

Acupuncture combined with Chinese herbal medicine in the treatment of perimenopausal insomnia

A systematic review and meta-analysis

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Abstract

Background: Perimenopausal insomnia (PMI) is a relatively common menopausal symptom that can cause serious problems for the women themselves and their families. Today, the world is facing the trend and challenges of an aging population. It is reported that about 1.5 million women worldwide enter menopause every year, with sleep disorder identified as a core symptom. The efficacy of acupuncture combined with traditional Chinese medicine for treating PMI has been recognized by patients and doctors.

Methods: We searched 8 databases to identify 15 randomized controlled trials evaluating the effects of acupuncture combined with traditional Chinese medicine on sleep in patients with PMI compared with Western medicine alone. Subsequently, data extraction and analysis were performed to assess the quality and risk of bias of the study method design, and a meta-analysis of the data was performed.

Results: This study included 15 randomized controlled trials involving 1188 patients with PMI. The results show that acupuncture combined with traditional Chinese medicine seems to be more effective than Western medicine in the treatment of PMI: efficiency (RR: 1.18; 95% CI: 1.08, 1.29; $P = .001$); the Pittsburgh Sleep Quality Index (PSQI) (WMD: -2.77 ; 95% CI: 4.15–1.39; $P < .0001$); follicle-stimulating hormone (FSH) (WMD: -31.45 ; 95% CI: 42.7–20.2; $P < .001$) and the Hamilton Anxiety Score (HAMA) (WMD: -2.62 , 95% CI: -3.93 , -1.32 ; $P < .0001$). Compared with western medicine, E_2 (WMD: 5.07; 95% CI: 5.78–15.92; $P = .36$) and LH (WMD: -4.86 ; 95% CI: 11.5–1.78; $P = .151$) had no difference.

Conclusion: The current analysis results show that acupuncture combined with Chinese medicine seems to have a more positive effect than western medicine alone in improving sleep and FSHF in PMI patients, but no difference has been found in improving E_2 and LH. This study provides a basis for acupuncture combined with Chinese medicine to treat PMI. However, due to the higher risk of evaluation in included studies, more rigorous randomized controlled trials and higher quality studies are needed to validate included studies.

Abbreviations: E_2 = estradiol, FSH = follicle-stimulating hormone, HAMA = Hamilton Anxiety Score, LH = luteinizing hormone, PMI = perimenopausal insomnia, PSQI = Pittsburgh Sleep Quality Index, RCT = randomized controlled trial, RR = risk ratio, VIP = Chinese Scientific Journal Database, WMD = weighted mean difference.

Keywords: acupuncture₁, Chinese herbal medicine₂, hormone levels₃, perimenopause insomnia₃, sleep quality₄

1. Introduction

Sleep disorders, such as difficulty in falling asleep, sleep deprivation or inability to fall asleep, can greatly affect the quality of life and can happen regardless of any triggers. Menopause is not only a natural process of women normal aging but also an important period in a woman life. The scope of menopause will also vary in different races, nationalities and lifestyles.^[1] During

menopause, many clinical symptoms that last or accompany the rest of life and heavily affect people life quality will occur, such as depression, anxiety, irritability, paranoia, insomnia, etc. Perimenopausal insomnia (PMI) is a common menopausal symptom that will bring serious problems to women and their families. PMI will also give rise to a poor quality of life, low work efficiency, anxiety and depression.^[2]

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Nowadays, the world is facing the challenge of population aging. It is reported that about 1.5 million women worldwide enter menopause every year,^[3] and sleep disorders are identified as typical symptoms.^[4] Studies have found that sleep disorders are very common in middle-aged women and the prevalence of insomnia increases significantly from premenopause to perimenopause and then to postmenopause, with the highest incidence in perimenopause.^[5] Epidemiological investigation shows that the prevalence of moderate to severe insomnia among climacteric women in Japan is 50.8%, which is much higher than in Europe and North America.^[6] In Korea, 14.3% of middle-aged women suffer from insomnia at least 3 times a week. This prevalence of insomnia is similar to that in Singapore and France.^[7] An American sleep survey shows that 59% of perimenopausal women suffer sleep disorders at least several nights a week,^[8] whereas women who have experienced other perimenopausal symptoms (hot flashes and depression) are more likely to have insomnia.^[9,10] A study on insomnia in perimenopausal women from China showed that the rate of difficulty falling asleep continued to increase from the premenopausal stage (28.12%) to the postmenopausal stage (50.29%).^[11] In addition, 25% of perimenopausal women and 30% of postmenopausal women said they had only a few nights or less of sleep per month.^[12] It is generally believed that the occurrence or aggravation of insomnia is associated with menopause, but there is no clear or effective explanation at present. Some studies believe that hot flashes and sweating are unique vasomotor symptoms in menopause,^[13] so a connection between sleep disorders and vasomotor status and mood in women during perimenopause seems to be an explanation.^[14] But more importantly, the reduction of endogenous estrogen is a directly influential factor that cannot be ignored in PMI.^[15] Therefore, our understanding of PMI symptoms contributes to the choice of appropriate treatment methods. Hormone replacement therapy seems to be an effective treatment and has proved helpful for reducing sleep latency and the total number of wakes at night and also for increasing the total sleep time of menopausal women.^[16] However, it should be noted that hormone replacement therapy has always been controversial, with many patients stopping or refusing to use it for fear of adverse reactions. Patients are more inclined to choose natural drugs and complementary replacement therapy.^[17]

Acupuncture and traditional Chinese herbs are the mainstay of traditional Chinese medicine (TCM) and also used as effective methods for treating perimenopausal symptoms.^[18] Acupuncture is one of the simplest, safest and most popular alternative therapies.^[19] Studies have confirmed that acupuncture is effective in the treatment of PMI.^[20] A recent randomized controlled trial (RCT) claimed that acupuncture can significantly improve the clinical symptoms of PMI,^[21] and can also be used as a treatment for comorbid PMI and depression.^[19] In the TCM syndrome differentiation and treatment system, the treatment of PMI mainly focuses on premenopausal and postmenopausal symptoms and insomnia. TCM syndrome differentiation mostly includes: kidney deficiency and liver depression; disharmony of heart and kidney; liver depression and spleen deficiency; kidney deficiency in yin and yang; heart, gallbladder and qi deficiency; heart and spleen deficiency; and other syndromes. According to the symptoms, doctors will select the prescription and medication using the principles of syndrome differentiation and treatment, which has advantages in the clinical treatment of PMI. In order to better observe the clinical effect of acupuncture combined with TCM in the treatment of PMI compared with Western medicine, we conducted a meta-analysis of the RCT on acupuncture combined with TCM for the treatment of PMI.

2. Methods

The study was conducted in accordance with the preferred reporting item of the systematic review and meta-analysis

(PRISMA)^[22] and was in line with the CHARMS checklist. The study was approved by PROSPERO on May 9, 2022, with registration number of 420222323909.

2.1. Search strategy

We comprehensively searched the following 8 databases: Embase, PubMed, Web of Science, Cochrane Library, sinomed, Chinese National Knowledge Infrastructure, Wan Fang Data Knowledge Service Platform, Chinese Scientific Journal Database (VIP database) and Sinomed. During the search, we used “menopause,” “perimenopause,” “lose sleep,” “insomnia,” “acupuncture,” “randomized control,” “Random Allocation” and “clinical controlled trial” as the subject words and selected the bibliographies of qualified RCTs and controlled clinical trials published as of August 31, 2023. Finally, we adjusted the retrieval format to adapt to different databases. At the same time, the literature was supplemented by a manual search of retrospective references of the included literature and references of the same or similar topics in a systematic review report (the detailed search strategy is provided in the Supplementary Material, <http://links.lww.com/MD/K617>).

