

INNOVATIVE AND PATIENT-CENTERED STRATEGIES TO IMPROVE MATERNAL QUALITY OF LIFE AND PERINATAL WELLBEING

Ph.D. Thesis

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***A cheerful heart is good medicine,
but a crushed spirit dries up the bones.***

(Proverbs, 17:22)

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1. LIST OF ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
BMI	Body Mass Index
CI	Confidence Interval
CINEMA	Confidence in Network Meta-Analysis
CS	Cesarean Section
EPDS	Edinburgh Postnatal Depression Scale
HG	Hyperemesis Gravidarum
MD	Mean Difference
NMDAR	N-methyl-D-aspartate Receptor
NVP	Nausea and Vomiting in Pregnancy
NVPQOL	Nausea and Vomiting in Pregnancy Quality of Life
OR	Odds Ratio
PCIA	Patient-Controlled Intravenous Analgesia
PICO	Population–Intervention–Control–Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PUQE	Pregnancy-Unique Quantification of Emesis
RCT	Randomized Controlled Trial
REML	Restricted Maximum Likelihood
RoB2	Risk of Bias 2
ROBVIS	Risk-of-Bias VISualization
SD	Standard Deviation
SEM	Standard Error of the Mean
SSRIs	Selective Serotonin Reuptake Inhibitors
TRD	Treatment-Resistant Depression
VAS	Visual Analog Scale

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to improve the quality of life for women during pregnancy and the postpartum period. To achieve this, my mission is to find innovative solutions that prevent complications in pregnancy and the postpartum period, ensuring healthier outcomes and greater well-being for mothers and their families.



2.2. Scientometrics

Number of all publications:	6
Cumulative IF:	24.5
Av IF/publication:	4.1
Ranking (SCImago):	D1: 3, Q1: 3
Number of publications related to the subject of the thesis:	2
Cumulative IF:	9.4
Av IF/publication:	4.7
Ranking (Sci Mago):	D1: 1, Q1: 1
Number of citations on Google Scholar:	10
Number of citations on MTMT (independent):	5
H-index:	2

The detailed bibliography of the student can be found on pages 53-54.

2.3. Future plans

My future plans involve completing my pediatric specialist training, followed by further specialization in sports medicine. Alongside my clinical work, I will continue mentoring PhD students, fostering their growth in research and practice. I am committed to lifelong learning, refining my skills, and teaching scientific methodology, all while providing compassionate care to children and their families.

3. SUMMARY OF THE THESIS

This PhD thesis addresses two critical maternal health issues: postpartum depression (PPD) and nausea and vomiting in pregnancy (NVP).

The first study, a systematic review and meta-analysis of 14 trials, found that perioperative esketamine significantly reduces PPD risk in women undergoing cesarean sections, with lower depression rates on postpartum days 3–7 (OR = 0.43) and 28–42 (OR = 0.59), and minimal adverse effects like dizziness and hallucinations. The second study, a network meta-analysis of 24 randomized controlled trials, evaluated interventions for NVP, revealing that quince, vitamin B6 with pomegranate and mint, ginger, acupressure, and pharmacological options like dimenhydrinate and doxylamine-pyridoxine effectively reduce symptoms with generally mild side effects.

These findings highlight esketamine as a promising, rapid-acting option for PPD prevention and support the use of both pharmacological and non-pharmacological interventions for NVP. The thesis emphasizes the need for patient-centered, evidence-based care to enhance maternal well-being during pregnancy and postpartum. Future research should focus on long-term safety, dosage optimization, and broader applicability of these interventions.

