Research article

Effectiveness and safety of acupuncture for insulin resistance in women with polycystic ovary syndrome: A systematic review and meta-analysis

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ABSTRACT

Objective: To perform a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate acupuncture’s clinical effect on insulin resistance (IR) in women with polycystic ovary syndrome (PCOS).

Methods: PubMed, Cochrane Library, Embase databases, and Chinese databases, including China National Knowledge Infrastructure, Technology Journal Database, and Wanfang Database, were searched without language restrictions from inception to December 20, 2021. Only RCTs in which acupuncture had been examined as the sole or adjunctive PCOS-IR treatment were included. Our primary endpoint was the homeostasis model assessment of insulin resistance (HOMA-IR). The secondary outcomes were fasting blood glucose (FBG), fasting insulin (FINS), body mass index (BMI), and adverse events.

Results: Our analysis included 17 eligible RCTs (N = 1511 participants). Compared with other treatments, acupuncture therapy yielded a greater mean reduction in HOMA-IR (MD = 0.15; 95% CI, 0.27 to 0.03; P = 0.01) and BMI (MD = 1.47; 95% CI, 2.46 to −0.47; P = 0.004). Besides acupuncture was associated with a lower risk of adverse events than other treatments (RR, 0.15; 95% CI, 0.10 to 0.22; P < 0.01). Additionally, the combination treatment of acupuncture and medicine is more effective in improving HOMA-IR (MD = −0.91; 95% CI, −1.11 to −0.71; P < 0.01), FBG (MD = −0.30; 95% CI, −0.56 to −0.04; P = 0.02), FINS (MD = −2.33; 95% CI, −2.60 to −2.06; P < 0.01) and BMI (MD = −1.63; 95% CI, −1.94 to −1.33; P < 0.01) than medicine alone.

Conclusions: Acupuncture is relatively effective in improving HOMA-IR and BMI in PCOS-IR. Besides, it’s safer than other treatments and could be an adjuvant strategy for improving PCOS-IR. Further large-scale, long-term RCTs with strict methodological standards are justified.

1. Introduction

Polycystic ovary syndrome (PCOS), a complex endocrine and metabolic disorder, is characterized by androgen excess (hirsutism and/or hyperandrogenemia) and ovarian dysfunction (oligo-ovulation and/or polycystic ovarian morphology). To date, its pathogenesis remains unclear. However, insulin resistance (IR) is considered the primary pathological basis for the associated reproductive dysfunction [1,2]. The prevalence of IR in clamp studies in women with PCOS diagnosed based on the Rotterdam criteria and in

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age-appropriate lean healthy control women is reportedly 75% of lean and 95% of overweight women (weight status according to WHO criteria) [3]. IR both promotes and interacts with hyperandrogenemia, which affects the function of the hypothalamic-pituitary-ovarian axis and causes abnormal follicular development [4]. Additionally, regardless of age, gestational diabetes mellitus, impaired glucose tolerance, and type 2 diabetes are all significantly more prevalent in patients with PCOS [5].

Some studies have found that improving IR and reducing hyperinsulinemia can reduce systemic androgen concentrations and improve some characteristics of PCOS [6]. Metformin is often recommended to adult women or adolescents with PCOS or women with body mass index (BMI) > 25 kg/m² for management of weight and metabolic disorders [5]. However, the mechanism underlying metformin’s effects on PCOS-IR is not yet fully understood and it causes adverse effects, particularly diarrhea and nausea, in up to 25% of patients [7]. Thus, metformin has limitations related to adverse effects and patient compliance. There is therefore a need for inexpensive and easily administered treatments with few adverse effects. Correlation meta-analysis has shown that acupuncture has a beneficial effect on IR and fewer adverse reactions than other treatments [8,9]. A recent meta-analysis also found that acupuncture can improve glucose metabolism and insulin sensitivity in patients with PCOS [10]. However, there is no meta-analysis to evaluate the effectiveness and safety of acupuncture for PCOS-IR. In addition, the quality of the evidence is unclear. In the present study, we systematically reviewed data from recent studies, aiming to provide clarity concerning the role of acupuncture in the treatment of PCOS-IR and provide evidence-based medical evidence for clinical application.

2. Methods

This analysis was performed strictly following the PRISMA statement [11]. Additionally, this review was registered with PROSPERO at http://www.crd.york.ac.uk/PROSPERO(CRD42021285851).

2.1. Search strategy

PubMed, Cochrane Library, and Embase databases were searched without language restrictions from inception to December 20, 2021. We also searched Chinese databases, including the China National Knowledge Infrastructure (CNKI), Technology Journal (VIP), and Wanfang databases. The search terms consisted of four parts: acupuncture (acupuncture, electroacupuncture, and manual acupuncture), insulin resistance (insulin resistance and insulin sensitivity), polycystic ovary syndrome (polycystic ovary syndrome, polycystic ovarian syndrome and Stein–Leventhal syndrome), and randomized controlled trial. Details of the search strategies are presented in Appendix.

Additionally, ClinicalTrials.gov and the Chinese Clinical Trial Register were searched to identify ongoing or recently completed studies.

