. We assessed the risk of bias using RoB2, the Cochrane Methods Group's Cochrane Evaluation tool, revised in 2019. RoB2 evaluated the included articles on five dimensions:(1) bias in randomization, (2) bias from established interventions, (3) bias in missing outcome data, (4) bias in outcome measures, and (5) selective reporting of outcome bias. In addition, we examined the confidence of evidence using the CINeMA web application, which grades the confidence of the results as high, moderate, low, and very low [14].

Statistical analysis

Meta-Analysis

We utilized Stata 17.0 software for the extracted continuous variables to conduct traditional meta-analysis by employing a random-effects model. The effect sizes for biochemical androgen markers are expressed as SMD with 95% confidence intervals (CI), and the effect sizes for the Ferriman-Gallwey score (mFG) are expressed as WMD with 95% CI. The differences between the intervention and control groups were pooled using a random-effects model. Mean differences and standard deviations (SD) of outcome measures were collected to estimate pooled effects, provided these data were reported in at least three trials. The heterogeneity among studies was evaluated using the I^2 statistic and associated p-values. Specifically, I^2 values of 25%, 50%, and 75% respectively indicated low, moderate, and high statistical heterogeneity [15]. Subgroup analyses and meta-regression were conducted to explore potential sources of heterogeneity. For meta-analysis, we performed a priori subgroup analyses to assess the impact of (1) participant body mass index (BMI; < 28 kg/m^2 or ≥ 28 kg/m^2), (2) participant age (< 30 years or ≥ 30 years), (3) duration on primary outcomes, ensuring that each subgroup included at least two studies. Results were considered significant at I^2 value significantly decreased and $P \leq 0.05$.

To further enhance the clinical relevance of our findings, we estimated the range of serum testosterone reduction required to achieve the MCID, as recommended by Bernstein and Mauger (2016) [16]. In our analysis, we applied a distribution-based method following the approach outlined by Watt et al. (2021) [17] to establish the MCID value. We followed these steps to derive the MCID for serum testosterone: a) A pooled standard deviation (SD-pooled) was derived from parallel randomized controlled trials (RCTs) included in a systematic review. These trials reported data on the relevant blood markers, where ni represents the number of participants in each study group, and SDi represents the standard deviation associated with the mean change or baseline marker score for each study group. The results indicated that the MCID could be estimated as a minimum reduction of 12.47 ng/dL (with a 0.4 standard deviation threshold), ensuring that our findings can be effectively applied to benefit patients.

$$SD_{\{pooled\}} = \sqrt{\frac{\sum (n_i - 1)\, SD_i^2}{\sum (n_i - 1)}}$$

Network meta-analysis

We focused on primary outcomes and used network diagrams to illustrate comparisons of various non-pharmacological treatments for each outcome. Nodes represented interventions, and lines connecting the nodes signified direct comparisons. The size of the nodes and lines was proportional to the number of included studies. We evaluated inconsistency within loops between direct and indirect evidence by applying specific inconsistency techniques, considering consistency non-significant when the 95% confidence interval of inconsistent components included zero. The Surface Under the Cumulative Ranking (SUCRA) curve presented scores for the improvement in testosterone levels among PCOS patients for each treatment method, with larger areas under the curve indicating significantly superior effects. A minimally contextualized approach was used to assess the effectiveness of each intervention, with the control group as the reference and the decision threshold set at the MCID for testosterone levels. Each intervention—exercise, diet, electroacupuncture, exercise combined with diet, electroacupuncture combined with exercise, and dietary control—was initially compared to the control group. Based on whether each intervention crossed the MCID threshold, they were preliminarily categorized as having no significant difference, more effective, or less effective. Next, interventions categorized as “more effective” were further compared to refine their classification. Subsequently, we assessed the certainty of evidence for each intervention using the CINeMA framework, classifying them as high/moderate or low/very low certainty. Finally, we validated the consistency of each intervention’s classification with results from other pairwise comparisons and confirmed that ranking data (such as SUCRA scores) supported the classification to ensure internal coherence [18]. Additionally, meta-regression analysis was conducted in the R statistical environment, assuming that publication year, mean age, BMI, sample size, duration, and total sessions were the primary sources of heterogeneity. Sensitivity analyses were performed by removing one study at a time and recalculating the effect size to detect the influence of each study on the overall effect size and to determine whether any individual trial exerted undue influence. Publication bias was assessed using funnel plot and Egger’s regression asymmetry test [19].

Results

Literature search results

Figure 1 shows the PRISMA system review flow chart. In the preliminary review, a comprehensive search of the databases was conducted using the retrieval method, and a total of 2,149 relevant papers were retrieved. Endnote X9 software eliminates 396 duplicate citations, resulting in 1753 citations of titles and abstracts. We then screened titles and abstracts to exclude 916 studies, including 109 unrelated to the topic, 625 meetings, abstracts, and draft studies, and 182 animal studies. For the remaining 837 relevant research articles, 12 of which could not find the full text, we tried to contact the corresponding authors but failed to obtain, and finally assessed the eligibility of 825 relevant full-text articles. Of these, 42 lacked androgen related outcome measures, 496 were in treatment or control groups involving western medicines, traditional Chinese medicines, or oral natural supplements, 221 were not eligible for randomized controlled trials, and 17 were in subjects under 18 years of age or in healthy people as controls. 20 studies of different parameters in the same intervention (such as acupuncture point, frequency, exercise time or intensity, etc.), and 8 unpublished academic papers. In the end, 21 studies were included in the analysis. Ultimately, 17 studies were conducted a meta-analysis, while a NMA was performed on 18 studies.

General characteristics

Table 1 is a list of the study characteristics included. Among the 21 studies included, a total of 1196 patients were eligible for the analysis [20–40]. The interventions in these studies included physical exercise (including aerobic exercise, resistance training, yoga, tai chi), electroacupuncture, diet or their combination. Relevant characteristics were extracted, including age, sample size, intervention method and details, treatment cycle, follow-up duration, and the type of relevant androgen biomarker outcome.