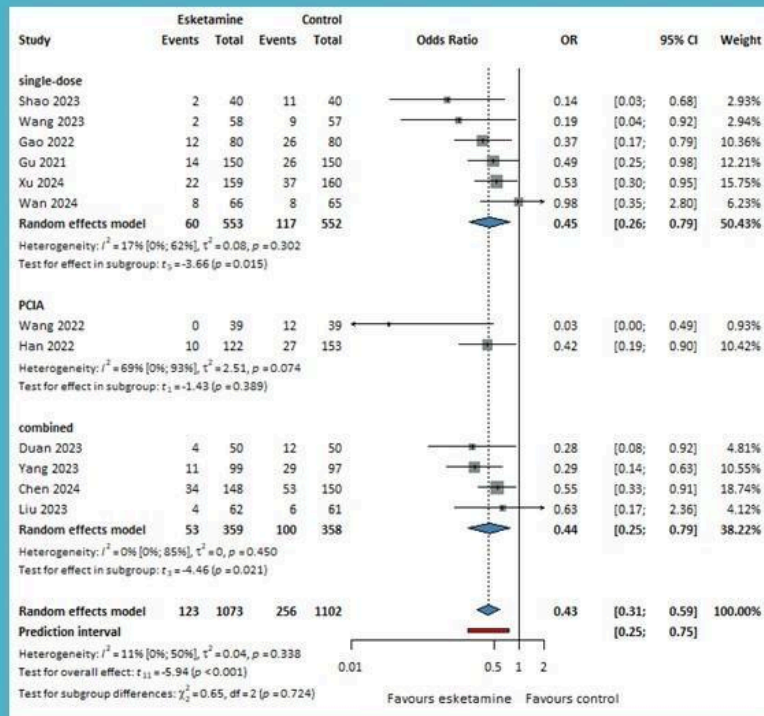
4. GRAPHICAL ABSTRACT

Study 1

Background: Postpartum depression (PPD) affects 14% of new mothers: serious public health concern but no pharmacological prevention known

Methods: Meta-analysis: Rates of PPD and adverse effects, assessment scale scores compared, esketamine vs placebo

Results and conclusions: Esketamine lowers PPD rates and scale scores, is also generally safe



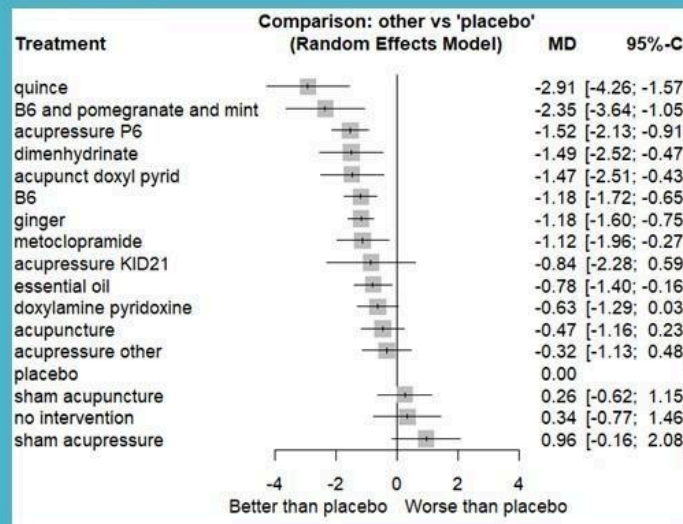
Study 2

Background: Nausea and vomiting in pregnancy (NVP) affects 80% of pregnancies: maternal morbidity and adverse pregnancy outcomes

Many available interventions: no comparative assessment of efficacy and safety so far

Methods: Network meta-analysis of available pharmacological and non-pharmacological interventions: efficacy measured by symptom severity scores

Results and conclusions: Both certain pharmacological and non-pharmacological interventions are effective



