Heliyon 10 (2024) e24439

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

The efficacy and safety of acupuncture and moxibustion for the management of nausea and vomiting in pregnant women: A systematic review and meta-analysis

Yao Hu [c,1], Qian Yang [a,1], Xianjin Hu [b,*]

[a] Science and Education Department, Chengdu Eighth People's Hospital (Geriatric Hospital of Chengdu Medical College), Sichuan, China
[b] Department of Cardiology, West China Hospital, Sichuan University, China
[c] Department of Traditional Chinese Medicine, Xiang He Community Healthcare Center, Chengdu, Sichuan, China

ARTICLE INFO

Keywords:
Acupuncture
Moxibustion
Nausea
Vomiting
Pregnancy
Meta-analysis

ABSTRACT

Background: Nausea and vomiting, which cause considerable multifaceted effects, are commonly experience in early pregnancy. Various therapeutic strategies are employed, including both conventional agents and complementary medicine. However, the effectiveness of complementary medicine remains controversial. The objective of this meta-analysis is to evaluate efficacy and safety of acupuncture and moxibustion in pregnant women.

Methods: We conducted a comprehensive search using electronic databases such as PubMed, Embase, ISI Web, Medline, Cochrane, clinicaltrial.gov, and several Chinese databases. A total of 21 randomized controlled trials were included in this study for quantitative analysis. Forest plots were utilized to evaluate the efficacy and safety of acupuncture and moxibustion. Egger's test was employed to assess publication bias.

Results: The pooled analysis revealed that the acupuncture/moxibustion group was more effective than control group in alleviating nausea and vomiting in early pregnant women (RR: 0.28; 95%CI: 0.21, 0.37). Similar results were observed when comparing the acupuncture group to traditional herbs (RR: 0.08; 95 % CI: 0.01, 0.60), conventional therapy (RR: 0.15; 95 % CI: 0.04, 0.57), and the blank control group (RR: 0.33; 95 % CI: 0.22, 0.51). Moxibustion also exhibited the ability to alleviate nausea and vomiting compared with the blank control group (RR: 0.21; 95 % CI: 0.08, 0.52). As for safety, there were no significant differences in severe adverse events between the acupuncture group and the control group (RR: 0.77; 95%CI: 0.52, 1.14), the blank control group (RR: 0.61; 95%CI: 0.34, 1.10), the sham acupuncture group (RR: 1.05; 95%CI: 0.63, 1.73), or the conventional therapy group (RR: 0.32; 95%CI: 0.06, 1.55).

Conclusion: Acupuncture and moxibustion might be effective for the management of nausea and vomiting in early pregnant women. Moreover, acupuncture might be a relatively safe treatment for pregnancy.

Abbreviations: CI, confidence intervals; CMS, Chinese medicine syndrome scale; NVP, Nausea and vomiting of pregnancy; PUQE, Pregnancy-Unique Quantification of Emesis; RCTs, randomized controlled trials; RR, relative risk; SD, standard deviation; WMD, weighted mean difference.

* Corresponding author.
E-mail address: huxianjin_zj@163.com (X. Hu).

[1] These authors have contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e24439
Received 24 September 2023; Received in revised form 5 January 2024; Accepted 9 January 2024
Available online 11 January 2024

1. Introduction

Nausea and vomiting of pregnancy (NVP) is a common condition that affects 50–90 % of pregnant women and as many as 18 % pregnant women take medicine to treat it [1]. Among pregnant women experiencing nausea and vomiting, symptoms are classified as mild in about 40 % of cases, moderate in 46 %, and severe in 14 % [2]. Typically, these symptoms begin around 6–8 weeks of gestation and subside by 16–20 weeks [3]. There is a more severe form of NVP known as hyperemesis gravidarum, which can lead to malnutrition, dehydration, gastrointestinal complications, and financial burdens during early pregnancy. Moreover, hyperemesis gravidarum is associated with an increased risk of gestational anemia, preeclampsia, and other adverse maternal and birth outcomes [4–6].

Various metabolic and neuromuscular factors have been proposed as the potential pathogenesis of NVP(7). Nevertheless, the exact cause of this condition remains unknown. The management of NVP encompasses a range of treatment strategies, including outpatient dietary advice, administration of antiemetic drugs, and hospitalization and intravenous fluid replacement in severe or persistent cases. When circumstances allow, non-pharmacological therapies are preferred in order to minimize potential drug side effects to the fetus in this specific population. Acupuncture and moxibustion commonly used as alternative therapies in gynecological and obstetrical conditions [7,8]. However, it remains unclear that the efficacy and safety of acupuncture and moxibustion in early pregnant women who suffering from nausea and vomiting.

The aim of this meta-analysis is to evaluate the efficacy and safety of acupuncture and moxibustion for the management of NVP. We wonder whether these therapies could be viable choices in clinical practice for the management of NVP.

2. Methods

This meta-analysis was initiated on July 5th, 2023. A comprehensive search of electronic databases was conducted, resulting in the inclusion of 21 randomized controlled trials (RCTs) encompassing a total of 2392 participants [9–29]. Registration of the study protocol was done in advance in PROSPERO (No. CRD42023442685). PRISMA 2020 checklist was utilized and completed (Appendix 1).

2.1. Criteria for considering studies

RCTs were deemed eligible for inclusion in this meta-analysis if they investigated the use of acupuncture or moxibustion as interventions for managing nausea and vomiting in pregnant women. We also examined reviews and meta-analyses as additional resources. Exclusion criteria consisted of the following: 1) laboratory studies, cross-sectional studies, cohort studies, non-randomized controlled trials, case-control studies, case reports, letters, commentaries, and summaries; 2) studies conducted on patients with nausea and vomiting from pathological causes; 3) studies that did not report the alleviation of symptoms, changes in clinical scales of nausea and vomiting, or adverse events; 4) studies with inappropriate experimental or control groups; and 5) studies where data could not be extracted.

2.2. Search methods for identification of studies

A systematic search was conducted in several electronic databases, including Pubmed, EMBase, ISI Web, Medline, Cochrane, clinicaltrial.gov, as well as Chinese databases like CNKI, VIP, and WANFANG. The search encompassed various search methods such as mesh terms, title, abstract, and all fields, and it covered the period from the inception to July 2023. The detailed search strategies utilized in this process are provided in Appendix 2. Furthermore, in order to identify potential additional resources, reviews, meta-analyses, and the references of the eligible studies were carefully examined. No restrictions on language or region were applied during the search process.

2.3. Main outcomes

The primary outcomes of this meta-analysis included the following: 1) the comparison of ineffective cases after intervention between the acupuncture/moxibustion group and the control group; and 2) the assessment of changes observed on different scales such as the Chinese medicine syndrome scale (CMS), Pregnancy-Unique Quantification of Emesis (PUQE), or nausea scores. The secondary outcomes focused on: 1) the occurrence of severe adverse events, including threatened abortion, spontaneous abortion, stillbirth, neonatal death, and neonatal congenital abnormalities; and 2) the needle-related adverse events such as pruritus, itching, pain, or bruising around acupoints.

2.4. Data collection and synthesis

All studies obtained from electronic databases were imported into EndNote X9, and duplicate records were eliminated. Two reviewers, Yao Hu and Qian Yang, independently assessed the title, abstract, and full text of each study. 17 studies were originally published in Chinese [10,11,15–29], out of which 10 had English titles and abstracts. The data from these studies was initially extracted in Chinese and subsequently translated by two reviewers. The titles were translated by these two reviewers, and original titles have been included in references. Any discrepancies were resolved by another reviewer, Xianjin Hu. The workflow for these procedures is detailed in Fig. 1.

Based on a predetermined form, data were separately retrieved by two reviewers. Conflicts were resolved by another reviewer. The following information was collected from each study: first author, publication year, country, sample sizes of the different groups, participants' characteristics (age and gestation), interventions, acupoints and duration in each group, and the main outcomes (effective or ineffective cases in different group, scales used to evaluate symptoms in pregnancy, and adverse events). As for efficacy assessment, the original studies employed varying hierarchies, typically consisting of three or four categories. In our meta-analysis, we opted for a simplified approach, consolidating these into two classes—effective or ineffective.