2.2. Inclusion criteria

2.2.1. Types of study
All randomized controlled trials (RCTs) involving the use of acupuncture for treating PCOS-IR were included.

2.2.2. Types of participants
Patients diagnosed with PCOS-IR, regardless of race, or educational and economic status, were included. IR was evaluated by the homeostasis model assessment of insulin resistance (HOMA-IR) index, which was calculated as fasting blood glucose (FBG) × fasting insulin (FINS)/22.5, and a value ≥ 2.14 [12].

2.2.3. Types of intervention
Interventions in the experimental group comprised acupuncture or electroacupuncture either combined with medicine or not. Controlled interventions with sham acupuncture or medicine were included.

2.2.4. Types of outcome measure
Studies that reported at least one clinical outcome related to PCOS-IR were included. The primary outcome was HOMA-IR. The secondary outcomes were FBG, FINS, BMI, and adverse events, such as adverse gastrointestinal events and subcutaneous bruising.

2.3. Exclusion criteria

2.3.1. Types of study
Nonrandomized controlled trials, randomized crossover trials, reviews, case reports, protocols, and experimental animal articles were excluded.

2.3.2. Participants
Participants with Cushing’s syndrome, androgen-secreting neoplasms, and cervical, endometrial, or breast cancers were excluded.

2.3.3. Types of intervention
We did not include trials in which non-penetrating acupuncture (such as via laser stimulation, acupressure, or transcutaneous
electrical nerve stimulation) was used or in which another traditional Chinese medicine was administered to the experimental group. RCTs that compared different forms of acupuncture or herbal medicine were also excluded.

2.4. Study identification and data extraction

Two independent appraisers (Y. Liu and J.Q. Hu) assessed the eligibility of the searched articles by the above criteria. The following

Fig. 1. Literature screening process and results.
data were extracted independently from all included studies by two reviewers (H.Y. Fan and T.Y. Wu): the number of participants, age, interventions, intervention duration, outcomes, and the number of participants with any adverse events. Any disagreements regarding study identification and data extraction were resolved by discussion and adjudication with a third investigator (J. Chen).

2.5. Quality assessment

Two reviewers (Y. Liu and H.Y. Fan) independently assessed the risk of bias of RCTs using the Cochrane Collaboration’s “risk of bias” tool, which is based on the following six separate domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. The assessments were categorized into three levels of bias: low risk, high risk, or unclear risk. For example, if the investigators described a random component in the sequence generation process, such as using a computer random number generator or coin tossing, “low risk” would be allocated for the domain of random sequence generation. Disagreements were resolved by a third investigator (J. Chen).

We also used Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to assess the quality of evidence, using GRADEpro GOT online software.

Table 1
Characteristics of included studies.

| Study ID  | Country | Sample size (TG/CG) | Intervention | Duration of intervention (months) | Age (years) | BMI (kg/m²) | HOMA-IR | Outcomes |
|-----------|---------|---------------------|--------------|-----------------------------------|-------------|-------------|---------|----------|
| Dong,2021 | China   | 27/27               | EA SA        | 4                                 | 23.3 ± 2.7/ | 22.9 ± 5.5/ | 2.4 ± 2.1/ | HOMA-IR, FBG, FINS, BMI |
| Gu,2019   | China   | 39/39               | EA SA        | 4                                 | 26.95 ± 4.5/| 28.06 ± 4.3/| 3.16 ± 3.81/| HOMA-IR, FBG, 2h-PBG, FINS, BMI, adverse events |
| Lai,2012  | China   | 60/60               | A M          | 4                                 | 26.72 ± 2.6/| 27.1 ± 1.1/ | 4.07 ± 0.75/| HOMA-IR, FBG, 2h-PBG, FINS, BMI, adverse events |
| Li,2014   | China   | 53/51               | A + M        | 6                                 | 27.1 ± 2.5/ | 29.1 ± 3.1/ | 3.7 ± 1.4/  | HOMA-IR, FBG, FINS, BMI, adverse events |
| Mao,2021  | China   | 54/54               | EA M + P     | 3                                 | Not available| 28.33 ± 2.6/| 3.68 ± 0.57/| HOMA-IR, BMI |
| Peng,2017 | China   | 50/50               | A SA         | 3                                 | 28.58 ± 3.82/| 23.94 ± 2.6/| 14.28 ± 13.37/| HOMA-IR, BMI |
| Wen,2021  | China   | 114/114             | EA SA + P    | 4                                 | 27.68 ± 4.3/| 25.53 ± 4.3/| 4.1 ± 1.95/  | HOMA-IR, FBG, FINS, BMI, adverse events |
| Yao,2018  | China   | 50/50               | EA M         | 6                                 | 27.8 ± 4.8/ | 28.5 ± 1.7/ | 3.91 ± 1.4/  | HOMA-IR, BMI |
| Yin,2016  | China   | 30/30               | A + M        | 3                                 | 27.54 ± 2.03/| Not available| 4.8 ± 0.7/   | HOMA-IR, FBG, 2h-PBG, FINS, BMI, adverse events |
| Yu,2020   | China   | 36/34               | EA M         | 3                                 | 30 ± 6/31/  | Not available| 5.01 ± 3.52/| HOMA-IR, FBG, 2h-PBG, FINS, BMI, adverse events |
| Zheng,2013| China   | 43/43               | A M          | 6                                 | 26.5 ± 3.0/ | 29.4 ± 3.7/ | 3.9 ± 1.4/   | HOMA-IR, FBG, 2h-PBG, FINS, BMI, adverse events |
| Liang,2015| China   | 30/30               | A + CC       | 4                                 | 28.64 ± 3.07/| 29.21 ± 3.8/| 4.75 ± 1.53/| HOMA-IR, FBG, FINS, BMI, adverse events |
| Zhang,2017| China   | 64/64               | A + M        | 3                                 | 28.3 ± 4.2/ | 28.73 ± 2.8/| 3.94 ± 1.37/| HOMA-IR, FBG, FINS, BMI, adverse events |
| Guo,2014  | China   | 20/20               | EA SA        | 2                                 | 27.9 ± 4.3/ | 29.03 ± 2.65| 5.11 ± 0.45/| HOMA-IR, FBG, FINS |
| Kong,2015 | China   | 29/26               | EA SA        | 4                                 | 28.14 ± 3.78/| 27.88 ± 4.06/| 4.59 ± 3.82/| HOMA-IR, FBG, FINS |
| Su,2014   | China   | 30/30               | A + M        | 3                                 | 17.00 ± 1.82/| 25.84 ± 1.75/| 6.58 ± 1.97/| HOMA-IR, FBG, FINS, BMI, adverse events |
| Wang,2020 | China   | 30/30               | EA M         | 3                                 | 26.43 ± 3.52/| 27.58 ± 2.76/| 8.48 ± 0.89/| HOMA-IR, FBG, FINS |