Quality assessment

According to the Cochrane Collaboration’s tool (RoB2), double check results showed that seven RCT were of high quality, while the other fourteen were considered to be of some concern. The overall quality of the incorporated articles is very high. Figure 2 shows the risk-of-bias graph and risk-of-bias summary for selected studies (The result of the Rob2 double check is presented in Supplementary Files 2). For all outcomes, the overall certainty of the evidence was low. For the primary outcome, we assessed the confidence in the evidence comparing with the control group, with 100% of the evidence rated as low

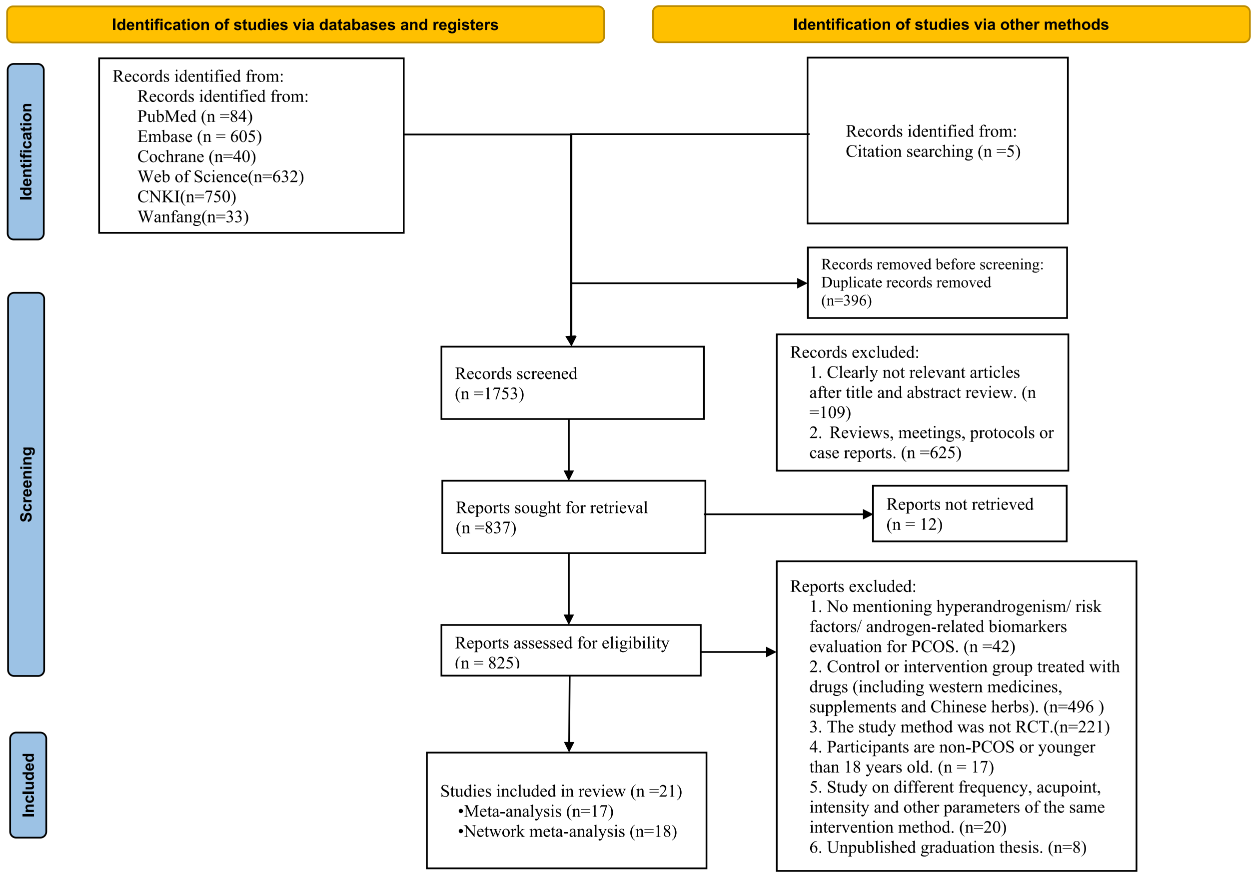

Fig. 1 PRISMA flow diagram of study selection process

or very low. For comparisons between two NPIs, 40% of the evidence was rated as very low (Supplementary File 2).

Meta analysis

Biochemical hyperandrogenism

Testosterone 16 studies with 1013 participants evaluated the impact of NPI on Testosterone levels. Meta-analysis showed that testosterone levels in the NPI group were significantly reduced (SMD = -0.57; 95% CI: -0.86 to -0.29; $p < 0.01$), with high heterogeneity ($I^2 = 78.4\%$). The subgroup analysis results showed that the BMI < 28 kg/m^2 group exhibited moderate to high heterogeneity ($I^2 = 70.3\%$), while the BMI ≥ 28 kg/m^2 group showed very low heterogeneity ($I^2 = 0.0\%$). In terms of age, participants aged ≥ 30 years had high heterogeneity ($I^2 = 88.5\%$), whereas those aged < 30 years had relatively low heterogeneity ($I^2 = 45.9\%$). Regarding intervention duration, studies with intervention periods of ≤ 3 months showed high heterogeneity ($I^2 = 86.4\%$), while those with durations > 3 months exhibited very low heterogeneity ($I^2 = 0.0\%$) (Fig. 3).

FAI 4 studies with 284 participants assessed the effect of NPI on FAI. The meta-analysis results indicated that FAI levels in the NPI group were significantly lower (SMD = -0.02; 95% CI: -0.27 to 0.24; $p > 0.05$), but there was considerable heterogeneity ($I^2 = 91.2\%$).

SHBG 7 studies with 424 participants examined the influence of NPI on SHBG. The meta-analysis found no significant difference in SHBG levels between the two groups (SMD = 0.06; 95% CI: -0.15 to 0.27; $p > 0.05$), with low heterogeneity ($I^2 = 13.4\%$).

DHEAS 4 studies with 284 participants investigated the effect of NPI on DHEAS levels. The meta-analysis indicated no significant difference between the control group and the NPI treatment group (SMD = -0.32; 95% CI: -0.71 to 0.08; $p > 0.05$), with moderate heterogeneity ($I^2 = 52.9\%$).

DHEA 3 studies evaluated the impact of treatment on DHEA levels. The meta-analysis indicated no significant difference between the control group and the NPI treatment group (SMD = -0.26; 95% CI: -0.63 to 0.11; $p > 0.05$), with low heterogeneity ($I^2 = 0.0\%$).

A4 and FT 5 studies and 3 studies respectively assessed the levels of A4 and FT. The meta-analysis results showed