We extracted information of the change in the scale scores between baseline and the end if there was multiple assessment during the intervention. However, the data was not normal distribution and median and interquartile range was calculated in two studies [14,23]. We assumed this part of data was slightly skewed distribution and transformed median and interquartile to mean and standard deviation (SD) via the formula reported in previous studies [30,31]. CMS exhibited some discrepancies across different studies according to various traditional Chinese symptoms. In our meta-analysis, scores range 0–10 was used in Lyu J's research [18], 0–21 in Yuting Z's [23], 0–27 in Yangfan Z's [19], 0–30 in Guihua S's [17] and 0–90 in Yan C's [24]. However, it was not reported in Yuling Z's trial what the score range was. To avoid increasing artificial bias in the meta-analysis, data from this trial were excluded from the pooled analysis of CMS. Additionally, we standardized all CMS to the centesimal system. In Xiaoke W's trials, the researchers compared the efficacy and safety between the experimental group and the control group using various measurement tools such as PUQE, visual analogue

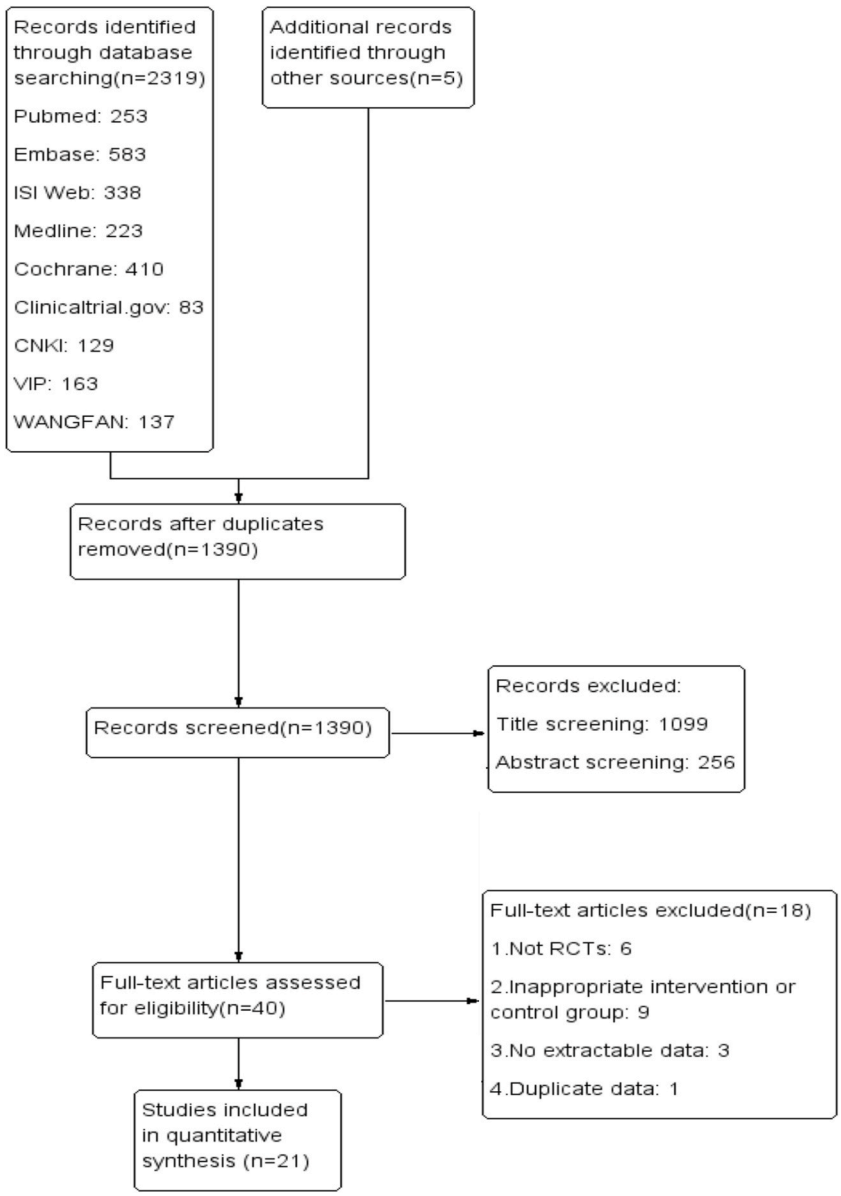


Fig. 1. Flow diagram.

Table 1
Characteristics of selected studies.

Author	Year	Country	Sample		Age		Gestation (weeks)		Intervention		Acupoints	Duration	Outcome
			EG	CG	EG	CG	EG	CG	EG	CG			
C. Smith	2002	Australia	146	147	29.8 ± 4.9		8.5 ± 1.8		Acupuncture	Sham acupuncture	According to TCM diagnosis	4 weeks	Perinatal outcome
C. Smith[a]	2002	Australia	146	143	29.8 ± 4.9		8.5 ± 1.8		Acupuncture	Blank control group	According to TCM diagnosis		
C. Smith**	2002	Australia	147	147	29.8 ± 4.9		8.5 ± 1.8		Acupuncture	Sham acupuncture	PC6		
C. Smith***	2002	Australia	147	143	29.8 ± 4.9		8.5 ± 1.8		Acupuncture	Blank control group	PC6		
D.Habek	2004	Croatia	10	8	20.4 ± 4.7	20.8 ± 4.1	7 (6–9)[b]	8 (7–12)[b]	Acupuncture + Conventional therapy	Sham acupuncture + Conventional therapy	PC6	1 week	Symptoms alleviation
Guihua S	2017	China	49	48	31.02 ± 1.05	31.12 ± 1.15	9.33 ± 0.20	9.35 ± 0.19	Acupuncture + Modified Sini San	Modified Sini San	SP4/GB34/LR3/PC6/ST36/RN12	NR	Symptoms alleviation/CMS/HCG level
Guohui Y	2020	China	35	34	26.91 ± 4.13	27.29 ± 4.66	NR		Filiform needle + Conventional therapy + Metoclopramide	Conventional therapy + Metoclopramide	Wrist and ankle	5 days	Symptoms alleviation
Hong Z	2009	China	31	31	28.58 ± 4.57	28.68 ± 3.76	8.90 ± 1.66	8.97 ± 1.58	Acupuncture + Moxibustion + Conventional therapy	B6 acupoint injection at PC6 + Conventional therapy	RN12$^{\Delta}$/RN10$^{\Delta}$/ST22$^{\Delta}$/PC6/ST36	5 days	Symptoms alleviation/Nausea scale (VAS)
Honghua Z	2005	China	50	50	Ranked data		Ranked data		Acupuncture + Moxibustion	Modified Suye Huanglian decoction	RN12/SP9/PC6/ST36	1–2 weeks	Symptoms alleviation
Honghua Z[a]	2005	China	50	50	Ranked data		Ranked data		Acupuncture + Moxibustion	Conventional therapy	RN12/SP9/PC6/ST36		
Hongyu X	2013	China	47	47	26 ± 4	27 ± 4	NR		Acupuncture	Conventional therapy	RN12/ST36/PC6	10 days	Symptoms alleviation
Juanzhe M	2013	China	30	30	26.3[c]		NR		Acupuncture + Conventional therapy	Conventional therapy	RN12/BL21	5 days	Symptoms alleviation
Knight B	2001	UK	22	17	30.7[c]	30.3[c]	7.8 ± 1.0	8.0 ± 1.0	Acupuncture	Sham acupuncture	According to TCM diagnosis	3 weeks	Symptoms alleviation/Hospital anxiety and depression scores/Nausea scale (VAS)/Adverse events
Lihua J	2014	China	20	20	25. 09 ± 3. 42	26. 03 ± 3. 19	9. 03 ± 2. 15	8. 98 ± 2. 28	Filiform needle + Conventional therapy	Conventional therapy	RN10/RN11/RN12/PC6/ST36	5 days	Symptoms alleviation/Perinatal outcome
Lyu J	2021	China	40	40	27.65 ± 3.85	27.53 ± 3.77	8.23 ± 1.20	8.15 ± 1.14	Acupuncture + Subcutaneous embedding (thumb-tack needle)	Thumb-tack needle for subcutaneous embedding	PC6/ST36/SP4	4 weeks	Symptoms alleviation/CMS
Ruying W	2008	China	53	42	27 ± 3	27 ± 4	NR		Acupuncture	Conventional therapy	CV17/RN12/SP6/PC6/ST36	6 days	Symptoms alleviation/Blood biochemistry
Shujie L	2007	China	47	47	20–37[d]		NR		Acupuncture	Conventional therapy	RN12/PC6/ST36	10 days	Symptoms alleviation
Xiaoke W	2023	China	88	88	28.8 ± 4.0	28.6 ± 4.5	9.3 ± 2.1	9.4 ± 2.2	Acupuncture + (Doxylamine–pyridoxine)	Sham acupuncture + (Doxylamine–pyridoxine)	According to TCM diagnosis	2 weeks	PUQE/VAS score/GWB score/SAS score/SDS score/NVPQOL/Perinatal outcome/Adverse events
Xiaoke W[a]	2023	China	88	88	29.6 ± 4.6	29.2 ± 4.2	8.8 ± 1.9	9.1 ± 2.1	Acupuncture + Placebo	Sham acupuncture + Placebo	According to TCM diagnosis		
Xumei L	2012	China	32	32	29.05 ± 8.25	27.32 ± 7.26	7.52 ± 2.52	8.42 ± 2.39	Moxibustion + Conventional therapy + Citicoline	Conventional therapy + Citicoline	RN12/PC6/ST36	6–10 days	Symptoms alleviation
Yan C	2021	China	30	30	30 ± 9	29 ± 9	7.9 ± 2.7	8.1 ± 3.1	Moxibustion + Conventional therapy	Conventional therapy	CV17/RN14/RN12/BL12/BL17/BL20/BL21	4 days	Symptoms alleviation/CMS/PUQE
Yangfan Z	2012	China	30	30	26.73 ± 2.15	26.9 ± 2.72	9.28 ± 1.62	9.78 ± 1.62	Acupuncture + Conventional therapy	Conventional therapy	SP4/GB34/LR3/PC6/ST36/RN12	5–10 days	Symptoms alleviation/CMS/HCG level