5. INTRODUCTION

Maternal health extends far beyond the successful completion of pregnancy and childbirth, encompassing the physical, psychological, emotional, and social well-being of women throughout the entire perinatal period. (Lagadec et al., 2018; Mogos et al., 2013) Pregnancy and the postpartum period represent profound physiological and psychosocial transitions during which women may experience a wide range of symptoms and complications that can substantially affect their quality of life, daily functioning, and family well-being. (Finlayson et al., 2020; "Screening and Diagnosis of Mental Health Conditions During Pregnancy and Postpartum: ACOG Clinical Practice Guideline No. 4," 2023; Vogel et al., 2024) Consequently, modern perinatal care increasingly emphasizes patient-centered approaches that recognize women's individual needs, preferences, and values while promoting safe and effective interventions for both mother and child. Achieving this goal requires innovative, evidence-based strategies that not only prevent or treat maternal complications but also support overall well-being, minimize treatment burden, and facilitate informed clinical decision-making. (Pascuzzi et al., 2025) This thesis contributes to this objective through two complementary research projects: the first investigates perioperative esketamine as a novel strategy for preventing postpartum depression after cesarean section, while the second evaluates the comparative effectiveness and safety of pharmacological and non-pharmacological interventions for nausea and vomiting in pregnancy.

5.1. Study 1

5.1.1. *What is the topic?*

Postpartum depression (PPD) is a form of clinical depression that affects mothers after giving birth, presenting a significant public health concern. The prevalence of PPD is estimated to be 14% worldwide. (Liu et al., 2022) The condition is characterized by emotional, physical, and behavioral symptoms that can profoundly affect the mother and the infant. Symptoms may include persistent sadness, anxiety, fatigue, changes in appetite, suicidal idealization, and sleep disturbances. (Lee et al., 2022; Nguyen et al., 2023) In addition to certain genetic factors, hormonal fluctuations and psychosocial stressors associated with childbirth also contribute to the development of PPD. (Meltzer-Brody, 2011) Untreated PPD can negatively affect the mother-infant bond,

parenting abilities, and overall family dynamics, underscoring the importance of effective treatment and prevention strategies. (Pearlstein et al., 2009) Currently, no pharmacological prevention is known.

Women who have undergone cesarean section (C-section) may face an increased risk of PPD compared to those who have delivered vaginally. (Sadat et al., 2013; Xu et al., 2017) The physical and emotional experience of a C-section, which involves abdominal surgery, can induce specific stressors that contribute to a higher likelihood of developing PPD. In addition, the surgical procedure itself may affect the sense of control of a woman and self-determination during childbirth, potentially contributing to feelings of frustration or anxiety. (Grisbrook et al., 2022)

5.1.2. What is the problem to solve?

The onset of PPD is typically observed within the first six weeks postpartum, although it can manifest at any point within the first year. The trajectory of PPD can vary widely, ranging from episodic depressive episodes to chronic and debilitating symptoms if left untreated. (Miguez & Vazquez, 2023; Xiong et al., 2022) Current prevention and treatment efforts often rely on psychosocial interventions, such as counseling and support networks, and pharmacological treatments, including selective serotonin reuptake inhibitors (SSRIs). (Sockol et al., 2013) However, these approaches face limitations. SSRIs, for example, often require weeks to achieve therapeutic efficacy and may not be suitable during the early postpartum period due to concerns about breastfeeding safety or potential side effects. (Brown et al., 2021) These gaps highlight the need for novel and rapidly acting treatments that can be safely implemented to prevent the progression of PPD.

5.1.3. What is the importance of the topic?

Esketamine, a derivative and enantiomer of ketamine, has emerged as a novel and promising treatment for treatment-resistant depression (TRD), addressing the considerable limitations of current options in efficacy and patient acceptability. Unlike traditional antidepressants targeting serotonin and norepinephrine, esketamine acts on the glutamatergic system, specifically the N-methyl-D-aspartate (NMDA) receptor, offering a novel mechanism of action and a rapid onset of antidepressant efficacy. Studies support the safety, tolerability, and efficacy of esketamine nasal spray,

demonstrating its superiority over existing therapeutic strategies. Furthermore, its effectiveness and later response in patients with comorbidities represent novel and interesting findings, addressing unmet medical needs in this challenging population. (Johnston et al., 2023; Martinotti et al., 2022; Popova et al., 2019; Reif et al., 2023) Administered mainly intranasally, esketamine has shown rapid antidepressant effects, relieving depressive symptoms within hours to days. (Vasiliu, 2023) Although esketamine offers a novel and innovative approach for individuals with treatment-resistant depression, available data confirm its efficacy, safety, and good tolerability; however, it is essential to monitor its administration and consider potential side effects. (Di Vincenzo et al., 2024; Nikayin et al., 2022)

Esketamine may be of particular relevance in the context of PPD. However, it is crucial to approach its use with caution, taking individualized treatment plans into account while assessing potential risks and benefits, especially for lactation considerations of new mothers. (Wolfson et al., 2023) We aimed to evaluate the effectiveness and safety of perioperative esketamine administration for PPD prevention in women undergoing cesarean section.