Table 1 Characteristics of studies used for analysis

First Author/Year	Region	Age	BMI	Sample	Intervention	Control	Follow-up	Outcome of interest
Lu/2023	China	T:27.3 ± 2.6 C:28.0 ± 2.8	T:27.7 ± 5.0 C:28.3 ± 4.5	51	Exercise + diet	Usual care	12 weeks	Testosterone
Liu/2023	China	T:30.2 ± 2.6 C:31.3 ± 3.1	None	65	EA	Sham-EA	6momth	Testosterone, A4, mFG
Philbois/2022	Brazil	T1:29.0 ± 4.0 T2:29.0 ± 5.0 C2:29.0 ± 5.0	T1:27.8 ± 4.2 T2:27.7 ± 5.7 C2:29.2 ± 5.4	75	Exercise: HIIT /MICT	No intervention	16 weeks	Testosterone, mFG
Li/2022	China	T:23.2 ± 4.3 C:22.9 ± 4.6	T:28.4 ± 4.0 C:29.5 ± 4.4	42	Exercise: Tai chi	Self-control	12 weeks	Testosterone, A4, SHBG, DHEAS
Dong/2022	China	T:23.3 ± 2.7 C:22.3 ± 2.4	T:22.9 ± 5.5 C:21.9 ± 5.3	43	EA	Sham-EA	16 weeks	Testosterone, mFG
Shi/2021	China	T:31.0 ± 3.2 C:30.5 ± 3.1	T:27.9 ± 1.7 C:27.9 ± 1.7	92	Exercise + diet	Self-control	None	Testosterone
Ribeiro/2021	Brazil	T1:28.9 ± 4.3 T2:29.1 ± 5.2 C:28.5 ± 5.7	T1:28.4 ± 5.6 T2:28.6 ± 4.7 C:29.0 ± 5.2	87	Exercise: CAT/IAT	No intervention	16 weeks	Testosterone, A4, SHBG, FAI
Yin/2021	HK	T:29.2 ± 2.3 C:28.1 ± 3.4	T:21.2 ± 4.5 C:21.3 ± 3.3	15	Meditation: I-BMS	No intervention	3 month	Testosterone
Zhao/2021	China	T:27.0 ± 5.0 C:30.0 ± 6.0	None	60	EA	Sham-EA	12 weeks	Testosterone
Zhang/2020	China	T:29.0 ± 2.0 C:28.0 ± 3.0	T:24.6 ± 1.0 C:24.5 ± 1.1	40	EA + exercise + diet	exercise + diet	12 weeks	Testosterone, SHBG, FAI, mFG
Patel/2020	USA	T:20.9 ± 1.2 C:31.2 ± 2.3	T:35.1 ± 1.5 C:35.4 ± 3.3	22	Exercise: mindful yoga	No intervention	6 month	FT, DHEA, DHEAS, A4
Gilani/2019	Iran	24.0 ± 3.7	T:24.5 ± 4.0 C:22.9 ± 2.8	40	Exercise: Endurance training	No intervention	8 weeks	Testosterone, SHBG, FAI, A4, DHEAS
Lopes/2018	Brazil	T1:30.2 ± 5.1 T2:29.4 ± 4.1 C:28.8 ± 6.0	T1:29.3 ± 5.6 T2:29.0 ± 4.8 C:29.9 ± 5.3	69	Exercise: CAT / IAT	No intervention	16 weeks	Testosterone, SHBG, FAI
Peng/2017	China	T:28.5 ± 3.8 C:28.6 ± 3.3	T:23.9 ± 2.6 C:24.9 ± 2.9	100	EA	Sham-EA	3 month	Testosterone
Deng/2017	China	T:25.4 ± 2.3 C:26.1 ± 2.1	T:27.4 ± 1.5 C:27.5 ± 1.3	60	Exercise + diet	Usual care	3 month	Testosterone
Almenning/2015	Norway	27.2 ± 5.5	T1:26.1 ± 6.5 T2:27.4 ± 6.9 C:26.5 ± 5.0	25	Exercise: HIIT /ST	No intervention	10 weeks	Testosterone, FAI, SHBG, DHEAS
Jiang/2014	China	None	T:29.4 ± 4.3 C:30.5 ± 4.7	92	Exercise + diet	Usual care	6 month	Testosterone
Nybacka/2013	Sweden	T1:29.9 ± 5.5 T2:31.3 ± 4.8 C:31.8 ± 4.9	T1:35.4 ± 4.9 T2:34.8 ± 5.2 C:38.1 ± 7.0	43	Exercise + diet	Diet /Exercise	4 month	Testosterone, FT, SHBG
Johansson/2013	Sweden	T:30.1 ± 3.5 C:29.5 ± 2.8	T:26.9 ± 0.3 C:27.2 ± 1.3	26	EA	Self-control	10-13 weeks	Testosterone, FT, SHBG, DHEA, DHEA-S, DHT, mFG
Jedel /2011	Sweden	T1:29.7 ± 4.3 T2:30.2 ± 4.7 C:30.1 ± 4.2	T1:29.1 ± 8.8 T2:27.7 ± 6.4 C:26.8 ± 5.5	59	EA /Exercise	No intervention	32 weeks	Testosterone, FT, SHBG, DHEA, DHEAS, DHT, mFG
Al-Sherbeny/2011	Egypt	None	T1:38.4 ± 3.1 T2:37.6 ± 2.9 C:36.8 ± 3.8	90	Exercise + diet/ Exercise + diet	Diet	6 month	Testosterone, SHBG, FAI

T Treatment group, *C* Control group, *A4* Androstenedione, *FT* Free Testosterone, *DHT* Dihydrotestosterone, *FAI* Free androgen index, *SHGB* Sex hormone-binding globulin, *DHEA* Dehydroepiandrosterone, *DHEA-S* Dehydroepiandrosterone sulfate, *HIIT* High-intensity interval training, *CAT* Continuous aerobic training, *IAT* Intermittent aerobic training, *AE* Aerobic exercise, *RE* Resistance movement, *EA* Electroacupuncture, *I-BMS* Integrative Body-Mind-Spirit, *mFG* Ferriman-Gallwey scores