A, acupuncture; BMI, body mass index; CC, clomiphene citrate; CG, control group; EA, electroacupuncture; M, metformin; P, placebo; SA, sham acupuncture; TG, treatment group.
2.6. Data synthesis

We assessed the effect and safety of acupuncture for treating PCOS-IR based on five outcomes: HOMA-IR, FBG, FINS, the incidence of adverse events, and BMI. We analyzed HOMA-IR, FBG, FINS, and BMI as continuous variables and reported absolute differences after the intervention. Adverse events were treated as a categorical variable and the risk ratio was calculated.

We calculated pooled estimates of the mean differences (MD) in HOMA-IR, FBG, FINS, and BMI between intervention groups using a random-effects model (DerSimonian–Laird method) to minimize the additional uncertainty associated with interstudy variability regarding the effects of different interventions. We also calculated pooled risk ratio (RR) estimates for categorical outcomes with a random-effects model (DerSimonian–Laird method).

We used the Cochran Q test to assess heterogeneity between studies. P values less than 0.05 were considered to denote statistical significance. We also did $I^2$ testing to assess the magnitude of heterogeneity between studies, values greater than 50% were regarded as indicative of moderate-to-high heterogeneity. If necessary, subgroup analyses according to the type of intervention were conducted. We used RevMan (version 5.4) for all statistical analyses.

3. Results

3.1. Search results

A flow chart of study selection is shown in Fig. 1. Our preliminary search found a total of 723 articles. Removing duplicate articles and reading the title and summary filters left 132 full-text articles, 111 of which were excluded because they did not meet the inclusion criteria. Four more articles were excluded because their data were unavailable, and we received no responses from the corresponding authors. Finally, 17 studies including 1511 patients were included in this review.

3.2. Description of included studies

The 17 eligible RCTs including 1511 patients were conducted in China. Three of them were listed in English databases and fourteen in Chinese databases. All participants had been diagnosed with PCOS under the Rotterdam criteria and had HOMA-IR greater than 2.14, enabling diagnosis of IR [12]. Acupuncture was compared with sham acupuncture in five studies [13–17], acupuncture was compared with medicine in five studies [18–22], and acupuncture combined with medicine was compared with medicine alone in seven studies [23–29]. Table 1 summarizes the basic characteristics of these studies.

3.3. Assessment of risk of bias

The participants were randomized using a random number table or computer program in nine studies, while the remaining two studies [15,17,18] only mentioned “random”. The assessment of allocation was described in three articles [13,19,22]. For blinding, three trials [15,19,23] were classified as “low risk” and the others as “unclear risk”. Three articles [13,19,21] stated explicitly that third-party researchers processed the data. Five studies [13,14,19–21] reported the loss of follow-up. There was attrition bias in two of these studies [13,19] as a result of differences in the proportion of missing outcome data between the experimental and comparison groups. The other three trials had a low risk of attrition bias, having reported that no participants dropped out or were excluded from the primary analysis. Details of the assessments are shown in Figs. 2 and 3.
Fig. 3. Assessment of risk biases of the included studies.
3.4. Meta-analysis of primary outcomes

3.4.1. Acupuncture alone

A pooled meta-analysis of the ten trials found that acupuncture treatment led to a mean greater reduction in the HOMA-IR (MD = -0.15; 95% CI, -0.27 to -0.03; P = 0.01; Fig. 4) than other treatments, with no significant between-study heterogeneity (I[2] = 38%). In this analysis, no publication bias was evident (Fig. 5).