2.2. Inclusion and exclusion criteria

According to inclusion and exclusion criteria, eligible studies were identified, data were extracted and cross-checked and any ambiguity was resolved through discussion and consensus. The experimental groups received acupuncture (manual acupuncture, electroacupuncture, ear acupuncture, warm acupuncture) combined with Chinese herbal medicine whereas the control groups were treated with Western medicine.

The inclusion criteria were as follows: RCTs or controlled clinical trials; patients diagnosed with PMI under the internationally recognized diagnostic criteria for PMI, regardless of age, course and case origin, without other diseases; and the treatment group used acupuncture combined with Chinese herbal medicine while the control group used Western medicine.

The exclusion criteria were as follows: articles with repeated experiments; articles with no clear diagnostic criteria for PMI or irregular patient evaluation methods; articles with treatment other than acupuncture combined with traditional Chinese herbal medicine (such as moxibustion and acupoint injection) in the treatment group; and the control group used treatment other than Western medicine. The automated tool used to exclude literature was Endnote-X9.

2.3. Outcomes

The main results of the study included the Pittsburgh Sleep Quality Index (PSQI) and the total effective rate of treatment (the total effective rate is (the number of people with marked effect plus the number of cured people)/the total number of people). The secondary outcomes of the study included estradiol (E₂), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and the Hamilton Anxiety Rating Scale (HAMA) score.

2.4. Data extraction

Two reviewers extracted the data respectively, including study design, diagnostic criteria, PMI duration, sample size, age, intervention strategy, control method, treatment duration, follow-up duration and adverse events. Incomplete data were queried or followed-up with the original author by telephone and email.

2.5. Risks of bias

Two researchers used the Cochran Risk of Bias Tool 2.0 and the Newcastle-Ottawa Scale to evaluate the quality of the included

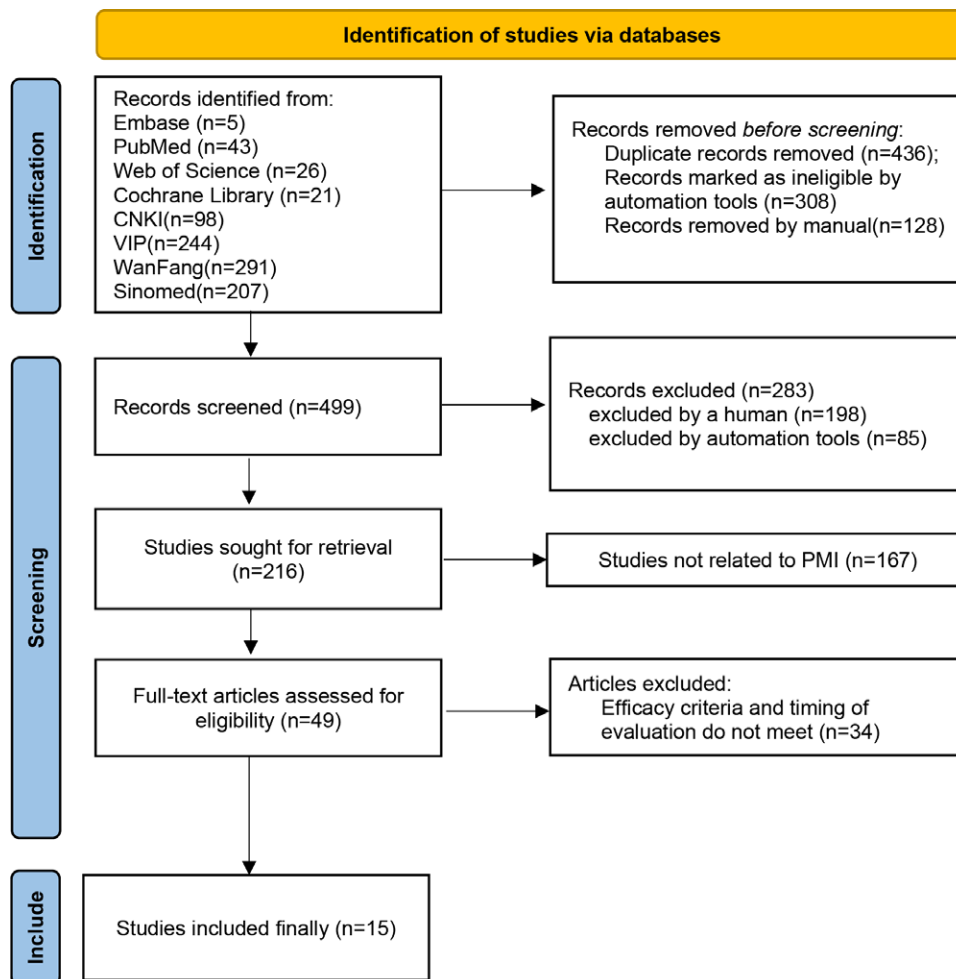


Figure 1. Flow diagram of the included and excluded studies in the systematic review.

studies and made judgments for each item, such as “high risk,” “low risk” and “ambiguous.” Each randomized controlled trial was evaluated according to the following 6 items: the randomization process; interventions that deviate from expectations; lack of result data; measurement results; select report results; and overall. If the methodology used is appropriate and properly and clearly described, the study is considered low risk; Otherwise, if the method cannot be accurately judged, it is rated as high risk, or there are some problems. Two investigators independently assessed these factors and, if necessary, consulted a third investigator (JF) to resolve differences.

2.6. Data analysis

The 2 researchers used stata16.0 for statistical analysis of the data. Secondary categorical variables are expressed as the risk ratio (RR) and the corresponding 95% CI. Continuous data are expressed as the weighted mean difference (WMD) or standardized mean difference and the corresponding 95% CI. To determine whether there is heterogeneity in the evaluation statistics, I^2 and P are used: $I^2 > 50\%$ or $P < .01$ indicates significant heterogeneity and that the random effect model is required; otherwise, the fixed effect model is used. If significant heterogeneity exists, subgroup analysis or meta-regression is performed to find the source of heterogeneity. For the statistical analysis, $P < .05$ is considered statistically significant. In addition, a sensitivity analysis was conducted to test the reliability of the results by excluding low-quality tests. A funnel plot and Egger diagram were used to detect publication bias. If significant publication

bias is found, the stability of the results is tested by the trim-and-fill method.

3. Results

A total of 935 articles were retrieved, all of which were published in journals; 436 duplicates were excluded; 85 articles were excluded by automation tool for ineligible; 198 articles are not RCT; 167 articles are not related for PMI; after careful reading, 34 articles were further excluded because the treated patients did not meet the inclusion requirements. The subsequent analysis included 15 articles (Fig. 1).

3.1. Basic characteristics of eligible studies

The main characteristics of the included study are shown in Table 1 (see end of article): study location, sample size of the treatment group and the control group, treatment method selected by the treatment group, treatment method used by the control group, time process of efficacy evaluation, efficacy evaluation indicators and adverse events.

1188 patients were involved in the 15 studies: 666 received acupuncture combined with traditional Chinese medicine and 582 received Western medicine. All were single center control experiments.

For the diagnosis of PMI, clear diagnostic criteria are found in 16 articles. For the efficacy criteria of PMI, PSQI was evaluated in 7 studies.^[23–29] The effective rate was used to evaluate the treatment effect^[24,25,28,30–36] in 10 studies. The extent of E_2 and FSH changes was

Table 1
Characteristics of included studies.