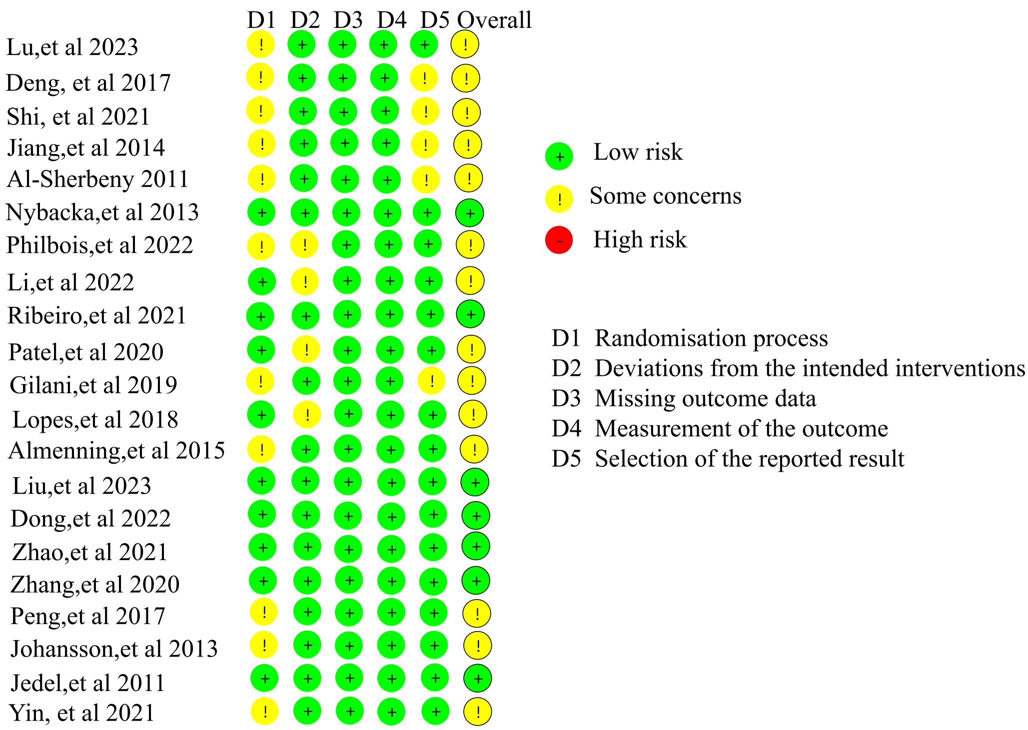

Fig. 2 Risk of Bias assessment

that NPI significantly reduced A4 (SMD = -1.37; 95% CI: -2.63 to -0.12; p = 0.03), however, there was no significant difference in FT between the two groups (SMD = -0.85; 95% CI: -1.88 to 0.19; $p > 0.05$) levels in PCOS patients compared to the control group, but both analyses exhibited high heterogeneity.

DHT 2 studies evaluated the effect of NPI on DHT. The meta-analysis revealed no significant difference in DHT levels between the two groups (SMD = -0.25; 95% CI: -0.66 to 0.16; p = 0.23), with low heterogeneity ($I^2 = 0.0\%$). (All the above results can be found in Table 2 and Supplementary File 1: Appendix 2.

Clinical hyperandrogenism

Ferriman-Gallwey score

Pooling date from 5 eligible study showed the NPI significantly reduced mFG score (WMD = -0.81; 95% CI: -1.26 to -0.37; $p < 0.01$), with low heterogeneity ($I^2 = 0.0\%$) (Table 2, Supplementary File 1: Appendix 2).

Minimal clinically important difference

To further enhance the clinical relevance of our findings, we estimated the range of decreased testosterone to achieve a MCID as recommended by Bernstein and Mauger [16]. In our analysis, we applied a distribution-based approach to establish a composite MCID value. We standardized the testosterone measurement units to ng/dL, and found that the reduction in testosterone levels in the NPIs group was statistically significant (WMD = -12.57; 95% CI: -18.92 to -6.23; $p < 0.01$) (Supplementary File 1: Appendix 3). Following the approach outlined by Watt et al. [17], we used the SD of the difference in testosterone levels to determine an MCID of 12.47(ng/dL) for 0.4 SD, indicating that the clinical and statistical difference in testosterone levels due to NPIs meets the threshold for minimal clinically important difference.

Network meta-analysis

Figure 4 shows the network plot of eligible comparisons for the effects of different NPIs on serum testosterone levels. A total of 18 studies involving 1,067 participants assessed the impact of various NPIs on serum testosterone. All NPIs were directly compared with the control group at least once. Among the five NPIs, two significantly reduced serum testosterone levels in PCOS patients compared to the control group: electroacupuncture (WMD = -15.08; 95% CI: -25.76 to -4.40) and diet combined with exercise (WMD = -20.06; 95% CI: -33.50 to -6.62) (Fig. 5). According to SUCRA results, diet combined with exercise ranked the highest, with a SUCRA probability of 74.7%. Electroacupuncture combined with diet and exercise ranked second with a SUCRA probability of 72.3%, and diet alone

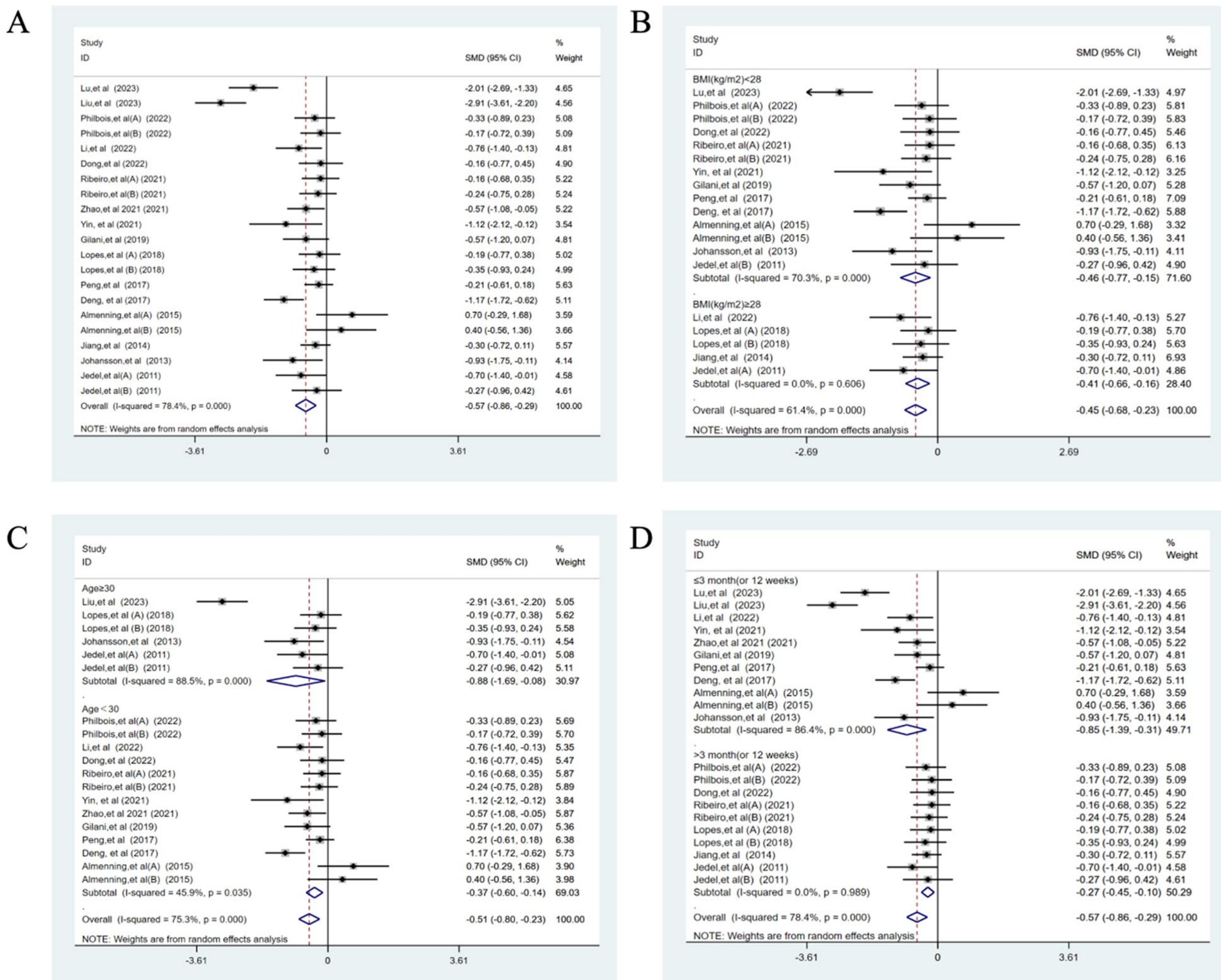

Fig. 3 Forest plots and Subgroup Analysis Results of NPIs on the Primary Outcome Testosterone. Note: A. Forest plots of the effects of NPIs on testosterone of PCOS. B. Subgroup Analysis Results of NPIs on the Primary Outcome Testosterone by BMI. C. Subgroup Analysis Results of NPIs on the Primary Outcome Testosterone by Age. D. Subgroup Analysis Results of NPIs on the Primary Outcome Testosterone by Duration