3.4.2. Combined with medicine

Comprehensive analysis of seven trials suggested that acupuncture combined with medicine in reducing HOMA-IR was superior to medicine alone (MD = -0.91; 95% CI, -1.11 to -0.71; P < 0.01; Fig. 4), with significant heterogeneity (I[2] = 82%). To further analyze the heterogeneity, we then performed subgroup analyses based on the type of intervention, which greatly reduced the statistical heterogeneity (Fig. 4).

3.5. Meta-analysis of secondary outcomes

3.5.1. FBG

(1) Acupuncture alone

Pooled analysis of the seven studies showed that no significant difference between acupuncture and other treatments (MD = 0.33; 95% CI, -0.66 to 0.00; P = 0.05; Fig. 6), with statistically significant heterogeneity (I[2] = 85%). Sensitivity analysis comparing acupuncture treatment with sham acupuncture or medicine identified no significant differences (MD = 0.02; 95% CI, -0.19 to 0.15; P = 0.82; Fig. 4).

![Fig. 4. Comparison of changes in HOMA-IR according to intervention.](image)
2.1 Acupuncture alone

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|-------------------|----|-------|--------------|----|-------|--------|---------------------------------|---------------------------------|
| Dong 2021         | 4.8               | 0.4| 25    | 4.9          | 0.4| 17    | 16.0%  | -0.10 [-0.35, 0.15]              |                                 |
| Gu 2019           | 4.62              | 1.34| 38    | 5.96         | 0.58| 38    | 13.0%  | -1.34 [-1.80, -0.88]             |                                 |
| Guo 2014          | 4.86              | 0.41| 20    | 4.88         | 0.61| 20    | 15.1%  | -0.02 [-0.34, 0.30]              |                                 |
| Kong 2015         | 4.98              | 0.89| 29    | 5.94         | 0.77| 26    | 13.4%  | -0.96 [-1.40, -0.52]             |                                 |
| **Subtotal (95% CI)** | **112**          |    | **101**| **57.5%** |    | **58**|        | **-0.58 [-1.16, 0.00]**          |                                 |

Heterogeneity: $\tau^2 = 0.32$; $\chi^2 = 32.85$, df = 3 ($P < 0.00001$); $I^2 = 91$
Test for overall effect: $Z = 1.95$ ($P = 0.05$)

2.1.2 Acupuncture vs medicine

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|-------------------|----|-------|--------------|----|-------|--------|---------------------------------|---------------------------------|
| Lai 2012          | 4.03              | 0.77| 60    | 4.02         | 0.81| 60    | 15.6%  | 0.01 [-0.27, 0.29]              |                                 |
| Wen 2021          | 5.17              | 0.54| 97    | 5.21         | 0.97| 96    | 16.3%  | -0.04 [-0.26, 0.18]             |                                 |
| Zheng 2013        | 4.6               | 1.4 | 43    | 4.6          | 1.6 | 43    | 10.6%  | 0.00 [-0.64, 0.64]              |                                 |
| **Subtotal (95% CI)** | **200**          |    | **199**| **42.5%** |    | **02**|        | **-0.02 [-0.19, 0.15]**          |                                 |

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.08$, df = 2 ($P = 0.96$); $I^2 = 0$
Test for overall effect: $Z = 0.23$ ($P = 0.82$)

| Total (95% CI) | 312 | 300 | 100.0% | -0.33 [-0.66, 0.00] |
|----------------|-----|-----|--------|---------------------|
Heterogeneity: $\tau^2 = 0.16$; $\chi^2 = 41.00$, df = 6 ($P < 0.00001$); $I^2 = 85$
Test for overall effect: $Z = 1.96$ ($P = 0.05$)
Test for subgroup differences: $\chi^2 = 3.28$, df = 1 ($P = 0.07$), $I^2 = 69.5$

2.2 Combined with medicine

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|-------------------|----|-------|--------------|----|-------|--------|---------------------------------|---------------------------------|
| Li 2014           | 4.6               | 1.3 | 53    | 4.8          | 1.1 | 51    | 13.0%  | -0.20 [-0.66, 0.26]              |                                 |
| Liang 2015        | 4.9               | 0.1 | 30    | 5            | 0.3 | 30    | 21.4%  | -0.10 [-0.21, 0.01]             |                                 |
| Su 2014           | 5.02              | 0.84| 30    | 5.15         | 0.78| 30    | 14.3%  | -0.13 [-0.54, 0.28]             |                                 |
| Yin 2016          | 3.9               | 0.6 | 30    | 4.6          | 0.7 | 30    | 16.3%  | -0.70 [-1.03, -0.37]            |                                 |
| Zhang 2017        | 4.95              | 0.42| 64    | 4.88         | 0.39| 64    | 20.9%  | 0.07 [-0.07, 0.21]              |                                 |
| **Subtotal (95% CI)** | **207**          |    | **205**| **85.9%** |    | **18**|        | **-0.18 [-0.40, 0.04]**          |                                 |

Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 18.38$, df = 4 ($P = 0.001$); $I^2 = 78$
Test for overall effect: $Z = 1.60$ ($P = 0.11$)

2.2.2 Electroacupuncture combined with medicine

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|-------------------|----|-------|--------------|----|-------|--------|---------------------------------|---------------------------------|
| Wang 2020         | 4.11              | 0.52| 30    | 5.05         | 1.04| 30    | 14.1%  | -0.94 [-1.36, -0.52]             |                                 |
| **Subtotal (95% CI)** | **237**          |    | **235**| **100.0%** |    | **04**|        | **-0.30 [-0.56, -0.04]**          |                                 |

Heterogeneity: Not applicable
Test for overall effect: $Z = 4.43$ ($P < 0.00001$)

| Total (95% CI) | 237 | 235 | 100.0% | -0.30 [-0.56, -0.04] |
|----------------|-----|-----|--------|---------------------|
Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 34.05$, df = 5 ($P < 0.00001$); $I^2 = 85$
Test for overall effect: $Z = 2.26$ ($P = 0.02$)
Test for subgroup differences: $\chi^2 = 16.04$, df = 1 ($P = 0.002$), $I^2 = 90.0$

Fig. 6. Comparison of changes in FBG according to intervention.
(2) Combined with medicine

Pooling the data of the six studies showed combination treatment led to a greater trend of improvement in FBG than medicine alone (MD = −0.30; 95% CI, −0.56 to −0.04; P = 0.02; Fig. 6), with statistically significant heterogeneity (I² = 85%). Forest plots generated in further sensitivity analysis suggested electroacupuncture was a significant factor in FBG (MD = −0.94; 95% CI, −1.36 to −0.52; P < 0.01; Fig. 6).

3.5.2. FINS

(1) Acupuncture alone

Seven studies (N = 613 participants) assessed the participants’ FINS after treatment. Pooled analysis of these studies showed that no significant difference in mean reduction of FINS between acupuncture and other treatments (MD = −1.53; 95% CI, −3.09 to 0.02; P = 0.05; Fig. 7), with statistically significant heterogeneity (I² = 56%). Further subgroup analysis showed no significant difference between acupuncture and medicine (MD = −0.22; 95% CI, −1.24 to 0.79; P = 0.66; Fig. 7). However, acupuncture showed a greater mean reduction in FINS than sham acupuncture (MD = −2.87; 95% CI, −5.54 to −0.19; P = 0.04; Fig. 7).

(2) Combined with medicine

Pooling the data of five studies found that the combination treatment benefited over medicine alone (MD = −2.33; 95% CI, −2.60 to −2.06; P < 0.01; Fig. 7), with no significant between-study heterogeneity (I² = 27%).

3.5.3. BMI

(1) Acupuncture alone

Eight studies reported the participants’ BMI after treatment. Analysis of pooled data of these studies showed that acupuncture was

### 3.1 Acupuncture alone

| Study or Subgroup | Experimental Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|------------------|----|-------|------|----|-------|--------|-----------------------------------|-----------------------------------|
| Dong 2011         | 9.8              | 7  | 25    | 9    | 3  | 18    | 12.7%  | 0.80 [-2.48, 4.08]                |                                   |
| Gu 2019           | 16.87            | 7.56| 38    | 21.22| 9.69| 38    | 10.3%  | -4.35 [-8.26, -0.44]              |                                   |
| Gue 2014          | 12.49            | 4.39| 20    | 15.92| 4.69| 20    | 15.0%  | 3.93 [-6.25, 0.61]                |                                   |
| Keng 2015         | 15.49            | 4.26| 29    | 20.97| 11.83| 26    | 7.7%   | -5.48 [-10.28, -0.68]             |                                   |
| **Subtotal (95% CI)** | **112**          |    | **102** | **45.8%** |     |        | **-2.87 [-5.54, -0.19]**         |                                   |

- Heterogeneity: Tau² = 4.00; Chi² = 6.60, df = 3 (P = 0.09); I² = 55%
- Test for overall effect: Z = 2.10 (P = 0.04)

1.2 Acupuncture vs medicine

| Study or Subgroup | Experimental Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|------------------|----|-------|------|----|-------|--------|-----------------------------------|-----------------------------------|
| Lai 2012          | 12.89            | 3.5 | 60    | 13.11| 3.8 | 60    | 24.5%  | -0.22 [-1.53, 1.09]               |                                   |
| Wen 2021          | 16.02            | 10.65| 97    | 18.7 | 20.79| 96    | 8.1%   | -2.68 [-7.35, 1.99]               |                                   |
| Zheng 2013        | 8.7             | 3.7  | 43    | 8.6  | 4.4 | 43    | 21.7%  | 0.10 [-1.62, 1.82]                |                                   |
| **Subtotal (95% CI)** | **200**          |    | **199** | **54.2%** |     |        | **-0.22 [-1.24, 0.79]**         |                                   |

- Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0%
- Test for overall effect: Z = 0.43 (P = 0.66)

Total (95% CI)

| Study or Subgroup | Experimental Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|------------------|----|-------|------|----|-------|--------|-----------------------------------|-----------------------------------|
| **Total (95% CI)** | **312**          |    | **301** | **100.0%** |     |        | **-1.53 [-3.09, 0.02]**         |                                   |