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Country	Sample		Age		Gestation (weeks)		Intervention		Acupoints	Duration	Outcome
			EG	CG	EG	CG	EG	CG	EG	CG			
Yangfan Z[a]	2012	China	30	30	27.9 ± 2.99	26.8 ± 2.01	8.64 ± 1.65	9.49 ± 1.70	Acupuncture + Conventional therapy + Gastric tocolysis soup	Conventional therapy + Gastric tocolysis soup	SP4/GB34/LR3/ PC6/ST36/RN12		
Yonghong X	2009	China	26	25	26[c]		NR		Moxibustion + Conventional therapy	Conventional therapy	PC6/ST36/ RN12/SP4	10 days	Symptoms alleviation
Yuling Z	2017	China	42	42	26. 43 ± 6. 53	26. 93 ± 6. 67	8.78 ± 1.48	8.62 ± 1.50	Acupuncture + Conventional therapy + BaoTai HeYun decoction	Conventional therapy + BaoTai HeYun decoction	SP4/GB34/LR3/ PC6/ST36/RN12	10 days	Symptoms alleviation/CMS
Yuting Z	2020	China	30	30	31.03 ± 4.40	29.63 ± 3.40	10.07 ± 2.32	10.16 ± 2.25	Filiform needle + Conventional therapy	Conventional therapy	PC6/ST36	2 weeks	PUQE/CMS
Yuting Z[a]	2020	China	30	30	29.56 ± 4.03	29.63 ± 3.40	10.03 ± 2.21	10.16 ± 2.25	Subcutaneous embedding (thumb-tack needle) + Conventional therapy	Conventional therapy	PC6/ST36		
Zhongnan M	2009	China	30	30	28.23 ± 4.73	28.63 ± 4.86	8.3 ± 1.6	8.33 ± 1.58	Acupuncture + Conventional therapy	Conventional therapy	BL11/ST37/ PC6/SP4/RN12/ ST36	1 week	Symptoms alleviation/Blood biochemistry
Zhongnan M[a]	2009	China	30	30	28.23 ± 4.73	28.87 ± 4.59	8.3 ± 1.6	8.57 ± 1.66	Acupuncture + Conventional therapy	Herbs + Conventional therapy	BL11/ST37/ PC6/SP4/RN12/ ST36		

EG: experimental group; CG: control group; NR: not reported; CMS: Chinese medicine syndrome score scale; TCM: Traditional Chinese Medicine; PUQE: pregnancy-unique quantification of emesis; SAS: Zung self-rating anxiety scale; SDS: Zung self-rating depression scale; GBW: global assessment of well-being; NVPQOL: NVP quality of life questionnaire; VAS: visual analogue scale; HCG: Human chorionic gonadotropin; SF-36: The Mos 36-item short form health survey.

[Δ]Moxibustion acupoints.

[a] It represents different experimental and control groups for the same research.

[b] Median (Interquartile range).

[c] Mean.

[d] Range of age.

scale, global assessment of well-being scale, Zung self-rating anxiety scale, Zung self-rating depression scale, NVP quality of life questionnaire, perinatal outcome, and adverse events. However, only data of PUQE and adverse events could be extracted. In most of the included studies, fluid infusion, conventional therapy, and electrolyte balance were the fundamental treatments for nausea and vomiting in pregnant women and were referred to as conventional therapy in this meta-analysis. If the control group only received conventional therapy, it was considered as the experimental group compared with a blank control group when the experimental received intervention (acupuncture and/or moxibustion) plus conventional therapy. To calculate the SD for studies that did not disclose the SD of changes in the scale score, we used the Excel spreadsheet provided by the Cochrane website, which allowed us to derive the SD from the p-value or standard error. If there was no other method available to accurately calculate the SD, we used the

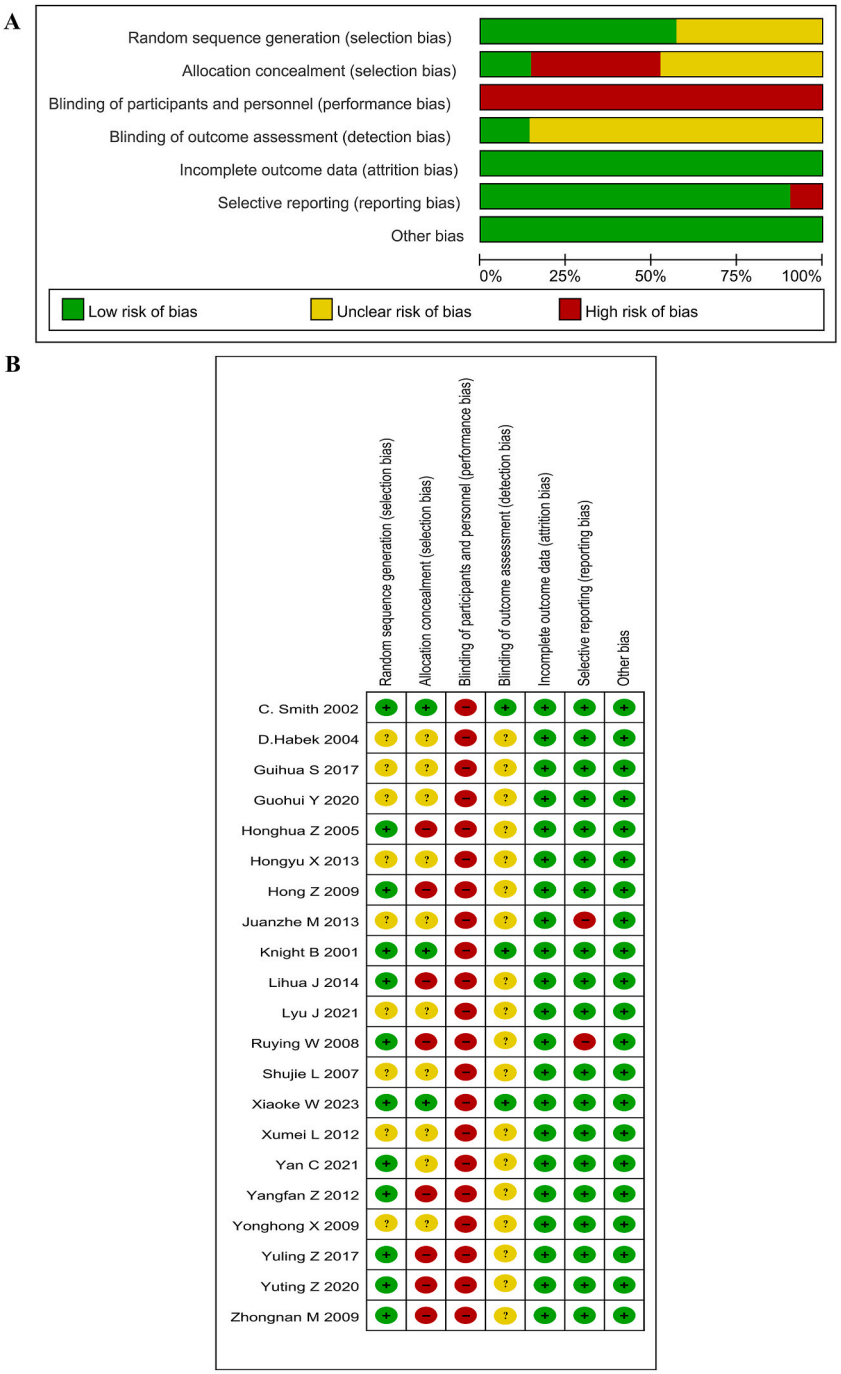
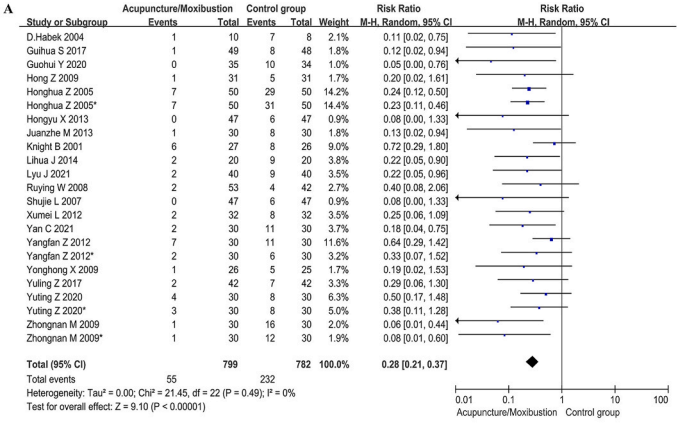


Fig. 2. Risk of bias of included RCTs (A: bias summary; B: bias graph).



(caption on next page)

Fig. 3. Forest plot of ineffective rate between acupuncture/moxibustion group and control group (A: acupuncture/moxibustion vs. control group; B: acupuncture vs. traditional herbs; C: acupuncture vs. conventional group; D: acupuncture vs. sham acupuncture; E: acupuncture vs. blank control group; F: moxibustion vs. blank control group; G: acupuncture combined with moxibustion vs. control group; H: acupuncture combined with moxibustion vs. acupoint injection). *It represents different experimental and control groups for the same research.

upper limit of the p-value in the studies to estimate the SD of changes. It's worth noting that using the upper limit of the p-value may lead to more conservative results.

2.5. Quality assessment

Two reviewers independently evaluated the risk of bias in the included trials using the Cochrane Collaboration tool (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias). Any discrepancies between the two reviewers were resolved by another reviewer.