Table 2 Effects of non-pharmacological interventions on various androgen biomarkers and hirsutism

	No. of trials	Samples (NPI: control)	Meta-analysis			Heterogeneity (I^2%)
			SMD	95%CI	*p*-Value	
T	16	1013(525:488)	-0.57	-0.86, -0.29	0.00	78.4
FAI	4	284(138:146)	-0.02	-0.27, 0.24	0.89	0.0
SHGB	7	424(223:201)	0.06	-0.15, 0.27	0.55	13.4
DHEAS	6	236(134:102)	-0.32	-0.71, 0.08	0.12	52.9
DHEA	3	120(74:46)	-0.26	-0.63, 0.11	0.18	0.0
A4	5	286(146:140)	-1.37	-2.63, -0.12	0.03	95.2
FT	3	120(74:46)	-0.85	-1.88, 0.19	0.11	84.4
DHT	2	98(61:37)	-0.25	-0.66, 0.16	0.23	0.0
mFG	5	238(143:95)	-0.81	-1.26, -0.37	0.00	0.0

NPI Non-pharmacological interventions, *T* Testosterone, *FAI* Free androgen index, *SHBG* Sex hormone-generating globulin, *DHEAS* Dehydroepiandrosterone sulfate, *DHEA* Dehydroepiandrosterone, *A4* Androstenedione, *FT* Free testosterone, *DHT* Dihydrotestosterone, *mFG* Ferriman-Gallwey scores

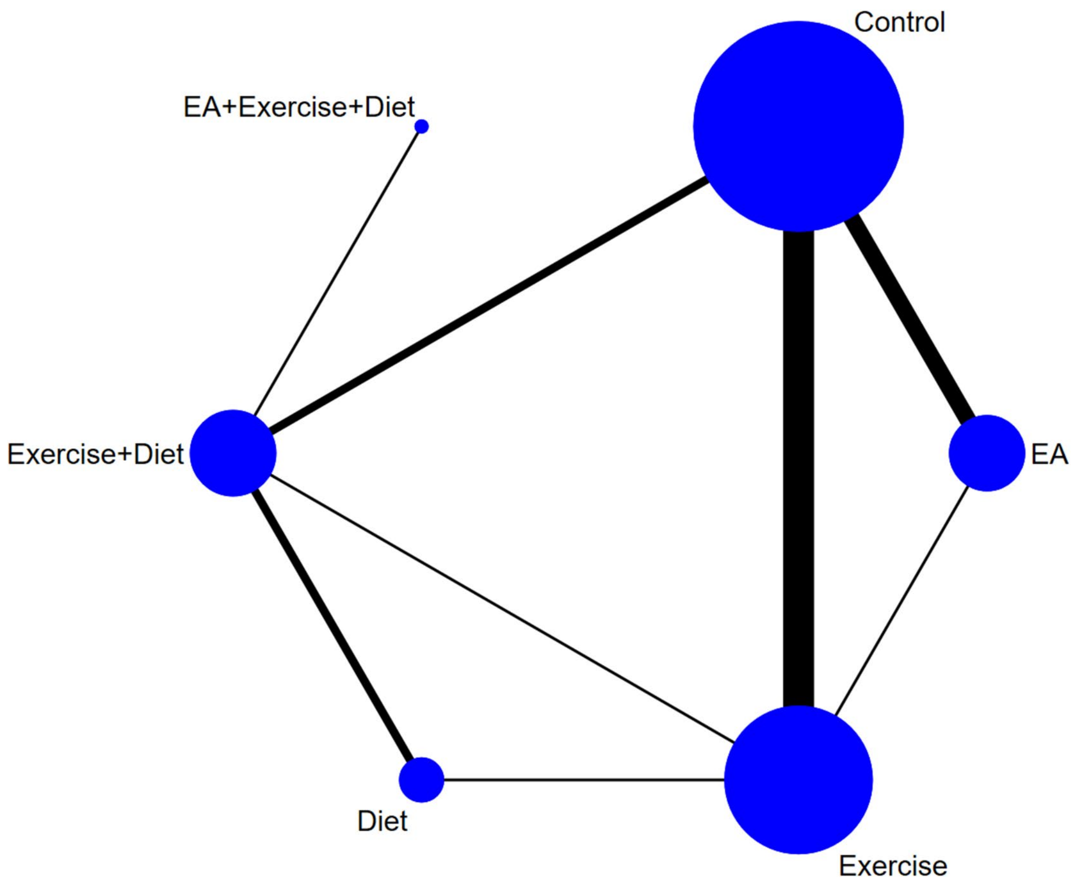

Fig. 4 Network plot of eligible comparisons of testosterone in 6 regimen groups

ranked third with a probability of 63.3%. The remaining interventions ranked as follows: electroacupuncture (SUCRA: 57.6%), exercise (SUCRA: 29.2%), and no treatment or placebo (SUCRA: 2.9%) (Fig. 6). Pairwise comparison results showed no significant differences between the interventions (Fig. 5).

We further assessed the therapeutic effects of each intervention using the minimal contextualization approach. Using the control group as a reference, each intervention was compared against the testosterone MCID threshold of 12.47 ng/dL. "Electroacupuncture + Exercise + Diet", "Electroacupuncture", and "Exercise + Diet" were classified as "more effective." Next, the certainty of the evidence for each intervention's effect was assessed using the CINeMA method (Supplementary File 1: Appendix 4). The results indicated that the certainty of evidence for "Electroacupuncture + Exercise + Diet" and "Electroacupuncture" was low, while the certainty for "Exercise + Diet", "Exercise", and "Diet" was classified as very low. Finally, based on the SUCRA rankings, electroacupuncture combined with exercise and diet demonstrated the most significant clinical relevance and showed a clear advantage in improving testosterone levels, making it the preferred intervention (Table 3 and Supplementary File 1: Appendix 5).