Study	Country	Outcome measure	Experimental treatment	Control treatment	Sample size (I/C)	Age(y) [mean (SD)] (I/C)	Acupuncture points	Duration	Adverse events (I/C)
Chen2019	China	Efficiency	① and Chai Hu Jia Long Gu Mu Li Tang	Diazepam	60/60	46.6 (3.2)/46.2 (2.8)	GV ₂₀ , GV ₂₃ , LI ₄ , EX-HN ₁ , HT ₇ , SP ₆		
Yang2018	China	Efficiency, PSQI	② and Shu Gan Bu Shen Tang	Diazepam	80/82	51.2 (10.25)/50.7 (9.76)	CO ₁₈ , TF ₄ , CO ₁₂ , CO ₁₀	4w	
Chen2018	China	Efficiency	③ And Huang Lian E Jiao Tang	Estazolam	40/40	-	BL ₁₅ , BL ₂₃ , K ₁₇ , HT ₇ , PC ₇ , LR ₃		
Kang2021	China	HAMA, PSQI, Efficiency, FSH, LH, E ₂	① and Xiang Fu Tang	Estazolam	43/43	50.45 (3.92)/49.3 (3.15)	BL ₆₂ , KI ₆ , SP ₆ , BL ₂₀ , ST ₃₆	4w	
Lai2015	China	Efficiency	② and Chai Shao Long Mu Zao Ren Tang	Eszopi-clone	35/32	-	EX-HN ₁ , HT ₇ , SP ₆ , LR ₃		
Lu2022	China	PSQI, FSH, E ₂	① and Bai Zi Yang Xin Tang	Estazolam	46/46	46.13/46.13	GV20, EX-HN ₁ , BL ₁₅ , BL ₂₃ , ST ₂₅ , CV, EX-CA ₁	4w	0/10 (lethargy, fatigue)
Qiao2022	China	Efficiency, PSQI	① and Ning Shen Tang	Eszopi-clone	35/35	48.6 (1.5)/48.2 (1.0)	GV ₂₀ , GB ₂₀ , GV ₂₀ , SP ₆ , HT ₇ , PC ₇ , ST ₃₆ , KI ₃	30d	
Chen2015	China	FSH, LH, E ₂	① and Jia Wei Huang Lian Ejiao Tang	Alprazolam	30/30	47.87 (4.12)/47.03 (3.84)	EX-HN ₁ , PC ₇ , HT ₇ , SP ₆ , KI ₃ , BL ₁₅ , BL ₂₃	30d	
Du2017	China	PSQI, FSH, E ₂	① and Wu Mei Wan	Estazolam	42/41	50.61 (2.62)/50.45 (3.19)	EX-HN ₁ , PC ₆ , SP ₆	4w	8 Mild nervousness, gastrointestinal discomfort/26 drowsiness, dizziness
Fan2020	China	Efficiency, FSH, LH, E ₂	① and Bu Shen Shu Gan Ning Xin Tang	Nilestrol Tablets	40/40	50.16 (4.27)/49.88 (4.15)	GV ₂₀ , EX-HN ₁ , HT ₇ , PC ₆ , BL ₂₃ , BL ₁₇ , LR ₃ , BL ₁₅ , ST ₃₆ , SP ₆ , CV ₄	3m	2/6
Lai2018	China	Efficiency, PSQI	② and Geng Nian Ning Shen Tang	Eszopi-clone	40/40	52.35 (5.39)/51.13 (5.58)	EX-HN ₁ , HT ₇ , SP ₆ , LR ₃ , GB ₂₀	28d	
Qiao2021	China	Efficiency	① and Chai Hu Jia Long Gu Mu Li Tang	Diazepam, oryzanol	19/19	-	GV ₂₀ , EX-HN ₁ , HT ₇ , PC ₇ , SP ₆ , BL ₆₂ , KI ₆	28d	
Sun2013	China	Efficiency	① and Ning Shen Tang	Diazepam, oryzanol	28/28	48.32 (1.33)/48.97 (1.42)	GV ₂₀ , SP ₆ , ST ₃₆ , HT ₇	3w	
Yan2020	China	PSQI, HAMA, FSH, LH, E ₂	① and Xiang Fu Tang	Estazolam	59/57	50.8 (7.6)/49.6 (7.2)	EX-HN ₁ , HT ₇ , SP ₆ , BL ₁₉ , BL ₁₃ , GB ₂₀ , ST ₃₆	16w	1 Dizziness/dizzy 3, dry mouth 2, exhausted 1, Multilingualism 1, rash 1
Zhang2021	China	HAMA, FSH, LH, E ₂ , PSQI	① and Bai He Di Huang Tang	Estazolam	39/39	52.76 (2.81)/52.14 (2.63)	GV ₂₀ , HT ₇ , GV ₂₄ , EX-HN ₁ , GB ₁₃ , PC ₆ , SP ₆	4w	3/10

Experimental treatment: ①: acupuncture; ②: ear acupuncture; ③: Electroacupuncture; ④: lift needle. E₂ = estradiol, FSH = follicle stimulating hormone, HAMA = Hamilton Anxiety Scale, LH = luteinizing hormone, PSQI = Pittsburgh Sleep Quality Index.

recorded in 7 studies.^[23,24,26,27,29,32,37] Five studies recorded the changes of LH,^[24,27,29,32,37] and 3 studies used HAMA^[24,27,29] to identify the anxiety state of patients. Five reported adverse events^[23,26,27,29,32]

3.2. Risks of bias

The results of methodological evaluation are shown in Figure 2 and Table 2. Of the 15 studies, random grouping was mentioned in all 15, of which 8^[23,24,27-29,31,32,34] used the random number table method but the other 7^[25,26,30,33,35-37] did not mention the specific randomization method. None of the articles described the blind method or allocation concealment method.

3.3. Results of individual studies

3.3.1. Efficiency. A total of 839 patients in 10 studies^[24,25,28,30-36] reported the effective rate of acupuncture combined with traditional Chinese medicine in the treatment of PMI. The results of meta-analysis were shown in the forest figure (Fig. 3). The overall results showed that acupuncture combined with traditional Chinese medicine was superior to Western medicine alone in the effective treatment of PMI (RR: 1.18; 95% CI:

1.08, 1.29; $P = .001$), but the heterogeneity was significant ($I^2 = 55.5\%$, $P = .017$), so we used a random effects model.

Compared with Diazepam, acupuncture and moxibustion combined with traditional Chinese medicine had no advantages (RR: 1.19; 95% CI: 0.96, 1.49; $P = .112$), ($I^2 = 79.8\%$, $P = .002$), the difference was not statistically significant.

Compared with Eszopiclone, acupuncture combined with Chinese medicine appeared to be more effective (RR: 1.19; 95% CI: 1.07, 1.31; $P = .001$), ($I^2 = 0$, $P = .945$);

Compared with Nilestriol Tablets, acupuncture combined with Chinese medicines is more effective (RR: 1.23; 95% CI: 1.01, 1.51; $P = .039$), ($I^2 = 0$, $P = 0$), the difference was statistically significant.

Compared with Estazolam, acupuncture combined with Chinese medicine showed no difference (RR: 1.19; 95% CI: 0.99, 1.44; $P = .064$), ($I^2 = 50.9\%$, $P = .154$). Sensitivity analysis showed that the results were stable, but egger diagram showed that there might be publication bias (Fig. 4).