2.6. Statistical analysis

All analyses were performed with Review Manager (v5.3.5; RevMan, the Cochrane collaboration, Oxford, UK) and Stata 17. Continuous variables were calculated as weighted mean difference (WMD) with 95 % confidence intervals (CI), while binary variables were presented as relative risk (RR) with 95%CI. Considering the clinical and methodological heterogeneity among the trials, a random effects model was employed for the statistical analysis. Heterogeneity among the included trials was assessed using the standard Chi-square test (with statistical significance set at $p < 0.05$) and the I^2 statistic (with statistical significance set at $I^2 > 50$ %). Sensitive analysis would be performed for identifying the potential origin of inhomogeneity when $I^2 > 50$ %. Egger's test and funnel plot were performed to assess the potential publication bias.

3. Results

3.1. Features of the selected studies

Our meta-analysis comprised of 21 RCTs involving a total of 2392 pregnant women. The flow diagram depicting the selection process is presented in Fig. 1. After the initial search, 2319 articles were included (253 from Pubmed, 583 from Embase, 338 from ISI Web, 223 from Medline, 410 from Cochrane Library, 83 from clinicaltrial.gov, 129 from CNKI, 163 from VIP, 137 from WANGFAN). In addition, we reviewed related reviews, meta-analyses, and reference lists, which led to the inclusion of 5 additional studies in our analysis. Following the removal of duplicates and screening of titles and abstracts, a full-text assessment was conducted in 40 trials. Ultimately, 21 studies met the inclusion criteria and were included in the final quantitative analysis.

Detailed information from the 21 studies is provided in Table 1. Among these studies, 18 were conducted in China, while one study each was conducted in Australia, Croatia, and the UK. All studies followed a randomized controlled trial design and employed a 1:1 allocation ratio between the acupuncture/moxibustion group and the control group. There are 6 studies that included more than one experimental group which are denoted by asterisk in Table 1. The participants enrolled in these studies were pregnant women (with a mean age of 28.56 years) who experienced symptoms of nausea and vomiting in early pregnancy (with a mean gestation age of 8.76 weeks). The interventions in the experimental groups included acupuncture, moxibustion, or a combination of both, while the control groups received blank control, conventional therapy, traditional Chinese herbs, sham acupuncture, or acupoint injection. The interventions in the experimental groups included acupuncture, moxibustion, or a combination of both, while the control groups received blank control, conventional therapy, traditional Chinese herbs, sham acupuncture, or acupoints injection. The acupoints utilized varied across the different studies but were all related to the meridians responsible for the strengthening of the spleen and regulation of *qi*. The duration of the intervention ranged from 4 days to 4 weeks, with most of the studies lasting 1–2 weeks. The outcome, which we were interested in, were symptoms alleviation, scales, and adverse events. The primary outcome criteria for 12 trials were the improvement or disappearance of nausea symptoms and vomiting. These trials were conducted by D.Habek, Guihua S, Guohui Y, Hongyu X, Lihua J, Lyu J, Ruying W, Shujie L, Xumei Lu, Yan C, Yangfan Z, Yonghong X. In these studies, the assessment focused on alleviating or eliminating nausea symptoms and vomiting. Another set of trials, led by Hong Z, Honghua Z, Juanzhe M, Yuling Z, Zhongnan M, utilized a different approach, evaluating symptom alleviation through the reduction proportion of vomiting frequency. Various scales were employed across the trials for a more nuanced evaluation. CMS was used in 6 trials by Guihua S, Lyu J, Yan C, Yangfan Z, Yuling Z, and Yuting Z. PUQE was utilized in 3 trials conducted by Xiaoke W, Yan C, and Yuting Z. Additionally, the Visual Analogue Scale was employed in 3 trials led by Hong Z, Knight B, and Xiaoke W. Risk of bias of included studies is shown in Fig. 2-A and 2-B.

3.2. Main outcomes

In the pooled analysis, we counted the ineffective cases between experimental group and control group which is listed in Fig. 3. In Fig. 3-A, it is evident that the acupuncture/moxibustion group had a lower incidence of ineffective cases compared with the control group (RR: 0.28; 95%CI: 0.21, 0.37). In Fig. 3-B, 3-C, 3-D, and 3-E, we compare the effectiveness of acupuncture with traditional

Chinese herbs, conventional therapy, sham acupuncture, and blank control group, respectively. The results indicated that acupuncture was more effective than traditional herbs (RR: 0.08; 95%CI: 0.01, 0.60), conventional therapy (RR: 0.15; 95%CI: 0.04, 0.57), and the blank control group (RR: 0.33; 95%CI: 0.22, 0.51). However, no significant difference was observed between the acupuncture group and the sham acupuncture group (RR: 0.34; 95%CI: 0.06, 2.13). Regarding the pure moxibustion group (Fig. 3-F), it demonstrates effectiveness compared with the blank control group (RR: 0.21; 95%CI: 0.08, 0.52). In the case of acupuncture combined with moxibustion (Fig. 3-G), the experimental group showed a higher effectiveness than the control group (RR: 0.23; 95%CI: 0.14, 0.38). However, in the subgroup analysis (Fig. 3-H), no significant difference was observed between the acupuncture combined with moxibustion group and the acupoint injection group (RR: 0.20; 95%CI: 0.02, 1.61). As for heterogeneity, I^2 was less than 50 % for all comparisons except for the acupuncture group versus the sham acupuncture group ($I^2 = 69$ %). Due to the inclusion of only 2 studies in this subgroup analysis, it was challenging to perform a sensitivity analysis to determine the source of heterogeneity.

In Fig. 4, we compare the differences in Chinese medicine syndrome scores between the experimental group and the control group. In Fig. 4-A, it demonstrates a significant reduction in CMS scores in the acupuncture/moxibustion group compared with the control group (WMD: 18.26; 95%CI: 30.11, −6.41). Similarly, Fig. 4-B shows a notable reduction in CMS scores in the acupuncture group compared with the blank control group (WMD: 17.82; 95%CI: 29.91, −5.72). However, there were no significant differences in CMS scores between the moxibustion group and the blank control group (WMD: 28.86; 95%CI: 88.05, 30.33) as depicted in Fig. 4-C.

In the pooled analysis of PUQE scores, it is observed that the reduction in PUQE scores was more pronounced in the acupuncture/moxibustion group compared with the control group (WMD: 0.85; 95%CI: 1.36, −0.33) as depicted in Fig. 5-A. Similar results are observed in comparison between the acupuncture group and the blank control group (WMD: 2.43; 95%CI: 4.36, −0.5) in Fig. 5-B, the acupuncture group and the sham acupuncture group (WMD: 0.70; 95%CI: 1.21, −0.19) in Fig. 5-C. However, in Fig. 5-D, there are no significant differences between the moxibustion group and the blank control group (WMD: 2.78; 95%CI: 7.54, 1.98).

Nausea scores, evaluated using the visual analogue scale, are presented in Fig. 6. The comparison of nausea scores between the acupuncture group and control group did not show a significant reduction (WMD: 8.44; 95%CI: 26.16, 9.28). However, it is worth noting that there was considerable heterogeneity observed in the analysis of nausea scores ($I^2 = 66$ %).

Adverse events are counted in Fig. 7. In Fig. 7-A, we analyze the accidence of severe adverse events between the acupuncture group