Heterogeneity, inconsistency and sensitivity analysis

Potential threats to the transitivity assumption and sources of heterogeneity, including publication year, mean age, BMI, sample size, duration, and total sessions, were assessed through meta-regression analysis. The results indicated that none of these factors significantly influenced the network meta-analysis outcomes. The study conducted a sensitivity analysis on 21 studies reporting the primary outcome (serum testosterone). Excluding any single study did not alter the combined result of the remaining 20 studies, which remained consistent with the original pooled estimate (SMD = -0.57; 95% CI: -0.86 to -0.29). This indicates that the findings are robust and not influenced by any individual study. Node-splitting analysis did not reveal any global inconsistency (Supplementary File 1: Appendix 6).

Publication bias

The results of the funnel plot and Egger test demonstrated no evidence of publication bias in the primary outcome

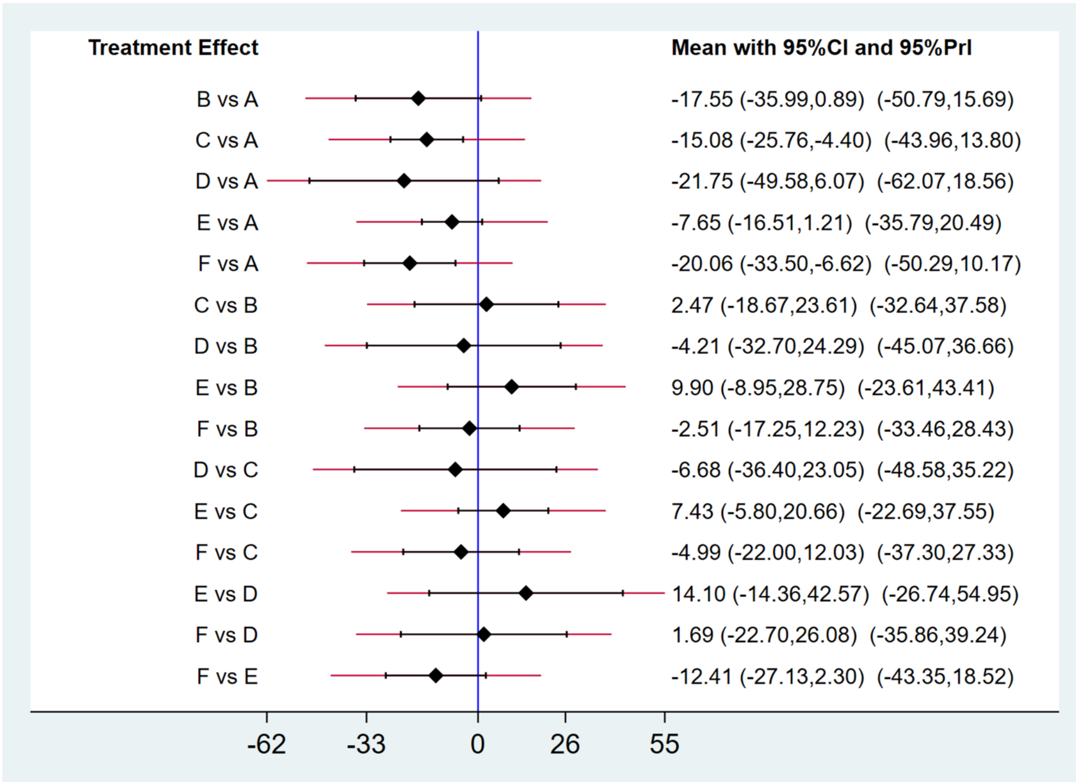

Fig. 5 Forest plot for the pairwise meta-analysis of testosterone levels

analysis covering 18 studies (Egger test $P=0.541$) (Supplementary Files 1: Appendix 7).

Discussion

This NMA evaluated the effectiveness of NPIs in reducing circulating androgen levels in women with PCOS. A total of 21 studies, encompassing 1,196 participants, were included. The results indicated that NPIs significantly reduced serum testosterone and androstenedione levels in PCOS patients and had a positive impact on the Ferriman-Gallwey score. However, NPIs did not demonstrate significant effects in increasing SHBG levels or in reducing FT, DHEAS, DHEA, DHT, and FAI. Moreover, the NMA revealed that a combined intervention of electroacupuncture with diet and exercise was most effective in lowering testosterone levels in PCOS patients. This combination was not only significantly superior to the control group but also exceeded the MCID threshold of 12.74 ng/dL, highlighting the clinical significance of multi-component interventions. In contrast, single-component interventions (such as exercise, diet, or electroacupuncture alone) exhibited some impact on testosterone levels, yet failed to show significant differences when compared to the control group. This indicates that single-component approaches may have limited efficacy in reducing testosterone levels and alleviating PCOS-related symptoms, especially when compared to multi-component interventions, thereby underscoring the potential benefits of multi-modal treatment strategies in managing PCOS. The CINeMA assessment indicated that the quality of evidence for certain interventions was low, suggesting a need for more rigorously designed trials in future research to enhance the reliability of the evidence.

In this network meta-analysis, heterogeneity across studies emerged as a critical concern. Despite the application of stringent selection criteria and robust statistical methods, substantial heterogeneity was still observed, particularly in the analysis of changes in testosterone levels. Subgroup analysis identified BMI, age, and intervention duration as key factors influencing the observed heterogeneity in intervention effects. Specifically, participants with a higher BMI (≥ 28 kg/m^2) demonstrated lower heterogeneity ($I^2=0.0\%$), whereas those with a lower BMI exhibited significantly greater heterogeneity ($I^2=70.3\%$). Additionally, the heterogeneity was lower in the subgroup of younger participants (< 30 years) and higher in the older subgroup (≥ 30 years). The definition of BMI ≥ 28 kg/m^2 as a criterion for obesity in women, combined with existing evidence highlighting the role of obesity in endocrine and metabolic disturbances in