3.4. PSQI

We conducted a meta-analysis on the PSQI results of 697 patients in 7 studies.^[23-29] Subgroup analysis showed (Fig. 5)

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	Randomization process	Deviations from intended	Missing outcome data	Measurement of the outcome	Selection of the reported	Overall
2	DU2017	Acupuncture combined with traditional Chinese medicine	Western medicine	PSQI	1	+	+	+	+	?	!
1	Chen2018	Acupuncture combined with traditional Chinese medicine	Western medicine	efficiency	1	+	+	+	+	!	!
3	Fan2020	Acupuncture combined with traditional Chinese medicine	Western medicine	FSH	1	+	+	+	+	!	!
4	Kang2021	Acupuncture combined with traditional Chinese medicine	Western medicine	HAMA	1	+	+	+	+	?	!
5	Lai2015	Acupuncture combined with traditional Chinese medicine	Western medicine	efficiency	1	!	+	+	+	?	!
6	Lu2022	Acupuncture combined with traditional Chinese medicine	Western medicine	PSQI	1	+	+	+	+	?	!
7	Qiao2022	Acupuncture combined with traditional Chinese medicine	Western medicine	PSQI	1	+	+	+	+	?	!
8	Sun2013	Acupuncture combined with traditional Chinese medicine	Western medicine	efficiency	1	!	+	+	+	+	!
9	Yan2020	Acupuncture combined with traditional Chinese medicine	Western medicine	Acupuncture combined	1	+	+	+	+	+	+
10	Yang2018	Acupuncture combined with traditional Chinese medicine	Western medicine	PSQI	1	!	+	+	+	?	!
11	Zhang2021	Acupuncture combined with traditional Chinese medicine	Western medicine	PSQI	1	+	+	+	+	+	+

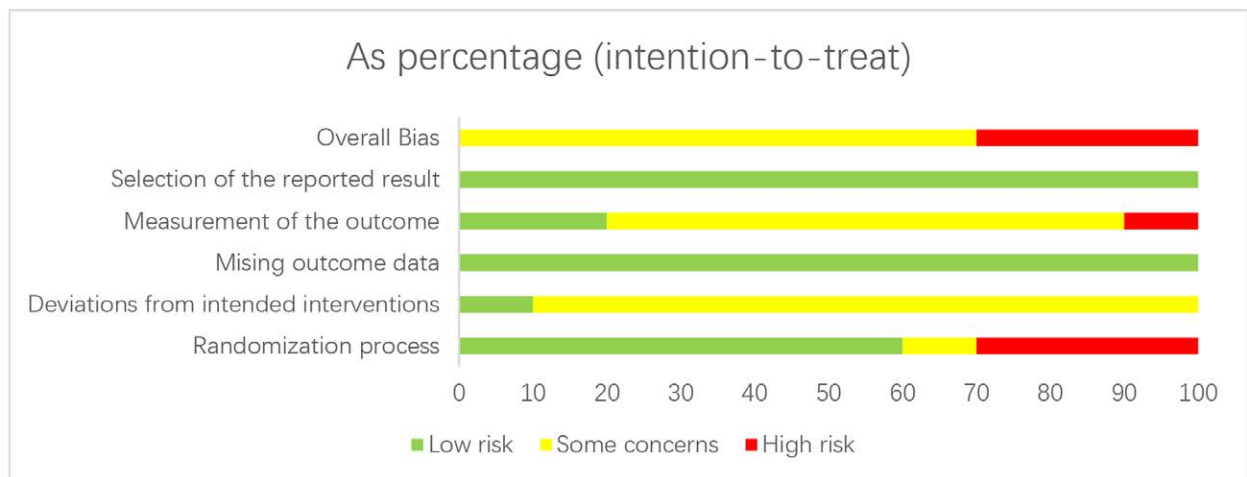
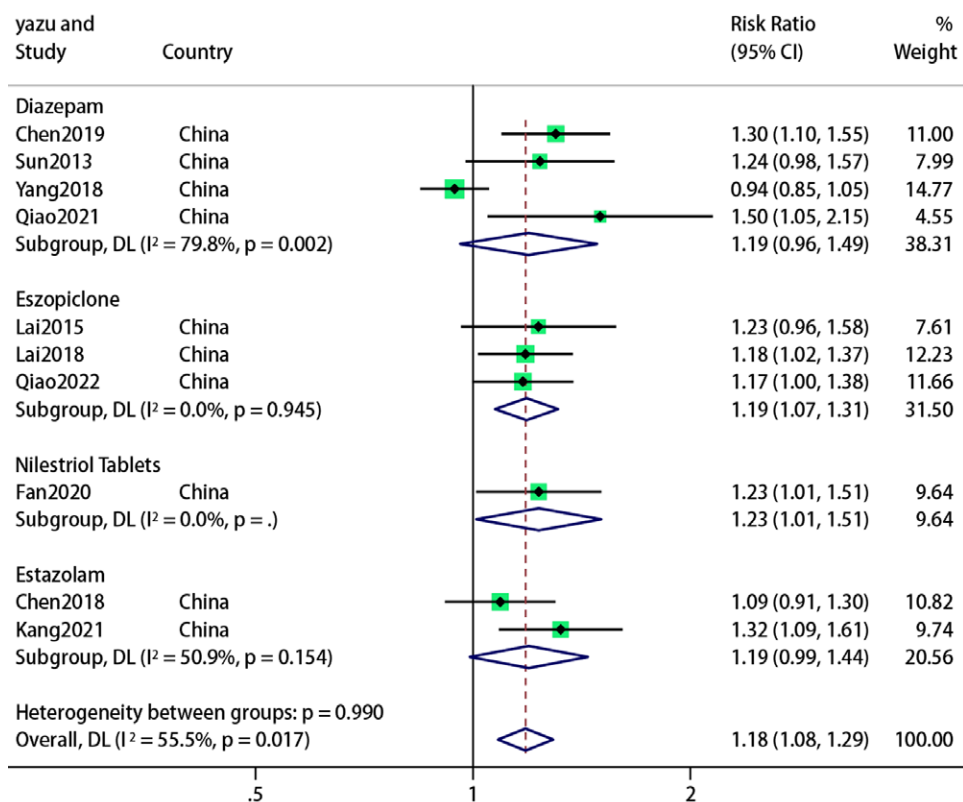


Figure 2. Risk of bias graph.

Table 2
Results of quality assessment using the Newcastle-Ottawa Scale for case-control studies.

Study	Selection				Comparability	Exposure			Scores
	Adequate definition of cases	Representativeness of the cases	Selection of controls	Definition of controls	Control for important factors	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Chen, 2015	✖	✖	-	✖	✖✖	-	✖	-	6
Chen, 2019	✖	✖	-	✖	✖✖	--	✖	-	6
Lai, 2018	✖	✖	-	✖	✖✖	-	✖	-	6
Qiao, 2021	✖	✖	-	✖	✖		✖	-	5

✖Scoring point.



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Figure 3. Forest plot of Efficiency.

that acupuncture combined with Chinese medicine was superior to Diazepam in improving PSQI (WMD: -4.49; 95% CI: 5.46-3.52; $P < .0001$) ($I^2 = 0\%$, $P < .00001$), Eszopiclone(WMD: -2.53; 95% CI: 3.71-1.35; $P < .0001$) ($I^2 = 0\%$, $P < .00001$), Estazolambut(WMD: -2.47; 95% CI: 4.17-0.77; $P = .004$) ($I^2 = 93\%$, $P = 0$); The overall results were (WMD: -2.77; 95% CI: 4.15-1.39; $P < .0001$),the heterogeneity was high ($I^2 = 92.2\%$, $P = 0$). Therefore, we adopted the random response model. Sensitivity analysis shows that the structure is stable (Fig. 6).