- Heterogeneity: Tau² = 2.12; Chi² = 13.50, df = 6 (P = 0.04); I² = 56%
- Test for overall effect: Z = 1.93 (P = 0.05)
- Test for subgroup differences: Chi² = 3.28, df = 1 (P = 0.07), I² = 69.5%

### 3.2 Combined with medicine

| Study or Subgroup | Experimental Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% CI |
|-------------------|------------------|----|-------|------|----|-------|--------|-----------------------------------|-----------------------------------|
| Li 2014           | 8.2              | 1.4 | 53    | 10.1 | 1.5 | 51    | 23.4%  | -1.90 [-2.46, -1.34]              |                                   |
| Liang 2015        | 10.27            | 0.59| 30    | 12.75| 0.67| 30    | 71.4%  | -2.48 [-2.80, -2.16]              |                                   |
| Su 2014           | 17.47            | 5.63| 30    | 20.47| 5.63| 30    | 0.9%   | -3.00 [-5.85, -0.15]              |                                   |
| Yin 2016          | 11.2             | 3.4 | 30    | 14.3 | 3.9 | 30    | 2.1%   | -3.10 [-4.95, -1.25]              |                                   |
| Zhang 2017        | 8.12             | 3.47| 64    | 9.32 | 6.57| 64    | 2.2%   | -1.20 [-3.02, 0.62]               |                                   |
| **Total (95% CI)** | **207**          |    | **205** | **100.0%** |     |        | **-2.33 [-2.60, -2.06]**         |                                   |

- Heterogeneity: Chi² = 5.48, df = 4 (P = 0.24); I² = 27%
- Test for overall effect: Z = 16.95 (P < 0.00001)

Fig. 7. Comparison of changes in FINS according to intervention.
4.1 Acupuncture alone

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|-------------------|----|-------|--------------|----|-------|--------|----------------------------------|----------------------------------|
| Gu 2019           | 26.03             | 4.55| 38    | 27.77        | 2.7 | 38    | 11.6%  | -1.74 [-3.42, -0.06]             |                                 |
| Kong 2015         | 25.84             | 3.84| 29    | 26.75        | 3.09| 26    | 10.9%  | -0.91 [-2.74, 0.92]              |                                 |
| Peng 2017         | 22.48             | 2.64| 50    | 24.25        | 2.19| 50    | 14.9%  | -1.77 [-2.72, -0.82]             |                                 |
| Subtotal (95% CI) | 148               |    |       | 134          |    |       | 45.4%  | -1.25 [-2.22, -0.28]             |                                 |

Heterogeneity: Tau² = 0.32; Chi² = 4.40, df = 3 (P = 0.22); I² = 32%
Test for overall effect: Z = 2.53 (P = 0.01)

4.1.2 Acupuncture vs medicine

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|-------------------|----|-------|--------------|----|-------|--------|----------------------------------|----------------------------------|
| Lai 2012          | 20.6             | 3.06| 60    | 24.63        | 3.03| 60    | 14.3%  | -4.03 [-5.12, -2.94]             |                                 |
| Wen 2021          | 24.85             | 4.34| 96    | 25.56        | 5.13| 96    | 13.1%  | -0.71 [-2.05, 0.63]              |                                 |
| Yao 2018          | 26.8             | 2.1 | 48    | 27.4         | 1.9 | 48    | 15.5%  | -0.60 [-1.40, 0.20]              |                                 |
| Zheng 2013        | 22.3             | 3.7 | 43    | 24.2         | 4.2 | 43    | 11.6%  | -1.90 [-3.57, -0.23]             |                                 |
| Subtotal (95% CI) | 247               |    |       | 247          |    |       | 54.6%  | -1.81 [-3.56, -0.06]             |                                 |

Heterogeneity: Tau² = 2.79; Chi² = 26.89, df = 3 (P < 0.0001); I² = 89%
Test for overall effect: Z = 2.02 (P = 0.04)

Total (95% CI) 390 381 100.0%  -1.47 [-2.46, -0.47]

Heterogeneity: Tau² = 1.50; Chi² = 31.52, df = 7 (P < 0.0001); I² = 78%
Test for overall effect: Z = 2.88 (P = 0.004)
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.59), I² = 0%

4.2 Combined with medicine

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% CI |
|-------------------|-------------------|----|-------|--------------|----|-------|--------|----------------------------------|----------------------------------|
| Li 2014           | 23.1             | 1.3 | 53    | 24.6         | 2.2 | 51    | 19.1%  | -1.50 [-2.20, -0.80]             |                                 |
| Liang 2015        | 22.07            | 1.06| 30    | 25.16        | 4.07| 30    | 4.1%   | -3.09 [-4.59, -1.59]             |                                 |
| Mao 2021          | 25.53            | 1.41| 54    | 27.23        | 1.89| 54    | 23.6%  | -1.70 [-2.33, -1.07]             |                                 |
| Su 2014           | 22.85            | 1.81| 30    | 24.17         | 2.79| 30    | 11.2%  | -1.13 [-2.06, -0.24]             |                                 |
| Wang 2020         | 25.27            | 1.01| 30    | 26.87        | 2.42| 30    | 10.6%  | -1.69 [-2.54, -0.86]             |                                 |
| Zhang 2017        | 23.47            | 1.21| 64    | 25.12        | 1.87| 64    | 31.3%  | -1.65 [-2.25, -1.10]             |                                 |
| Total (95% CI)    | 261               |    |       | 259          |    |       | 100.0% | -1.63 [-1.94, -1.33]             |                                 |