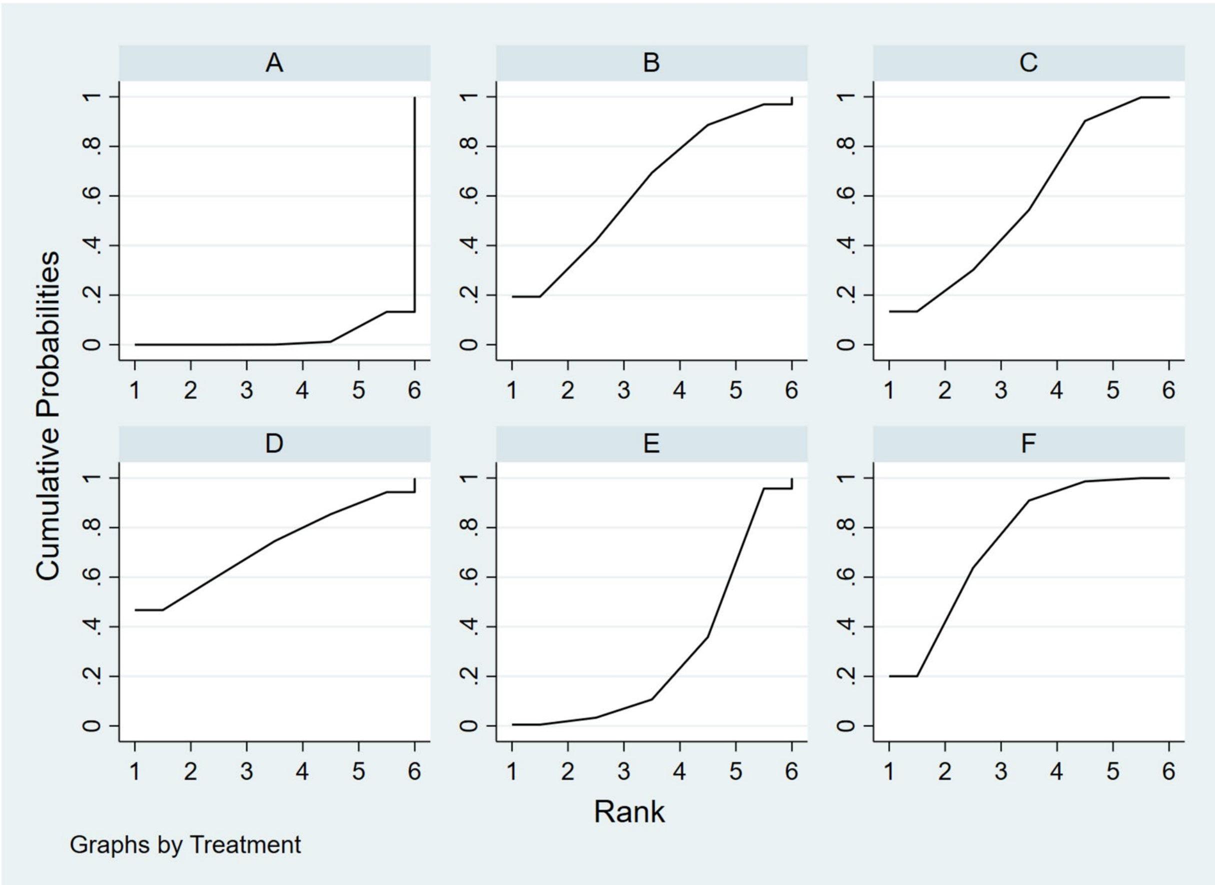

Fig. 6 SUCRA for PCOS patients' testosterone levels based on NPIs. Note: SUCRA, the surface under the cumulative ranking curve; EA, electroacupuncture. Control (**A**); Diet (**B**); EA (**C**); EA + Exercise + Diet (**D**); Exercise (**E**); Exercise + Diet (**F**)

Table 3 Final classification of 6 interventions, based on network meta-analysis of interventions for testosterone in women with PCOS

Number of studies	Sample Size (Total)	Intervention[a]	Intervention vs Control (mean difference (95% credible interval)	SUCRA (%)
1	20	Electroacupuncture + Exercise + Diet (L)	-21.75(-49.58,6.07)	72.3
6	176	Electroacupuncture (L)	-15.08(-25.76, -4.40)	57.6
8	168	Exercise + Diet (VL)	-20.06(-33.50, -6.62)	74.7
2	44	Diet (VL)	-17.55(-35.99,0.89)	63.3
8	167	Exercise (VL)	-7.65(-16.51,1.21)	29.2
15	378	Control	-	2.9

H High certainty evidence, *M* Moderate, *L* Low, *VL* Very low

[a] Letters in brackets represent the certainty of evidence for each intervention when compared with the reference

PCOS, suggests that obesity may notably influence intervention outcomes [41]. Moreover, the use of 30 years as an age threshold is informed by the age-related metabolic changes and reproductive status in PCOS patients, with younger and older patients displaying significant differences in hormone levels, metabolic health, and responses to treatment [7] The duration of the intervention was another critical factor. Studies with interventions lasting more than three months exhibited lower heterogeneity ($I^2 = 0.0\%$), while shorter interventions (≤ 3 months) were associated with higher heterogeneity ($I^2 = 86.4\%$). This discrepancy may be attributed to factors such as reduced patient compliance and natural symptom fluctuations over longer periods [42–44]. Furthermore, the diversity of intervention types represented another important source of heterogeneity. Variations in the frequency, intensity, and nature of interventions (e.g., exercise, diet, acupuncture) could contribute to inconsistencies in treatment effects. Although meta-regression analysis controlled for potential sources of heterogeneity, such as publication year and sample size, other unaccounted factors may still significantly influence the overall variability. Therefore, future research should further investigate these unconsidered factors and refine study designs to mitigate the impact of heterogeneity, thereby enhancing the reliability and generalizability of the findings.

Based on the current evidence, electroacupuncture combined with diet and exercise is recommended as a prioritized strategy for controlling testosterone levels in PCOS patients. Additionally, NPIs have shown some impact on the quality of life (QoL) of PCOS patients. Among the 21 studies included, four assessed QoL: two used the PCOSQ scale, one used the modified version (MPCOSQ), and another used the SF-36 scale. Due to the lack of QoL scale data in some studies, a pooled analysis was not feasible [20, 27, 29, 34]. Nevertheless, the results indicated that NPIs generally improved patients' quality of life compared to control groups. However, due to the small sample size, the robustness of this evidence needs to be enhanced (Supplementary File 1: Appendix 8). Furthermore, this network meta-analysis primarily focused on changes in androgen biomarkers, which limits the assessment of NPIs' effects on the quality of life in PCOS patients.

In patients with PCOS, elevated androgen levels are primarily assessed through total testosterone and free testosterone. When these markers are not elevated, A4 and DHEAS can be used to detect biochemical hyperandrogenism, which is a key diagnostic criterion for PCOS. Elevated androgen levels are closely associated with clinical symptoms such as hirsutism and acne [45, 46]. To verify whether the improvement in serum testosterone levels through NPI has clinical significance in symptom management for PCOS, we analyzed mFG score data, demonstrating that NPIs significantly improved mFG scores. Combined with the MCID value, this suggests that the impact of NPIs on testosterone levels has a positive effect on symptom improvement in PCOS. Previous studies have shown that hyperandrogenism in PCOS is associated with elevated insulin levels, excessive androgen synthesis, hypothalamic-pituitary-ovarian (HPO) axis dysregulation, and inflammatory responses. Hyperinsulinemia can promote ovarian androgen production and inhibit SHBG, thereby exacerbating PCOS characteristics. Recent evidence-based research, along with experimental data from our team, suggests that NPIs hold multidimensional potential in the management of PCOS. For example, exercise and dietary interventions can enhance insulin sensitivity, reduce chronic inflammation, and improve hormonal balance [47]. Low-carbohydrate and low-sugar diets may reduce chronic inflammation in PCOS patients by optimizing metabolism and fat distribution [48]. Gut microbiota imbalance is also closely linked to the metabolic issues in PCOS, with studies indicating that probiotic supplementation or increased dietary fiber can improve the gut microbiome, indirectly regulating androgen levels [49]. Our experiments further found that electroacupuncture can reduce the expression of ovarian cytochrome P45017α, thereby inhibiting androgen synthesis and improving the reproductive cycle and ovarian morphology in PCOS model rats by modulating GnRH/LH pulse frequency [50, 51].