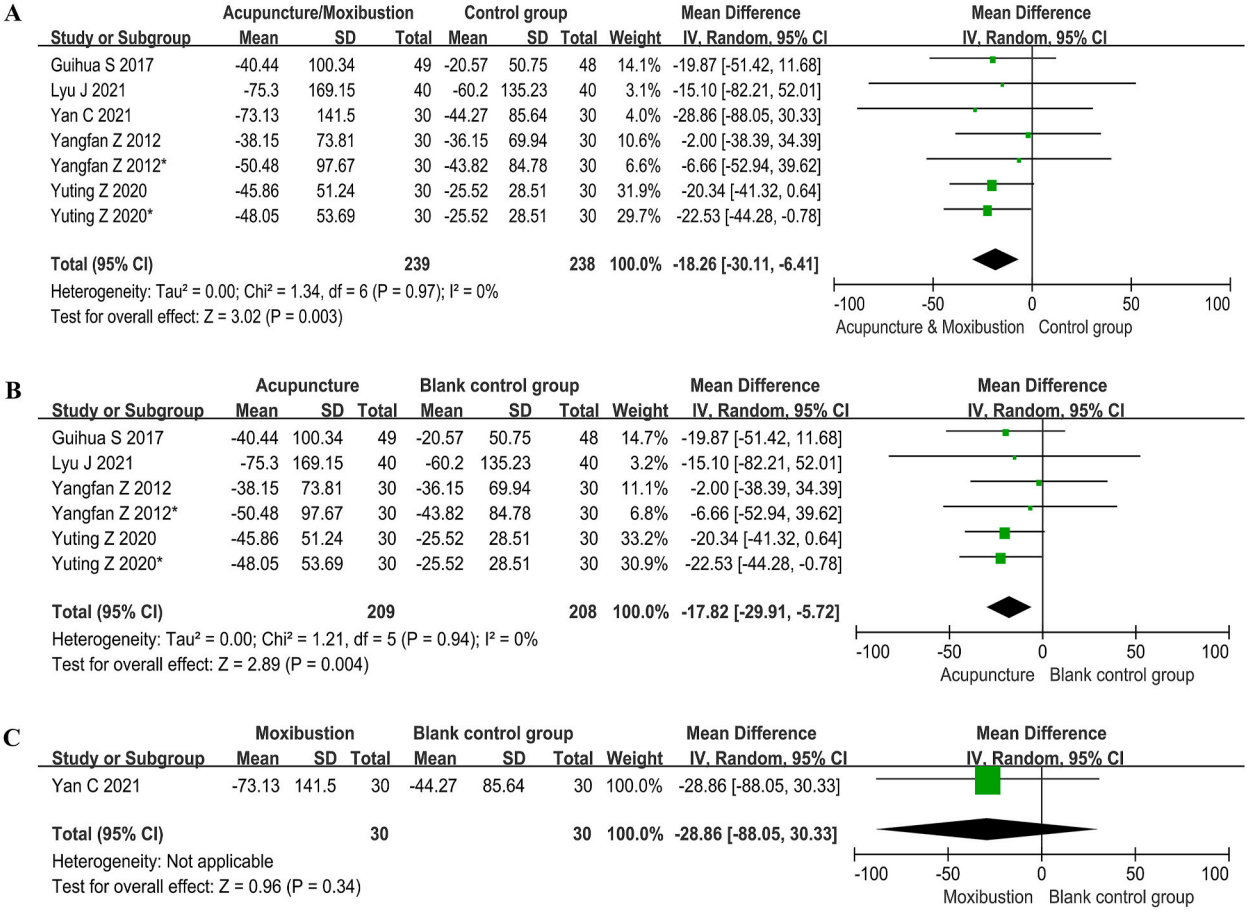


Fig. 4. Forest plot of Chinese medicine syndrome score scale between acupuncture/moxibustion group and control group (A: acupuncture/moxibustion vs. control group; B: acupuncture vs. blank control group; C: moxibustion vs. control group).

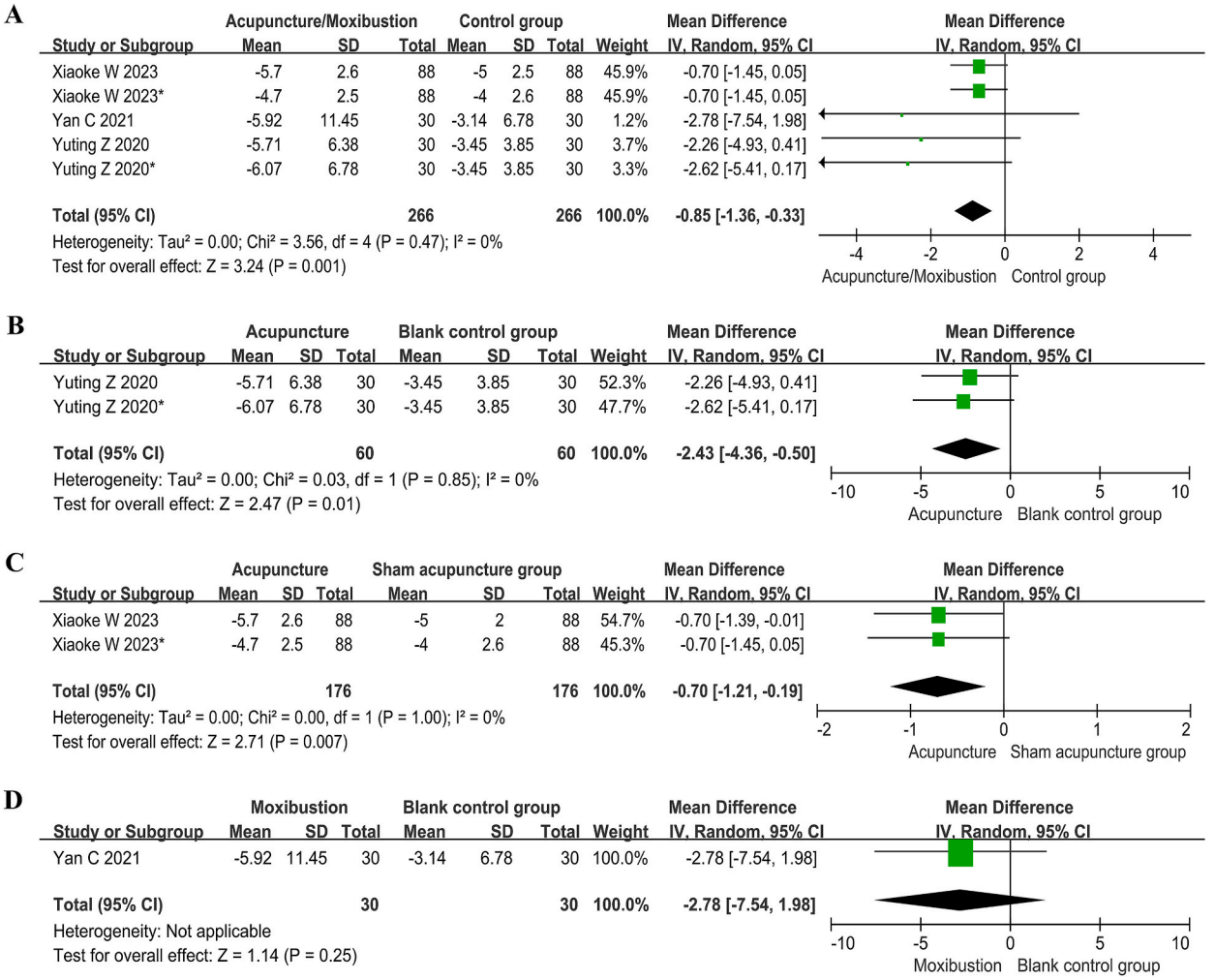


Fig. 5. Forest plot of PUQE between acupuncture/moxibustion group vs. control group (A: acupuncture/moxibustion vs. control group; B: acupuncture vs. blank control group; C: acupuncture vs. sham acupuncture group; D: moxibustion vs. blank control group).

and the control group. The results indicated no significant differences in the incidence of severe adverse events between these groups (RR: 0.77; 95%CI: 0.52, 1.14). Subgroup analysis of severe adverse events also revealed no significant differences between the acupuncture group and the blank control group (RR: 0.61; 95%CI: 0.34, 1.10) (Fig. 7-B), the sham acupuncture group (RR: 1.05; 95% CI: 0.63, 1.73) (Fig. 7-C), or the conventional therapy group (RR: 0.32; 95%CI: 0.06, 1.55) (Fig. 7-D). However, when examining needling-related adverse events, we observed a higher incidence in the acupuncture group compared with the sham acupuncture group (RR: 15.47; 95%CI: 5.30, 45.16) (Fig. 7-E).

3.3. Publication bias

Publication bias was assessed via funnel plot and Egger's test. In Fig. 8, it is observed that there was evident publication bias when

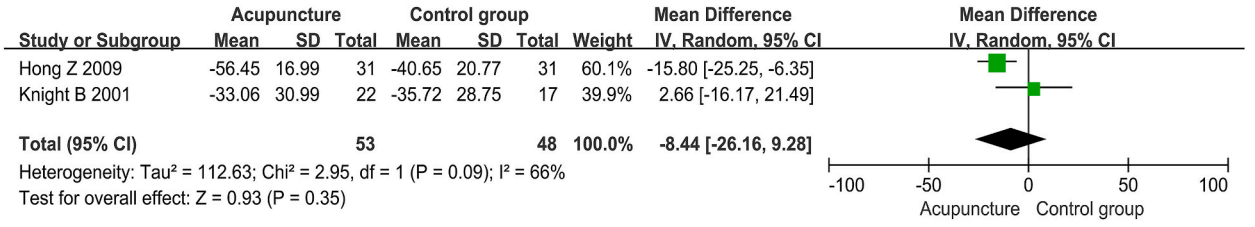
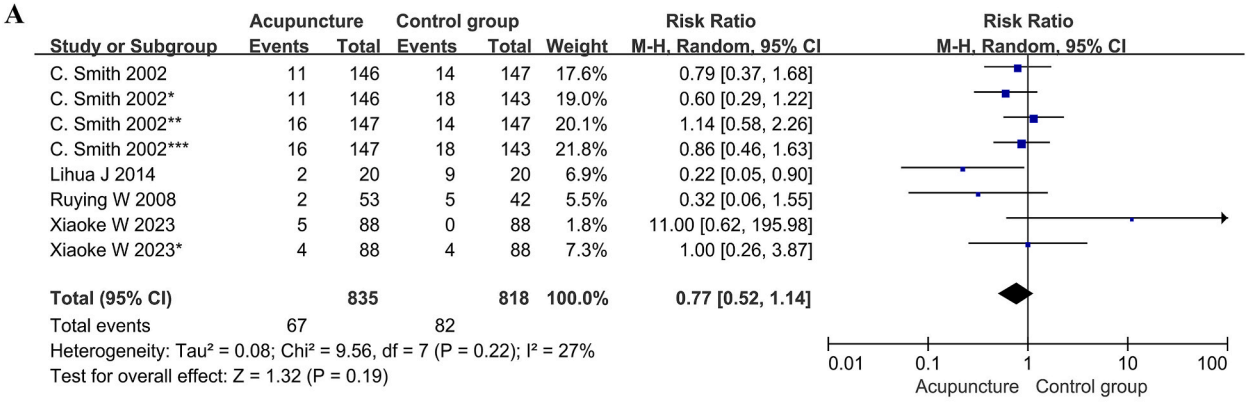
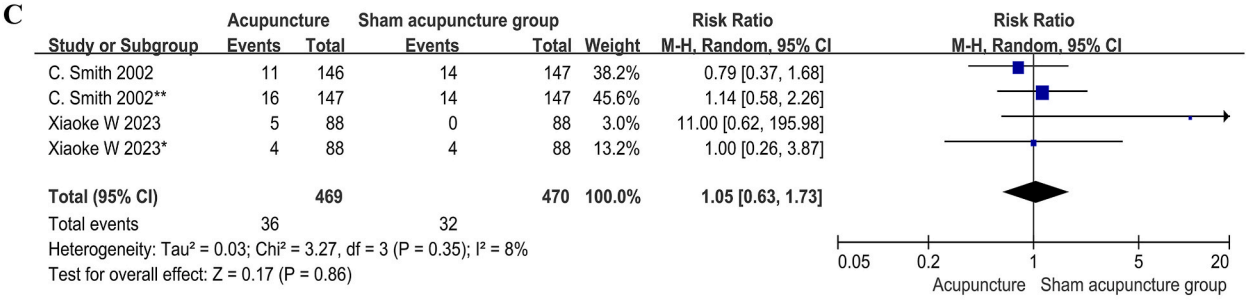
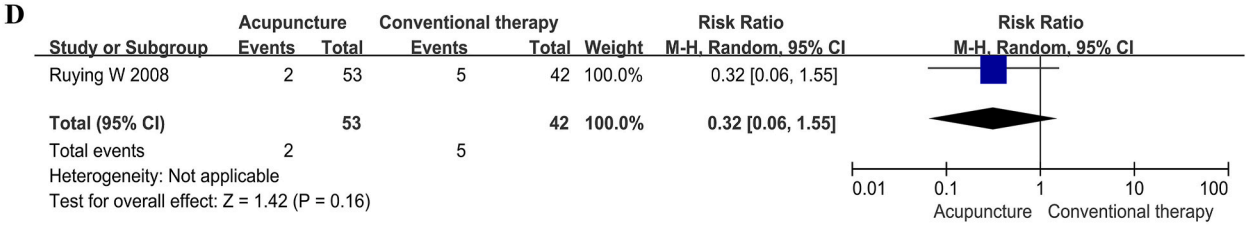