3.5. E₂ and FSH

A total of 7 studies^[23,24,26,27,29,32,37] included E₂ and FSH data of 595 patients. We conducted a meta-analysis of E2 and FSH

respectively. The forest map results of E₂ subgroup analysis showed that there was no difference in the results of acupuncture combined with TCM compared with Alprazolam (WMD: 5.07; 95% CI: 5.78-15.92; $P = .36$) ($I^2 = 0$, $P = 0$), but better than Nilestriol Tablets(WMD: -20.56; 95% CI: 24.24-17.06; $P < .001$) ($I^2 = 0$, $P = 0$) and Estazolam(WMD: 18.93; 95% CI: 10.74-27.13; $P < .001$) ($I^2 = 97.7\%$, $P = 0$). Overall, acupuncture combined with traditional Chinese medicine showed no difference with western medicine in improving E₂ levels in PMI patients (WMD: 11.43; 95% CI: 0.21-23.07; $P = .054$). However, the heterogeneity of the results was significant ($I^2 = 98.9\%$, $P = 0$), so we used the random effects model (Fig. 7). Sensitivity analysis showed that the results were stable (Fig. 8).

Subgroup analysis was performed on FSH data, and the results were shown in the forest diagram (Fig. 9). The overall

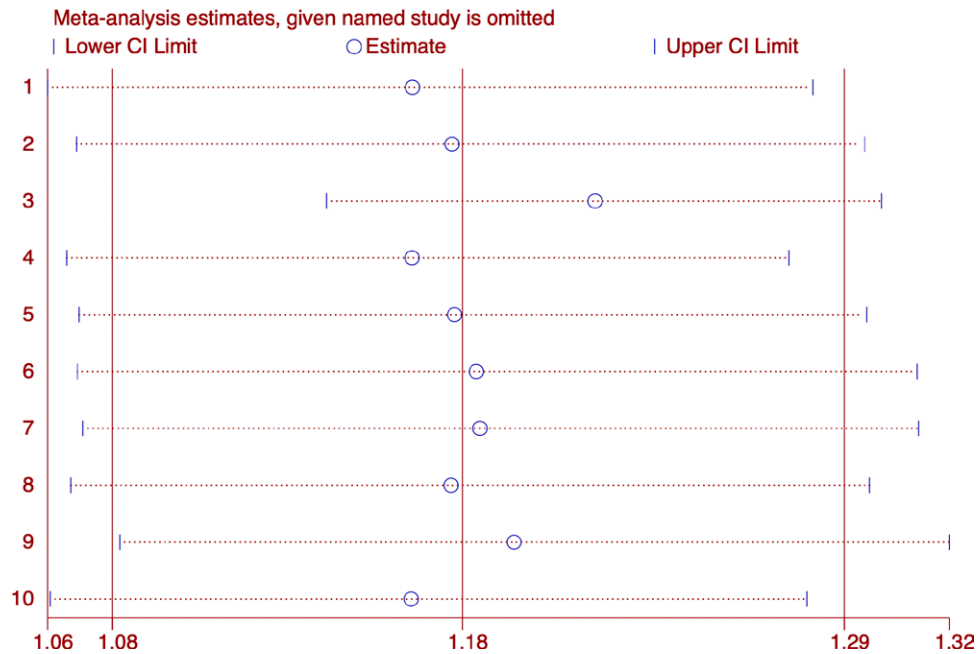


Figure 4. Efficiency sensitivity analysis.

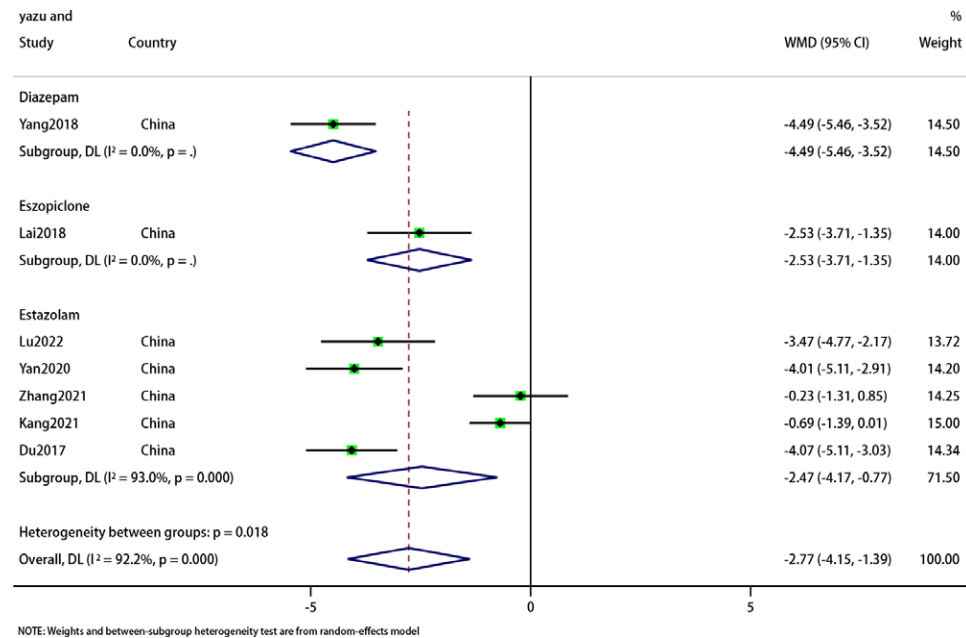


Figure 5. Forest plot of PSQI. PSQI = Pittsburgh Sleep Quality Index.

results indicated that acupuncture combined with Chinese medicine was superior to western medicine in improving FSH level in PMI patients (WMD: -31.45; 95% CI: 42.7-20.2; $P < .001$), the heterogeneity was significant ($I^2 = 96.8\%$, $P = 0$). Sensitivity analysis showed that the results were stable (Fig. 10).

3.6. LH

In the 5 studies recording LH changes, there were 420 patients.^[24,27,29,32,37] The forest map results of data analysis showed that the treatment effect of acupuncture combined with traditional Chinese medicine group was better than Western medicine group (WMD: -9.46; 95% CI: 13.91 to 5; $P < .001$), but

heterogeneity was high ($I^2 = 77.4\%$, $P = 0$). Subgroup analysis did not indicate that acupuncture combined with traditional Chinese medicine was different from Alprazolam (WMD: -4.86; 95% CI: 11.5-1.78; $P = .151$) (Fig. 11). Sensitivity analysis showed that the results were stable (Fig. 12).

3.7. HAMA

Three studies involving 280 patients recorded HAMA^[23,26,28] to evaluate patients' anxiety. Sensitivity analysis indicated that the results were stable. Forest map results showed that acupuncture combined with traditional Chinese medicine group had advantages than Western medicine group (WMD: -2.62,

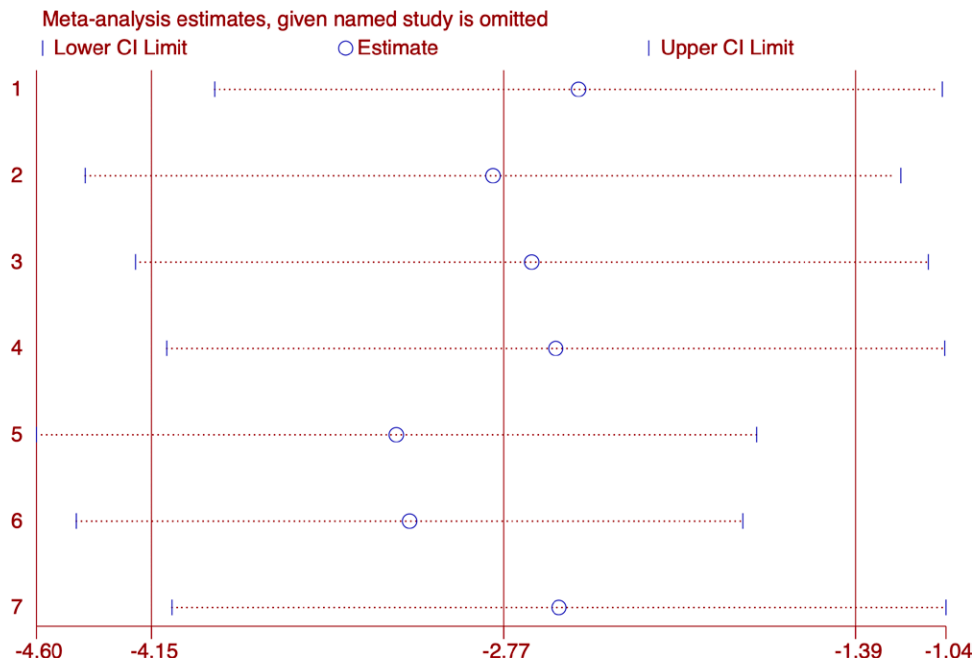


Figure 6. Sensitivity analysis of PSQI. PSQI = Pittsburgh Sleep Quality Index.