Heterogeneity: Chi² = 4.87, df = 5 (P = 0.43), I² = 0%
Test for overall effect: Z = 10.47 (P < 0.00001)

Fig. 8. Comparison of changes in BMI according to intervention.

associated with a greater reduction in BMI than other treatments (MD = -1.47; 95% CI, -2.46 to –0.47; P = 0.004; Fig. 8), with statistically significant heterogeneity (I² = 78%). Sensitivity analysis revealed that compared with sham acupuncture or medicine, acupuncture could more effectively reduce BMI (MD = -1.25; 95% CI, -2.22 to -0.28; P = 01; Fig. 8) (MD = -1.81; 95% CI, -3.56 to -0.06; P = 0.04; Fig. 8).

(2) Combined with medicine

Pooled analysis of the six studies showed combination treatment achieved a greater mean reduction in BMI than medicine alone (MD = -1.63; 95% CI, -1.94 to -1.33; P < 0.01; Fig. 8), without significant between-study heterogeneity (I² = 0).

3.5.4. Adverse events

(1) Acupuncture alone

Seven of the studies reported adverse events. Pooling data of these studies found that acupuncture was associated with a lower risk of adverse events than other treatments (RR, 0.15; 95% CI, 0.10 to 0.22; P < 0.01; Fig. 9), with no significant heterogeneity (I² = 44%). Most adverse events were digestive tract reactions or subcutaneous bruising and hematoma and resolved quickly. There were no distressing symptoms or liver or kidney injuries. Table 2 displays the reported details.

(2) Combined with medicine

Pooled analysis of two studies showed no significant difference in the RR of adverse events with combination treatment compared with medicine alone (RR, 0.80; 95% CI, 0.51 to 1.25; P = 0.32; Fig. 9), without significant between-study heterogeneity (I² = 0).
3.6 Quality of evidence

The quality of evidence assessed using the GRADE system varied from very low to moderate. According to this system, HOMA-IR and adverse events had moderate evidence levels because the means of assessing allocation were not described, and FBG, FINS, and BMI had a very low evidence level in the use of acupuncture alone. For combination treatment, furthermore, FINS and BMI had moderate evidence levels. Details of the assessment are shown in Table 3.

4. Discussion

4.1 Main findings

The purpose of this review was to evaluate the effectiveness of acupuncture for IR in patients with PCOS. We found acupuncture could be significantly associated with a greater reduction of HOMA-IR (based on moderate-certainty evidence), BMI (based on very low-certainty evidence), and adverse events (based on moderate-certainty evidence) than other treatments. However, we identified no significant differences for the other studied outcomes, namely, FBG and FINS (both based on very low-certainty evidence). Furthermore, we found that a combination of acupuncture and medicine yielded improvements in HOMA-IR, FBG (both based on very low-certainty evidence), FINS, and BMI (both based on moderate-certainty evidence). Therefore, our findings indicate that acupuncture is
the remaining six outcomes were based on very low-certainty evidence. Second, these studies lack follow-up data, hindering assess

Obesity increases the risk for many diseases, particularly insulin resistance, type 2 diabetes mellitus, and cardiovascular disease. In

The cause of PCOS is unknown. However, it is strongly associated with IR and the risk of type 2 diabetes in PCOS patients is 5–10	imes higher than that in the general population [30]. Clinical and experimental evidence has shown that acupuncture can be an acceptable, adverse effect-free, alternative or complement to the pharmacological induction of ovulation in women with PCOS and may also relieve other symptoms [31]. There is also evidence that acupuncture can be an insulin sensitizer and may therefore contribute to controlling obesity and type 2 diabetes [32,33]. Acupuncture ameliorates IR through enhancing autophagy [34], affecting insulin receptor signal transduction, and increasing the expression of insulin receptor substrates in the endometrium in a PCOS-like rat model [35,36].

4.2. Limitations

First, most studies examined were small and some described the specifics of assessing allocation and blinding poorly. Their quality was therefore mediocre. Besides, according to the GRADE system, only four outcomes were based on moderate-certainty evidence, and the remaining six outcomes were based on very low-certainty evidence. Second, these studies lack follow-up data, hindering assessment of the long-term efficacy of acupuncture for PCOS-IR.