To facilitate the clinical application of NPI approaches, we summarized the specific methods of the various interventions included in the literature. (Supplementary File 1: Appendix 9-A) outlines the acupuncture points and electroacupuncture parameters used in the studies. The most commonly utilised acupoints were from the Stomach Meridian of Foot-Yangming (six points across seven studies) and the Spleen Meridian of Foot-Taiyin (three points across seven studies), followed by acupoints from the Ren Meridian, Kidney Meridian of Foot-Shaoyin, and additional points. Most electroacupuncture studies recommended a continuous waveform with a frequency set at 2 Hz, with intensity adjusted based on patient tolerance or set to 1-3 mA, and treatment frequency at 2–3 times per week for at least 10–16 weeks. (Supplementary File 1: Appendix 9-B) details the protocols for strict exercise and diet management. These interventions aim to improve quality of life and alleviate symptoms in PCOS patients through dietary adjustments, increased physical activity, and lifestyle changes. Each intervention is focused and designed for optimal effectiveness. However, most studies did not address key parameters, such as dietary calorie control strategies or quality assurance measures, and information on exercise intensity standards was also limited, a common issue in such studies. Additionally, we observed that physical exercise significantly affects testosterone levels. (Supplementary File 1: Appendix 9-C) lists various forms of exercise, including high-intensity interval training (HIT), aerobic exercise, strength training, tai chi, and yoga. Interventions lasted 10–16 weeks under professional supervision to ensure safety and effectiveness. Training intensity was adjusted based on individual maximum heart rate (HRmax). Some studies incorporated mindfulness elements, such as mindful yoga, to enhance mental well-being. Most studies used heart rate monitoring to maintain target intensity, with some including adaptive training to help participants adjust to new exercise regimens. Overall, these studies suggest that varied exercise interventions have potential to promote health, improve physical fitness, and enhance mental well-being, aligning with the 2023 exercise guideline recommendations.

Strengths and Limitations

The findings of this study hold significant clinical implications for PCOS management. We recommend that clinicians prioritize multi-component treatment strategies, such as combining electroacupuncture with exercise and dietary management, and tailor interventions to individual needs. Existing research supports the effectiveness of NPIs (such as lifestyle adjustments and psychotherapy) in alleviating PCOS symptoms, which may offer better cost-effectiveness by potentially reducing long-term medication needs; however, this requires further validation through prospective studies [7, 52].

This study also has certain limitations. First, the small sample size and the diversity of intervention types may limit the generalizability and interpretability of the findings. Furthermore, heterogeneity among studies remains a concern. Although rigorous screening and statistical methods were employed, future research should prioritize large-scale RCTs to validate the efficacy of NPIs in the management of PCOS and enhance external validity. Second, this study only focused on a subset of non-pharmacological interventions, such as acupuncture, exercise, tai chi, yoga, and lifestyle management, while excluding other potential alternative therapies, such as natural supplements and herbal medicine. Future research should broaden the scope of NPIs to explore more comprehensive therapeutic options and strengthen the evidence base in this field. In addition, this study exclusively evaluated the efficacy of NPIs without comparing them to pharmacological treatments. Existing evidence suggests that pharmacological treatments, such as metformin, play a significant role in the management of PCOS, particularly in improving fertility outcomes. Metformin has been shown to effectively reduce insulin resistance and hyperandrogenism in PCOS patients, significantly enhancing pregnancy rates [53]. Future studies should compare the effectiveness of non-pharmacological and pharmacological treatments to provide a more comprehensive understanding of their relative benefits and guide clinical decision-making. Moreover, this study did not adequately assess the long-term effects of non-pharmacological interventions. Given that PCOS is a chronic condition, evaluating the long-term outcomes of interventions is critical. Future research should prioritize investigations into the sustained effects of these interventions to provide a more holistic perspective on their role in PCOS management. Finally, this study lacked a cost-effectiveness analysis. Future research should incorporate economic evaluations to compare the feasibility of non-pharmacological and pharmacological treatments, offering valuable insights for the long-term management of PCOS. Additionally, optimizing personalized treatment approaches requires further investigation into factors such as age and BMI that may influence intervention outcomes, enabling the development of tailored therapeutic strategies for individual patients.

Conclusion

This study demonstrates that NPIs, particularly the combination of electroacupuncture, diet, and exercise, can significantly reduce testosterone levels and improve Ferriman-Gallwey scores in PCOS patients. Compared to single interventions, multi-component approaches proved more effective, highlighting the importance of comprehensive treatment. While this study supports the potential of NPIs as complementary strategies to pharmacological treatment, further large-scale, high-quality trials are needed to confirm these findings. Clinically, personalized multi-component NPI plans are recommended for more effective management of PCOS symptoms.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13048-025-01595-5.

Supplementary Material 1.

Supplementary Material 2.

Authors' contributions

J.Q., X.G., and Y.Y. were responsible for full access to the study data and ensuring the integrity of the data and accuracy of the data analysis. Y.P. and C.Y. were responsible for study conception and design. J.Q., Y.Y., L.L., and Z.H. were responsible for data acquisition and interpretation. J.Q., X.G., and Y.Y. wrote the first draft of the manuscript. Y.P., C.Y., and X.S. critically reviewed the manuscript for important intellectual content. J.Q. conducted the statistical analysis. Y.P. provided administrative, technical, or material support. C.Y. supervised the study. All authors critically revised the manuscript andY.P. and C.Y. were responsible for the final approval of the manuscript.J.Q., X.G., and Y.Y. are co-first author, Y.P., C.Y. are Co- corresponding author.

Funding

This work was supported by the Shanghai 2021 "Science and Technology Innovation Action Plan" Medical Innovation Research Special Project (21Y11923900), the Shanghai Famous Old Chinese Medicine Experts Academic Experience Research Studio Construction Project (SHGZS-202232), the Shanghai 2022 "Science and Technology Innovation Action Plan" Medical Innovation Research Special Project, with grant number (22Y21920100), Chinese Medicine Inheritance Ancient Literature and Special Techniques Special Project 2022(GZY-KJS-2022–038), the Construction of Traditional Chinese Medicine Inheritance and Innovation Development Demonstration Pilot Projects in Pudong New Area-High-Level Research-Oriented Traditional Chinese Medicine Hospital Construction(YC-2023–0901) and Science and Technology Development Fund of Shanghai University of Traditional Chinese Medicine(23KFL013).

Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Competing interests
The authors declare no competing interests.

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Received: 19 September 2024 Accepted: 8 January 2025
Published online: 20 January 2025

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