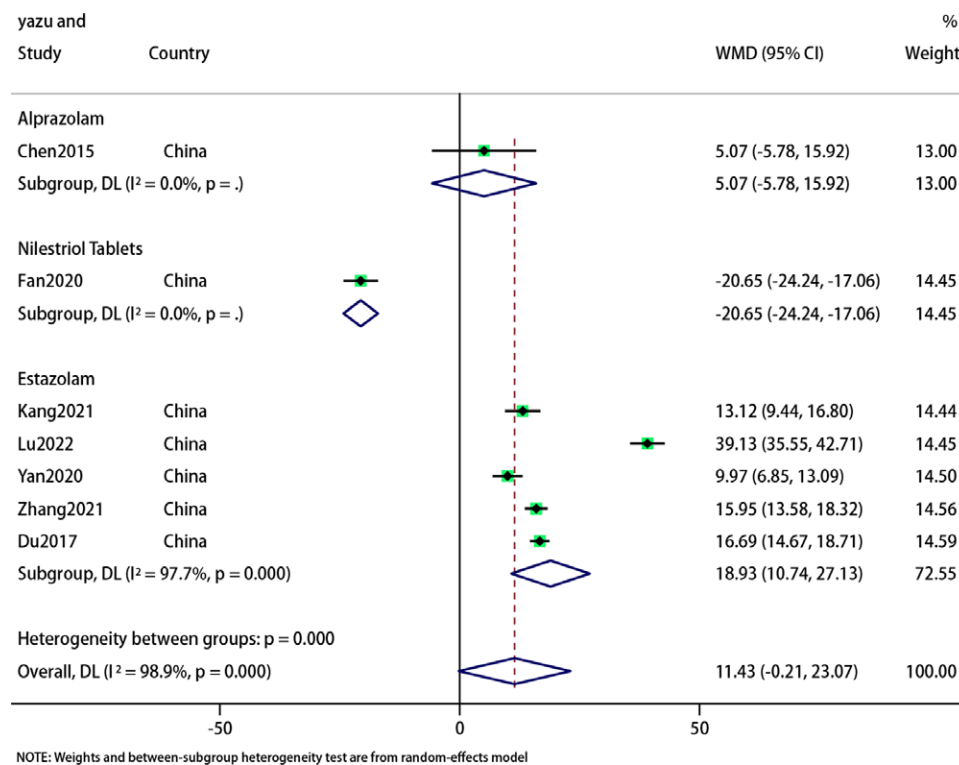


Figure 7. Forest plot of E_2 .

95% CI: -3.93, -1.32; $P < .0001$). The heterogeneity was high ($I^2 = 51.5\%$, $P = .127$) (Fig. 13).

3.8. AE

Adverse reactions were reported in 5 studies of 74 patients.^[23,26,27,29,32] Among them, 11 patients in acupuncture combined with traditional Chinese medicine group (1.49%) and 63 patients in Western medicine group (9.66%). The incidence

of adverse events in acupuncture combined with traditional Chinese medicine group was clearly lower than that in Western medicine group.

4. Discussion

PMI is common in climacteric women and their quality of life and working status will be heavily affected.^[38] PMI is mostly considered to be caused by the decline in estrogen but hormone

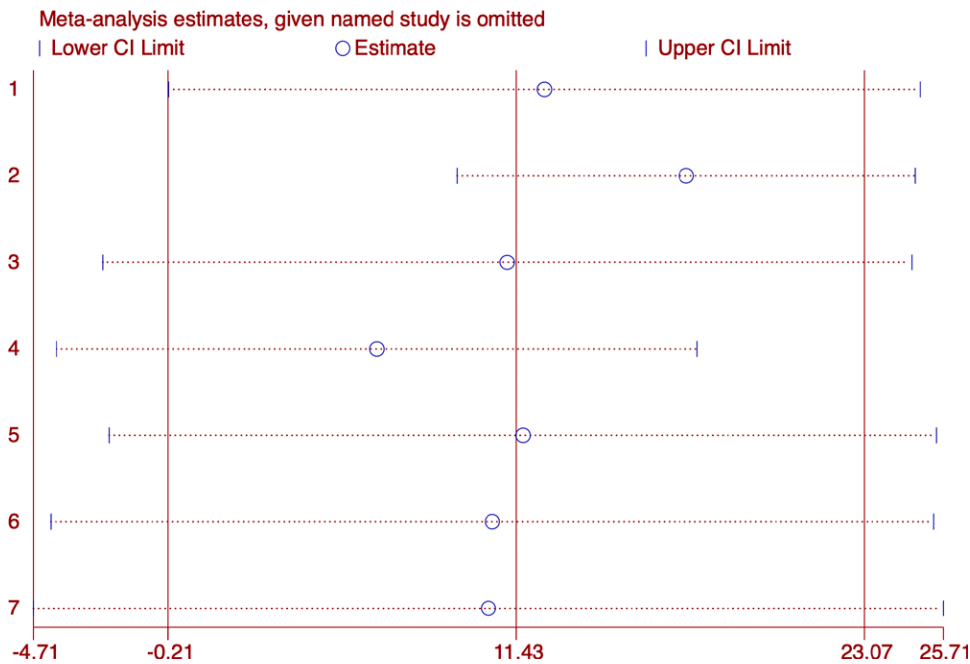


Figure 8. Sensitivity analysis of E₂.

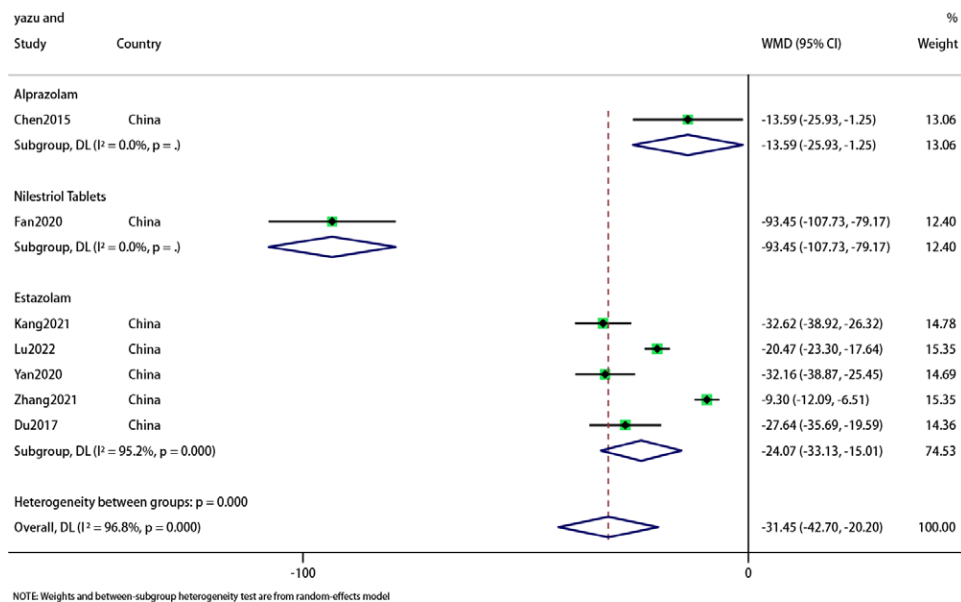


Figure 9. Forest plot of FSH. FSH = follicle-stimulating hormone.