Finally, there was heterogeneity in some outcomes. We then performed subgroup analyses based on the type of intervention, which greatly reduced the statistical heterogeneity; however, the likelihood of false-negative and false-positive findings regarding significance increased rapidly with increasing numbers of subgroup analyses. Of note, metabolic syndrome has varying clinical manifestations and biochemical characteristics, age distribution, and abnormal glucose metabolism. Furthermore, there were differences in the details of the interventions, severity of disease, dosage of medicine, and acupuncture protocols between studies. Therefore, considerable inter-study heterogeneity is possibly explained by different study designs and metabolic differences among the study populations. In addition, almost all cases of PCOS covered in this article were overweight and obese, and these cases usually have calorie restriction, which was not described in the studies included in this article.

4.3. Implications for further clinical research

Obesity increases the risk for many diseases, particularly insulin resistance, type 2 diabetes mellitus, and cardiovascular disease. In obesity, inflammation, with increased accumulation and inflammatory polarization of immune cells, takes place in various tissues, including adipose tissue, pancreatic islet, and so on, which may contribute to obesity-linked metabolic dysfunctions, including insulin resistance and type 2 diabetes mellitus [37]. Successful treatment of obesity, therefore, reduces IR [38]. Being a safe and simple treatment modality, acupuncture could be a good alternative or adjuvant therapy for PCOS-IR, especially for overweight patients. Because it has fewer adverse effects than other treatments, patient acceptance and compliance may be higher. It is gratifying that acupuncture is significantly more effective at weight loss than other treatments. Acupuncture can reduce body weight by reducing serum insulin levels in obese patients. This benign regulation of serum insulin is one of the mechanisms of acupuncture weight loss [39–41]. Unfortunately, the long-term effects of acupuncture are still unknown. Additional long-term follow-up studies are needed to clarify acupuncture’s role in treating PCOS-IR.

In addition, some comparative studies of acupuncture and sham acupuncture have found that these two interventions achieve equivalent results. A review of the designs of these studies revealed that sham acupuncture involved needling non-acupuncture or irrelevant acupuncture points, or superficial needling. However, the insertion of a needle into recognized acupuncture or non-

| Type                | Outcome | Certainty assessment | Certainty of the evidence |
|---------------------|---------|----------------------|---------------------------|
|                     |         | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | GRADE |
| Acupuncture alone   | HOMA-IR | serious a        | not serious b       | not serious b | not serious b | none | ⊝⊝⊝⊝ Moderate |
|                     | FBG     | serious a        | very serious b      | not serious b | not serious b | none | ⊝⊝⊝⊝ Very low |
|                     | FINS    | serious c        | not serious b       | not serious b | not serious b | none | ⊝⊝⊝⊝ Very low |
|                     | BMI     | serious a        | very serious b      | not serious b | not serious b | none | ⊝⊝⊝⊝ Very low |
|                     | adverse events | serious a | not serious b       | not serious b | not serious b | none | ⊝⊝⊝⊝ Moderate |
| Combined with medicine | HOMA-IR | serious a        | very serious b      | not serious b | not serious b | none | ⊝⊝⊝⊝ Very low |
|                     | FBG     | serious a        | very serious b      | not serious b | not serious b | none | ⊝⊝⊝⊝ Very low |
|                     | FINS    | serious a        | not serious b       | not serious b | not serious b | none | ⊝⊝⊝⊝ Moderate |
|                     | BMI     | serious a        | not serious b       | not serious b | not serious b | none | ⊝⊝⊝⊝ Moderate |
|                     | adverse events | serious a | not serious b       | not serious b | not serious b | not serious d | ⊝⊝⊝⊝ Very low |

a, the means of assessing allocation is not described.
b, I^2 ≥ 75% in the Q statistics indicates serious inconsistency in the meta-analysis.
c, the upper or lower confidence limit has crossed an effect size of 0.5 in either direction.
d, 0.50% < 12 < 75% in the Q statistics indicates serious inconsistency in the meta-analysis.
e, Total cohort is less than 400 and the upper or lower confidence limit has crossed an effect size of 0.5 in either direction.
Acupuncture points can produce a physiological effect, partly by activating the pain-inhibiting system in the spinal cord and diffusing noxious inhibitory controls [42–45]. In addition, sham acupuncture applied at non-acupuncture points may serve as an active control because acupoint areas can be enlarged by increased expression of nociceptive substances in individuals with painful conditions [46]. It has therefore been suggested that more research into applying non-penetrating sham acupuncture at non-acupuncture points is necessary [47]. This would avoid segmental analgesia and minimize any physiological effects in the sham acupuncture group.

4.4. Conclusion

This review of 17 RCTs shows that acupuncture can improve HOMA-IR and BMI significantly in individuals with PCOS-IR and that, it has fewer adverse effects than other treatments. Additionally, the combination treatment of acupuncture and medicine is more effective in improving HOMA-IR, FBG, FINS and BMI than medicine alone. Acupuncture may be an effective adjuvant strategy for improving PCOS-IR. However, the evidence for this conclusion is based on only a few studies with obvious limitations related to both sample size and methodology. Further large-scale, long-term RCTs with strict methodological standards are justified.

Author contribution statement

Yu Liu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.
Hua-Ying Fan: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.
Jin-Qun Hu, Tian-Yu Wu: Performed the experiments; Analyzed and interpreted the data.
Jiao Chen: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest’s statement

The authors declare no competing interests.

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Appendix A. Supplementary data

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