Fig. 6. Forest plot of nausea scores between acupuncture group and control group.







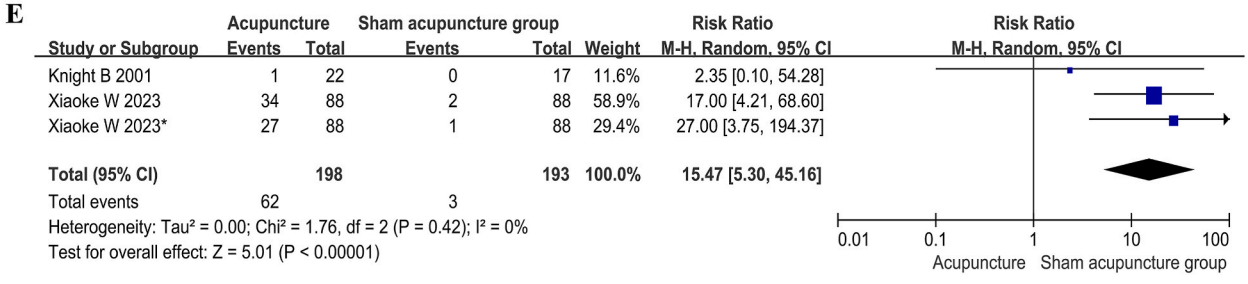


Fig. 7. Forest plot of adverse events between acupuncture group and control group (A: severe adverse events between acupuncture group and control group; B: severe adverse events between acupuncture group and blank control group; C: severe adverse events between acupuncture group and sham acupuncture group; D: severe adverse events between acupuncture group and conventional therapy group; E: needling-related adverse events between acupuncture group and sham acupuncture group).

comparing the ineffective rate between the acupuncture/moxibustion group and the control group (p = 0.002). As for the CMS, no significant publication bias is found in Fig. 9 (p = 0.620). The number of studies involving the PUQE scale and needle-related adverse events was limited. Hence, we only performed Egger's test and p-value was 0.009 and 0.488, respectively. The funnel plot and Egger's test could not be conducted in nausea scale which was evaluated in only two studies. In Fig. 10, it shows that there was no evident publication bias when comparing the incidence of severe adverse events (p = 0.971).

4. Discussion

This meta-analysis included several studies published in Chinese, selected through screening Chinese database. The aim of this study was to evaluate the efficacy and safety of acupuncture and moxibustion for the management of nausea and vomiting during early gestation in pregnant women. The main finding of our analysis suggested that acupuncture and moxibustion could effectively alleviate nausea and vomiting and were relatively safe treatment options for pregnant women. Nevertheless, there was a limited number of studies comparing the efficacy of moxibustion in treating nausea and vomiting. There was no significant difference in efficacy between the acupuncture and the sham acupuncture group. Similar results were observed between the acupuncture combined with moxibustion group and the acupoints injection group. The pooled analysis of various scales yielded substantially consistent results, except for the nausea scale, which may because by the limited number of studies and significant heterogeneity. In terms of adverse events, there was no significant discrepancy in severe adverse events between the acupuncture group and the control group. However, the incidence rate of needle-related adverse events was higher in the acupuncture group compared with the sham acupuncture group. No studies reported adverse events associated with moxibustion in our meta-analysis.

In previous studies, the pathogenesis of NVP had been unclear. The historical hypothesis included hormonal factors, *Helicobacter pylori*, gastrointestinal dysmotility, placenta-related factors, psychosocial factors, and genetics [32]. Generally, ginger, pyridoxine, antihistamines, metoclopramide, promethazine, ondansetron, and corticosteroids may improve symptom [33]. In addition to conventional approaches like fluid replacement, electrolyte balance, and antiemetic agents, there have also been studies exploring complementary and alternative treatments for NVP. Notably, the effectiveness of acupuncture for NVP has yielded inconsistent results across different studies [34]. In traditional Chinese medicine, NVP is believed to be primarily caused by the upward flow of excessive *qi* in the Chong Channel when the blood descends to nourish the fetus. This imbalance results in the inability of the stomach *qi* to descend, leading to nausea and vomiting [35]. Therefore, acupuncture or moxibustion on specific acupoints, which aim to strengthen the spleen and regulate *qi*, theoretically alleviate nausea and vomiting. In previous studies, however, the effect of acupuncture and moxibustion was inconsistent [36–39]. In our meta-analysis, we found that acupuncture was effective in managing NVP when compared with the Chinese traditional herbs, conventional therapy, and blank control groups. In a meta-analysis conducted in patients with chronic nonspecific low back pain [40], researchers found that sham acupuncture was not a true placebo control and might underestimate the efficacy of acupuncture. In our subset analysis comparing acupuncture and sham acupuncture revealed significant heterogeneity (I^2 = 69 %). All data was from the studies conducted by D. Habek in 2004 and Knight B in 2001. The results of these two studies present a paradoxical scenario, and the sample size was limited. These reasons could explain why there was no significant difference between the sham acupuncture groups and the acupuncture groups in our research. As for moxibustion, it was effective when compared with the blank control groups. Pregnant women who received acupuncture combined with moxibustion experienced reduced nausea and vomiting comparing to the control group, while the efficacy was like the acupoints injection group.

According to a systematic review that included 25 studies, the incidence of adverse events during pregnancy evaluated as certainly, probably or possibly causally related to acupuncture was 1.3 % [41]. Needling pain was the most frequent and all severe adverse events were considered unlikely to have been caused by acupuncture [41]. Compared with non-acupuncture-related intervention during pregnancy, adverse events seemed to be mostly minor [42]. A cohort study involving 20,799 pregnant women found no significant difference in the incidence of preterm delivery and stillbirth between the acupuncture group and the control group [43]. Additionally, a RCT with 278 patients suffering from postprandial distress syndrome reported that all adverse events were mild and self-limiting

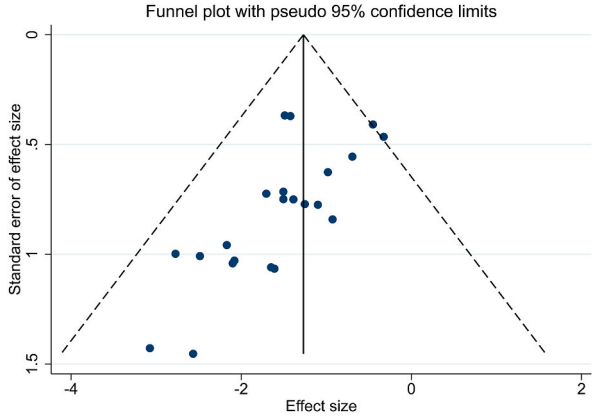


Fig. 8. Funnel plot for ineffective rate between acupuncture/moxibustion group and control group.