replacement therapy as a first-line treatment cannot be accepted or relied on by most patients due to risks, side effects and other problems.^[39] Acupuncture combined with TCM is effective in the treatment of PMI. At present, there is no systematic evaluation or meta-analysis of acupuncture combined with TCM in the treatment of PMI. The meta-analysis in this paper included 15 studies, involving 1188 patients, to summarize and analyze the clinical efficacy of acupuncture combined with TCM in the treatment of PMI.

It is worth noting that, compared with insomnia in the general population, PMI exerts a more negative influence on mental health than on the body, which can be a very dangerous factor characterized by a sluggish female heart response.^[40] There may be different triggers for PMI (hot flashes, hormonal changes). Studies have shown that hot flashes can predict the awakening

times on a polysomnograph of sleep per hour. The frequency of hot flashes may also influence the levels of E₂ and FSH.^[41] The number of hot flashes at night is inversely proportional to the level of E₂ and is directly proportional to the level of FSH.^[42] Other studies have shown that hot flashes during menopause are a symptom caused by vasomotor contraction. The vasomotor mechanism is believed to be as follows: the decrease of estrogen concentration leads to a decrease of endorphin concentration in the hypothalamus, which results in an increase of norepinephrine and serotonin release, thus causing hot flashes,^[43,44] and affecting sleep quality. There is evidence that the reproductive hormone levels are associated with the subjective and objective sleep quality of perimenopausal women.^[45] Significant changes in estrogen levels in menopausal women will cause decreased sensitivity of urethral smooth muscle and atrophy of urethral

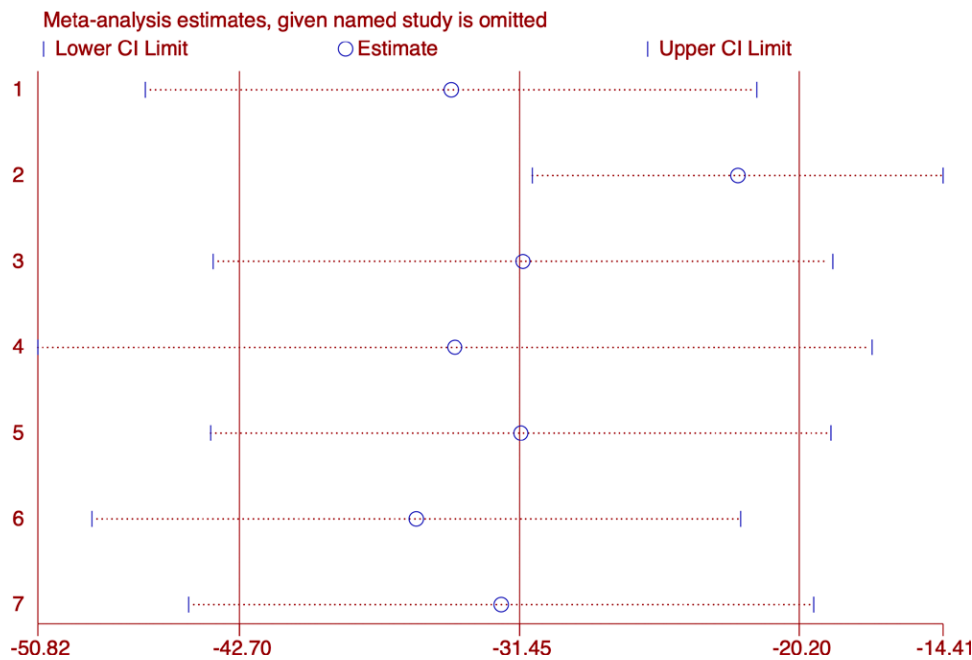


Figure 10. Sensitivity analysis of FSH. FSH = follicle-stimulating hormone.

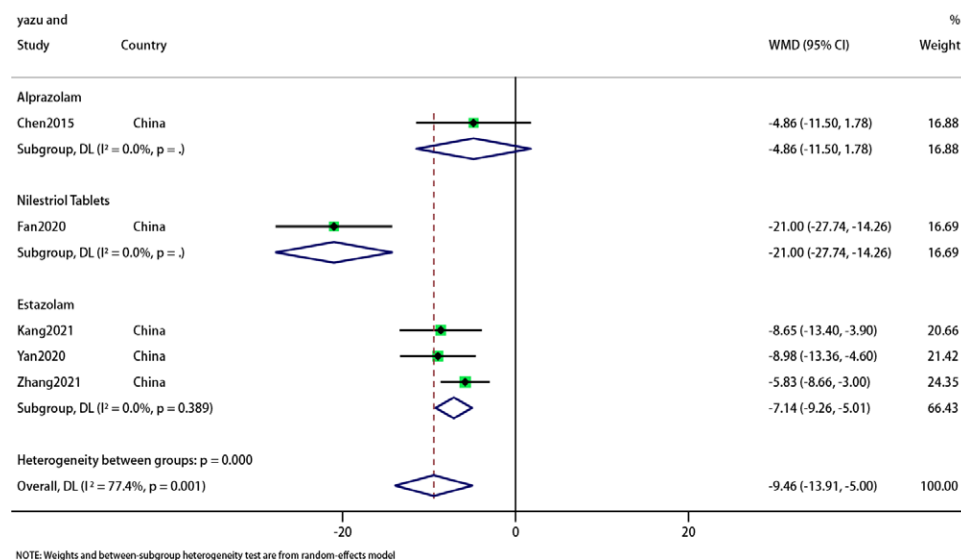


Figure 11. Forest plot of LH. LH = luteinizing hormone.

epithelium, increasing nocturia and producing other urinary tract symptoms that induce early awakening and affect sleep quality.^[46,47] In addition, climacteric women often suffer from depression, which aggravates their mental and psychological symptoms and takes its toll on their sleep quality.^[48]

In TCM, PMI belongs to the category of premenopausal and postmenopausal symptoms and insomnia, which is mainly caused by a deficiency of kidney essence. As mentioned in the Yellow Emperor Canon of Internal Medicine: “when a woman is 7 years old, her kidney Qi is full. When a woman is about 49 years old, because her kidney essence has been exhausted and her menstruation has stopped, she loses her fertility and her physical function begins to decline.” It is generally believed that the kidney-Tianguai-Chongren (Chong and Ren meridians in TCM 8 extraordinary meridians)-uterus system of TCM is similar to the hypothalamic-pituitary-ovarian axis system of Western medicine. Based on TCM theory and treatment

principles, TCM has clear advantages in the treatment of PMI. However, acupuncture and TCM are more commonly used in the treatment of PMI. Studies have shown that acupuncture can improve the sleep quality of perimenopausal women, as measured by the PSQI.^[49] The night sleep time of postmenopausal women after acupuncture treatment was notably prolonged.^[50] Recent RCTs on acupuncture and moxibustion in the treatment of PMI show that acupuncture and moxibustion are safe and effective for the treatment of PMI.^[21,51] Some try to explain the mechanism of acupuncture and moxibustion in the treatment of PMI: acupuncture and moxibustion can reduce oxidative stress in the rostral ventrolateral medulla and regulate the excitability of the sympathetic nerve, where the sympathetic nerve control center is located.^[52] Electroacupuncture can regulate the hyperactivity of the hypothalamic-pituitary-adrenal axis by improving the expression of RNA.^[53] In addition, acupuncture can also increase the E_2 , FSH and LH levels to stabilize the