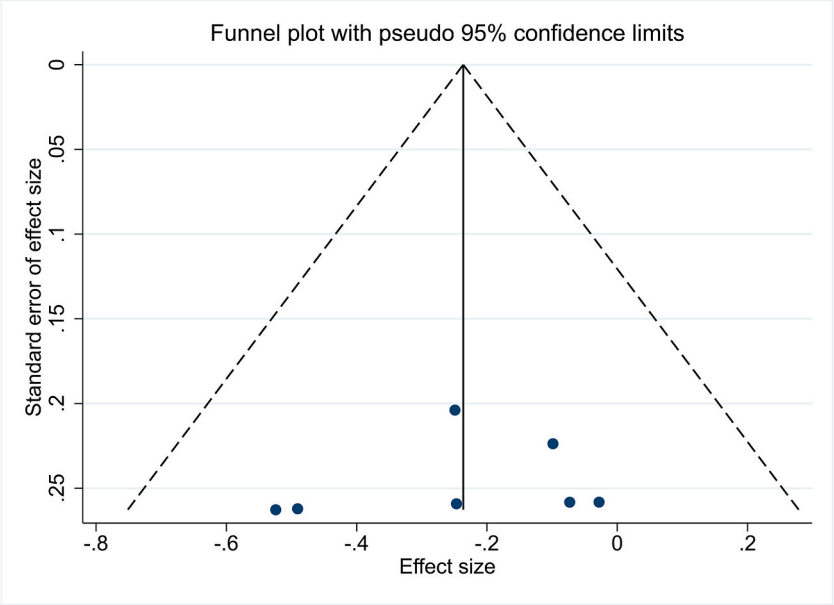


Fig. 9. Funnel plot for Chinese medicine syndrome score scale.

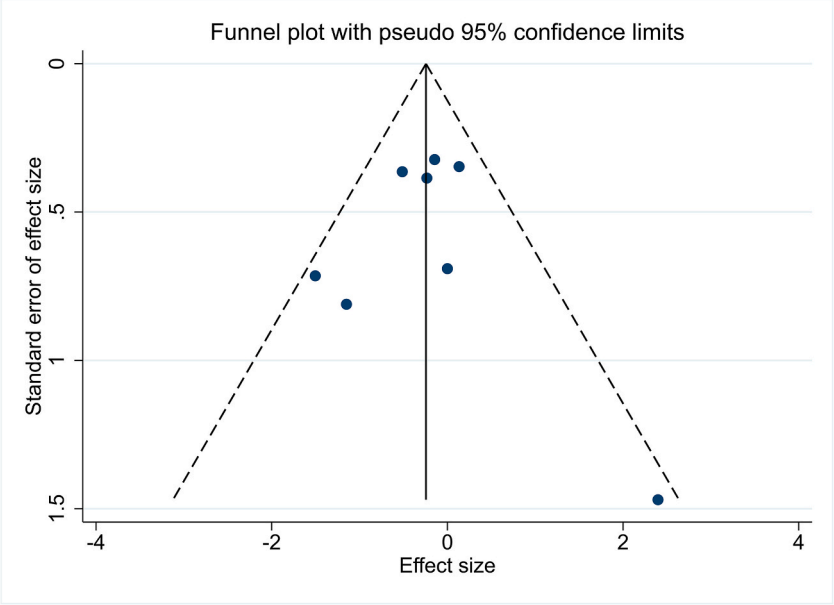


Fig. 10. Funnel plot for the incidence of severe adverse events.

[44]. In our study, we compared the incidence of severe adverse events between the acupuncture group and the control group, which included the blank control group, the conventional therapy group, and the sham acupuncture group. We observed that there was no significant difference in the incidence of severe adverse events between the experimental group and control groups. However, we did observe a higher frequency of needling-related adverse events in the acupuncture group compared with the sham acupuncture group. Similarly, in patients with episodic migraines, researchers found that the incidence of acupuncture-related adverse events, such as bleeding, subcutaneous hemorrhage, severe pain, palpitations, fainting, and local infection, was higher in the acupuncture group compared with the sham acupuncture group (8 % vs. 0 %) [45]. Hence, based on our findings, acupuncture was a relatively safe treatment option with few severe adverse events reported. However, it is unclear why there was a higher incidence of needling-related adverse events in the acupuncture group compared with the sham acupuncture group. It is important to note that this data was primarily derived from Xiaoke Wu's research in our meta-analysis. Thus, further clinical studies focusing on the incidence of

needling-related adverse events are necessary to gain a more comprehensive understanding. Moxibustion had the potential risk of allergy, burn and infection [46]. In a RCT performed in prehypertension and stage I hypertension, the most frequent adverse events of acupuncture were blistering [47]. In our study, there was no RCT reported moxibustion-related adverse events among early pregnant women for alleviating nausea and vomiting.

There are several limitations in our meta-analysis. Firstly, heterogeneity observed among the included studies, which may affect the interpretation of the results. In certain subgroup analysis, the I^2 value exceeded 50 %. Variations in population characteristics, different acupoints, and outcome measures may contribute to the observed heterogeneity. Secondly, the possibility of publication bias must be considered. Studies with negative or insignificant results might not be published and less likely to be included in our analysis. It might introduce a bias in favor of positive outcomes. Thirdly, the potential confounding variables in the original studies might impact the validity of the results, such as different acupoints selection. Thus, long-term cohort studies and randomized control trials are required to confirm the efficacy and safety of acupuncture and moxibustion in early pregnant women.

5. Conclusion

Acupuncture and moxibustion might be effective for the management of nausea and vomiting in early pregnant women. Acupuncture might be a relatively safe treatment option for NVP, as there was no observed increase in severe adverse events. However, needling-related adverse events might go up. The safety of moxibustion was not be assessed due to the limited availability of relevant RCTs.

Funding

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Yao Hu: Writing – original draft, Methodology, Data curation. **Qian Yang:** Writing – original draft, Methodology, Data curation. **Xianjin Hu:** Writing – review & editing, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24439.

References

[1] M.S. Fejzo, O.V. Sazonova, J.F. Sathirapongsasuti, I.B. Hallgrimsdottir, V. Vacic, K.W. MacGibbon, et al., Placenta and appetite genes GDF15 and IGFBP7 are associated with hyperemesis gravidarum, Nat. Commun. 9 (1) (2018) 1178, https://doi.org/10.1038/s41467-018-03258-0.
[2] C.R. Dean, M. Shemar, G.A.U. Ostrowski, R.C. Painter, Management of severe pregnancy sickness and hyperemesis gravidarum, BMJ 363 (2018) 5000, https://doi.org/10.1136/bmj.k5000.
[3] M.S. Fejzo, J. Trovik, I.J. Grooten, K. Sridharan, T.J. Roseboom, A. Vikanes, et al., Nausea and vomiting of pregnancy and hyperemesis gravidarum, Nat. Rev. Dis. Prim. 5 (1) (2019) 62, https://doi.org/10.1038/s41572-019-0110-3.
[4] T. Guttuso Jr., S. Messing, X. Tu, P. Mullin, R. Shepherd, C. Strittmatter, et al., Effect of gabapentin on hyperemesis gravidarum: a double-blind, randomized controlled trial, Am J Obstet Gynecol MFM 3 (1) (2021) 100273, https://doi.org/10.1016/j.ajogmf.2020.100273.
[5] V. London, S. Grube, D.M. Sherer, O. Abulafia, Hyperemesis gravidarum: a review of recent literature, Pharmacology 100 (3–4) (2017) 161–171, https://doi.org/10.1159/000477853.