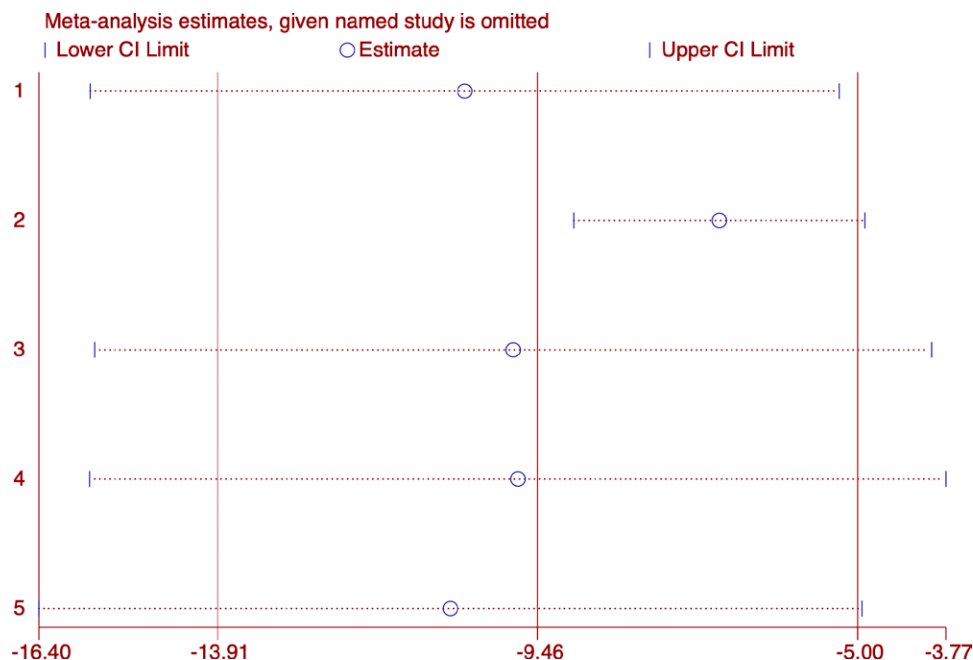


Figure 12. Sensitivity analysis of LH. LH = luteinizing hormone.

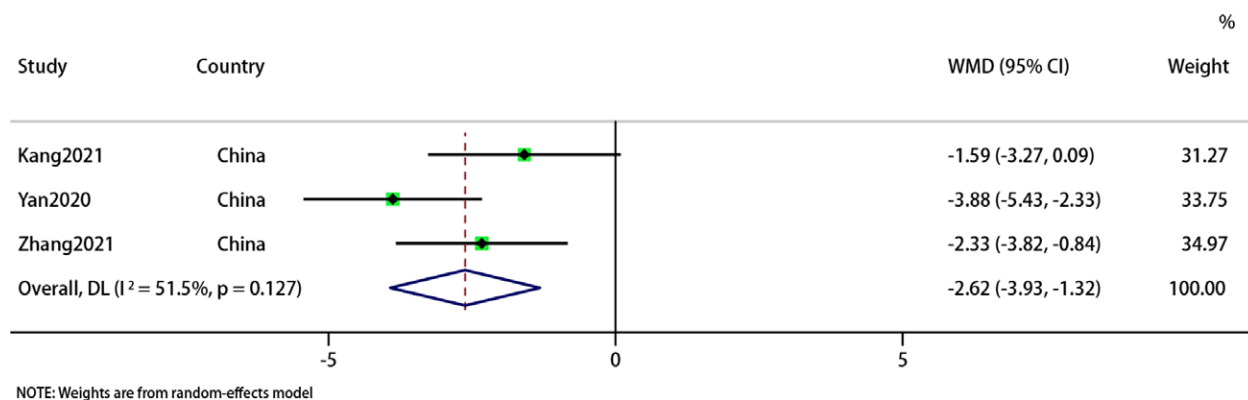


Figure 13. Forest plot of HAMA. HAMA = Hamilton Anxiety Score.

hormones.^[19,54] TCM is a kind of comprehensive treatment that follows the principle of syndrome differentiation and treatment and integrity, and its treatment effect is often for the whole body. Studies have shown that Chaihu Guizhi Ganjiang decoction can improve depression and reduce the concentrations of plasma IL-6 and sIL-6R, thus it can alleviate stress in perimenopausal and postmenopausal women and reduce the incidence rate of PMI.^[55] Pharmacological research shows that in a rat model with a low serum E₂ level, Erxian decoction can increase the production of ovarian E₂ by regulating ovarian aromatase and activating the detoxification pathway of liver catalase.^[56] Early published studies also showed that the use of Chinese herbs is a well-tolerated and valuable short-term alternative treatment for climacteric women with hot flashes, especially for perimenopausal women with palpitations, emotional disorders, insomnia and other symptoms.

5. Limitation

This study was evaluated in strict accordance with the PRISMA report list, but there were also some deficiencies. First of all, the editorial board of international medical journals requires that all clinical trials must be registered before they can be

published. However, all articles included in this paper have not been registered. Secondly, only 8 studies mentioned the generation of random sequences in detail, and no study specifically described allocation concealment, which may lead to selection bias. Secondly, none of the articles point out that the blind method is included in the result evaluation, which may lead to detection bias. Furthermore, we tried to ensure that all relevant studies (including those in the West and the East) were similar, but all the included studies and RCTs were conducted in China, which may limit the universality of the survey. More studies are needed to make the conclusion more applicable to other fields, which may contribute to publication bias, and also the corresponding conclusions may not be applicable to other fields as the lack of high-quality RCTs inevitably hindered a sound evaluation of the efficacy of TCM. Finally, TCM usually produces curative effects through the comprehensive combination of a variety of herbs. Because of its complex composition and mechanism, TCM has not been widely recognized abroad. Although acupuncture and moxibustion have been popularized in many countries, the relevant data on acupuncture and moxibustion combined with TCM in the treatment of PMI cannot be widely accessed abroad at present. In addition, the heterogeneity of several results is

high, which may be caused by the characteristics of the TCM. Under the guiding principles of syndrome differentiation and treatment and a holistic view, acupoint selection and medication adjustment should be carried out according to the symptoms of the different patients in the treatment process, which may be one of the reasons for the high heterogeneity. Furthermore, if the patient feels pain during acupuncture or the taste of the prescription is unacceptable this can change the treatment effect and evaluation of the patient, which will also result in high heterogeneity.

Therefore, it is necessary to conduct more rigorous RCTs on acupuncture combined with TCM in the treatment of PMI. There are several suggestions: clinical trials should be registered on the international platform; the quality of study design should be improved, including randomization, allocation concealment and blinding; and international cooperation should be carried out to obtain more research and ensure the universality of the research results.

6. Conclusion

The current analysis results show that acupuncture combined with Chinese medicine seems to have a more positive effect than western medicine alone in improving sleep and FSHF in PMI patients, but no difference has been found in improving E₂ and LH. This study provides a basis for acupuncture combined with Chinese medicine to treat PMI. However, due to the higher risk of evaluation in included studies, more rigorous randomized controlled trials and higher quality studies are needed to validate included studies.

Author contributions

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