[6] R. Lindberg, M. Lindqvist, M. Trupp, M.T. Vinnars, M.L. Nording, Polyunsaturated fatty acids and their metabolites in hyperemesis gravidarum, Nutrients 12 (11) (2020), https://doi.org/10.3390/nu12113384.
[7] K.C. Bishop, A.C. Ford, J.A. Kuller, S. Dotters-Katz, Acupuncture in obstetrics and gynecology, Obstet. Gynecol. Surv. 74 (4) (2019) 241–251, https://doi.org/10.1097/ogx.0000000000000655.
[8] S. Shah, L. Godhardt, C. Spofford, Acupuncture and postoperative pain reduction, Curr. Pain Headache Rep. 26 (6) (2022) 453–458, https://doi.org/10.1007/s11916-022-01048-4.
[9] X.K. Wu, J.S. Gao, H.L. Ma, Y. Wang, B. Zhang, Z.L. Liu, et al., Acupuncture and doxylamine-pyridoxine for nausea and vomiting in pregnancy : a randomized, controlled, 2 × 2 factorial trial, Ann. Intern. Med. 176 (7) (2023) 922–933, https://doi.org/10.7326/m22-2974.
[10] Z. Mao, C. Liang, Observation on therapeutic effect of acupuncture on hyperemesis gravidarum, Chin. Acupunct. Moxibustion 29 (12) (2009) 973–976, 0255-976.
[11] H. Zhang, Observation on therapeutic effect of acupuncture and moxibustion on hyperemesis gravidarum, Zhongguo zhen jiu = Chinese acupuncture & moxibustion 25 (7) (2005) 469–470, 0255-470.
[12] D. Habek, A. Barbir, J.C. Habek, D. Janculiak, M. Bobić-Vuković, Success of acupuncture and acupressure of the Pc 6 acupoint in the treatment of hyperemesis gravidarum, Forschende Komplementarmedizin und klassische Naturheilkunde = Research in complementary and natural classical medicine 11 (1) (2004) 20–23, https://doi.org/10.1159/000077192.
[13] C. Smith, C. Crowther, J. Beilby, Pregnancy outcome following women's participation in a randomised controlled trial of acupuncture to treat nausea and vomiting in early pregnancy, Compl. Ther. Med. 10 (2) (2002) 78–83, https://doi.org/10.1054/ctim.2002.0523.
[14] B. Knight, C. Mudge, S. Openshaw, A. White, A. Hart, Effect of acupuncture on nausea of pregnancy: a randomized, controlled trial, Obstet. Gynecol. 97 (2) (2001) 184–188, https://doi.org/10.1016/s0029-7844(00)01152-2.
[15] H. Zhang, L. Gu, Clinical observation on therapeutic effect of acupuncture and moxibustion and acupoint injection on hyperemesis gravidarum to search for a more effective method for treatment of hyperemesis gravidarum, CHINA PRACTICAL MEDICAL 4 (5) (2009) 46–48, https://doi.org/10.3969/j.issn.1673-7555.2009.05.026.
[16] L. Jin, D. Hu, Clinical observation on filiform needling combined with symptomatic and supportive therapy for 20 cases of intractable hyperemesis gravidarum, J. Tradit. Chin. Med. 55 (11) (2014) 939–941, https://doi.org/10.13288/j.11-2166/r.2014.11.011.
[17] G. Shang, J. Liu, B. Qi, J. Liu, H. Li, Effect observation of modified sini san combined with acupuncture for pregnant vomitting patients with the pattern of liver-stomach disharmony, Information on Traditional Chinese Medicine 34 (4) (2017) 113–115, https://doi.org/10.3969/j.issn.1002-2406.2017.04.034.
[18] J. Lyu, R. Wang, Q. Wang, Efficacy of needling eight confluence points combined with press-needle embedding in treating pernicious vomiting due to deficiency of spleen and stomach and its influence to the scores of SAS and SDS, Journal of Clinical Acupuncture and Moxibustion 37 (2) (2021) 32–35, https://doi.org/10.19917/j.cnki.1005-0779.021031.
[19] Y. Zhou, Gastric Tocolysis Soup Combined with Acupuncture Therapy Hyperemesis Gravidarum Incoordination between the Liver and Stomach Syndrome Clinical Observation [Master's Degree], Hunan University of Chinese Medicine, 2012.
[20] H. Xie, Therapeutic observation on acupuncture for hyperemesis gravidarum, Shanghai Journal of Acupuncture and Moxibustion 32 (9) (2013) 734–735, https://doi.org/10.3969/j.issn.1005-0957.2013.09.734.
[21] Y. Zhao, The effect of BaoTai HeYun decoction combined with acupuncture for treatment of hyperemesis gravidarum (original title: 保胎合孕汤联合针刺治疗妊娠剧吐疗效观察) , Journal of Sichuan Traditional Chinese Medicine 35 (2) (2017) 169–170, 1000-170.
[22] G. Yan, D. Lin, The effect of acupuncture at wrist and ankle for hyperemesis gravidarum (original title: 腕踝针辅治妊娠剧吐临床研究), Journal of Practical Traditional Chinese Medicine 36 (5) (2020) 593–594, 1004-594.
[23] Y. Zhao, Observation of the Effect of Press-Acupuncture Therapy on the Patients with Pregnancy Obstruction Due to Spleen and Stomachweakness [Master's Degree], Heilongjiang University of Chinese Medicine, 2020.
[24] Y. Chen, S. Hu, Y. Ning, J. Liao, D. Yu, The effect of huolong moxibustion for treatment of hyperemesis gravidarum with spleen and stomach weakness(original title: 火龙罐治疗脾胃虚弱型妊娠剧吐30例), Chin. Acupunct. Moxibustion 41 (4) (2021) 449–450, https://doi.org/10.13703/j.0255-2930.20200311-k0004.
[25] J. Ma, L. Meng, The effect of acupuncture for hyperemesis gravidarum (original title: 应用俞募配穴法治疗妊娠剧吐30例疗效观察), Journal of Sichuan of Traditional Chinese Medicine 31 (11) (2013) 134–135, 1000-135.
[26] X. Lu, The effect of citicoline combined with moxibustion in the treatment of hyperemesis gravidarum (original title: 胞二磷胆碱联合艾灸治疗妊娠剧吐), Zhejiang JITCWM 22 (10) (2012) 806–807, 1005-807.
[27] Y. Xu, The effect of moxibustion for treatment of hyperemesis gravidarum (original title: 艾灸穴位治疗妊娠剧吐的疗效观察), Today Nurse (9) (2009) 66–67, 1006-6411.
[28] R. Wang, The effect of acupuncture for hyperemesis gravidarum (original title: 取穴位法针刺治疗妊娠剧吐临床观察), Shanxi Med J (2) (2008) 135–136, 0253-9926.
[29] S. Liu, Clinical study on TCM and acupuncture combined treating hyperemesis gravidarum, JOURNAL OF LIAONING UNIVERSITY OF TCM (6) (2007) 145–146, https://doi.org/10.13194/j.jlunivtcm.2007.06.147.liushj.074.
[30] X. Wan, W. Wang, J. Liu, T. Tong, Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range, BMC Med. Res. Methodol. 14 (2014) 135, https://doi.org/10.1186/1471-2288-14-135.
[31] D. Luo, X. Wan, J. Liu, T. Tong, Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range, Stat. Methods Med. Res. 27 (6) (2018) 1785–1805, https://doi.org/10.1177/0962280216669183.
[32] C. Liu, G. Zhao, D. Qiao, L. Wang, Y. He, M. Zhao, et al., Emerging progress in nausea and vomiting of pregnancy and hyperemesis gravidarum: challenges and opportunities, Front. Med. 8 (2021) 809270, https://doi.org/10.3389/fmed.2021.809270.
[33] C. McParlin, A. O'Donnell, S.C. Robson, F. Beyer, E. Moloney, A. Bryant, et al., Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review, JAMA 316 (13) (2016) 1392–1401, https://doi.org/10.1001/jama.2016.14337.
[34] J.R. Niebyl, Nausea and vomiting in pregnancy, N. Engl. J. Med. 363 (16) (2010) 1544–1550, https://doi.org/10.1056/NEJMcp1003896.
[35] N.Q. Jiang, The application of Sanyinjiao (SP 6) for acupuncture treatment of gynecological and obstetrical disorders, Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan 30 (1) (2010) 51–52, https://doi.org/10.1016/s0254-6272(10)60013-1.
[36] J. Xu, I.Z. MacKenzie, The current use of acupuncture during pregnancy and childbirth, Curr. Opin. Obstet. Gynecol. 24 (2) (2012) 65–71, https://doi.org/10.1097/GCO.0b013e32834fead1.
[37] R.C. Boelig, S.J. Barton, G. Saccone, A.J. Kelly, S.J. Edwards, V. Berghella, Interventions for treating hyperemesis gravidarum, Cochrane Database Syst. Rev. 5 (2016), https://doi.org/10.1002/14651858.CD010607.pub2. Cd010607.
[38] A. O'Donnell, C. McParlin, S.C. Robson, F. Beyer, E. Moloney, A. Bryant, et al., Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review and economic assessment, Health Technol. Assess. 20 (74) (2016) 1–268, https://doi.org/10.3310/hta20740.
[39] A. Matthews, D.M. Haas, D.P. O'Mathuna, T. Dowswell, Interventions for nausea and vomiting in early pregnancy, Cochrane Database Syst. Rev. 2015 (9) (2015), https://doi.org/10.1002/14651858.CD007575.pub4. CD007575.
[40] B. Lee, C.Y. Kwon, H.W. Lee, A. Nielsen, L.S. Wieland, T.H. Kim, et al., Needling point location used in sham acupuncture for chronic nonspecific low back pain: a systematic review and network meta-analysis, JAMA Netw. Open 6 (9) (2023) e2332452, https://doi.org/10.1001/jamanetworkopen.2023.32452.
[41] J. Park, Y. Sohn, A.R. White, H. Lee, The safety of acupuncture during pregnancy: a systematic review, Acupunct. Med. 32 (3) (2014) 257–266, https://doi.org/10.1136/acupmed-2013-010480.
[42] C.E. Clarkson, D. O'Mahony, D.E. Jones, Adverse event reporting in studies of penetrating acupuncture during pregnancy: a systematic review, Acta Obstet. Gynecol. Scand. 94 (5) (2015) 453–464, https://doi.org/10.1111/aogs.12587.
[43] H.Y. Moon, M.R. Kim, D.S. Hwang, J.B. Jang, J. Lee, J.S. Shin, et al., Safety of acupuncture during pregnancy: a retrospective cohort study in Korea, BJOG 127 (1) (2020) 79–86, https://doi.org/10.1111/1471-0528.15925.

[44] J.W. Yang, L.Q. Wang, X. Zou, S.Y. Yan, Y. Wang, J.J. Zhao, et al., Effect of acupuncture for postprandial distress syndrome: a randomized clinical trial, Ann. Intern. Med. 172 (12) (2020) 777–785, https://doi.org/10.7326/M19-2880.
[45] S. Xu, L. Yu, X. Luo, M. Wang, G. Chen, Q. Zhang, et al., Manual acupuncture versus sham acupuncture and usual care for prophylaxis of episodic migraine without aura: multicentre, randomised clinical trial, BMJ 368 (2020) m697, https://doi.org/10.1136/bmj.m697.
[46] J.E. Park, S.S. Lee, M.S. Lee, S.M. Choi, E. Ernst, Adverse events of moxibustion: a systematic review, Compl. Ther. Med. 18 (5) (2010) 215–223, https://doi.org/10.1016/j.ctim.2010.07.001.
[47] K.M. Shin, J.E. Park, T.H. Yook, J.U. Kim, O. Kwon, S.M. Choi, Moxibustion for prehypertension and stage I hypertension: a pilot randomized controlled trial, Integr Med Res 8 (1) (2019) 1–7, https://doi.org/10.1016/j.imr.2018.11.002.