5.1.4. What would be the impact of our research results?

Previous studies have indicated that esketamine may reduce the short-term risk of PPD following C-sections. However, the evidence is limited, and further research is necessary to clarify esketamine's role in postpartum recovery. (Cao et al., 2024; Hung et al., 2024; Li, Zhou, et al., 2024; B. Ma et al., 2024; S. Ma et al., 2024; Nayyer et al., 2024; Parsaei et al., 2024; J. Wang et al., 2024; Wen et al., 2024; Wong et al., 2024) Several new randomized controlled trials have been published since the last meta-analysis. Therefore, a new systematic review and meta-analysis is needed to provide more comprehensive and reliable insights into this critical area of healthcare.

5.2. Study 2

5.2.1. What is the topic?

Nausea and vomiting in pregnancy (NVP) is a common condition affecting up to 80% of pregnant women, with symptoms typically emerging between the 4th and 9th weeks of gestation and often resolving by the end of the first trimester (Fejzo et al., 2019). While NVP is generally self-limiting, it can range from mild nausea to severe, persistent

vomiting known as hyperemesis gravidarum (HG), which may lead to dehydration, electrolyte imbalances, and weight loss, potentially requiring hospitalization (Lee & Saha, 2011). The condition not only affects maternal health but also has significant psychosocial and economic consequences, including reduced quality of life, increased healthcare utilization, and loss of productivity (Attard et al., 2002). In severe cases, NVP has been associated with adverse pregnancy outcomes such as low birth weight and preterm birth, emphasizing the need for effective management strategies (Lee & Saha, 2011).

5.2.2. *What is the problem to solve?*

Current treatment options for NVP include dietary and lifestyle modifications, pharmacologic therapies, and complementary approaches such as acupuncture and ginger supplementation (Matthews et al., 2014). First-line pharmacologic treatments often include pyridoxine (vitamin B6) and doxylamine, which are effective and safe for managing mild to moderate symptoms (Committee on Practice, 2018; Koren et al., 2010). For more severe cases, antiemetics such as ondansetron, metoclopramide, and promethazine may be prescribed, although concerns regarding their safety profiles persist (Pasternak et al., 2013). Non-pharmacologic interventions, including acupuncture, hypnosis, and cognitive behavioral therapy, have been explored with varying degrees of success (Matthews et al., 2014). Despite the variety of available interventions, there remains no universally accepted treatment protocol, and many pregnant women continue to suffer from inadequately managed symptoms.

5.2.3. *What is the importance of the topic?*

A significant gap exists in our understanding of the safety and efficacy of pharmacologic and non-pharmacologic interventions for NVP, particularly regarding fetal outcomes and long-term maternal health. Concerns about teratogenicity and adverse pregnancy outcomes have led to inconsistent prescribing practices and reluctance among healthcare providers to use certain medications (Pasternak et al., 2013). Additionally, research on the comparative effectiveness of different treatments remains limited, with few high-quality randomized controlled trials (RCTs) assessing the optimal management strategies for NVP across diverse populations. More robust evidence is needed to establish clear guidelines and improve patient-centered care.

5.2.4. What would be the impact of our research results?

Previous systematic reviews and meta-analyses have synthesized available data on the effectiveness and safety of NVP treatments. Yet, they often report heterogeneous findings due to differences in study design, sample size, and outcome measures (Matthews et al., 2014). While some reviews suggest a benefit of ginger and acupressure in mild cases, others highlight insufficient data to draw definitive conclusions on the long-term safety of pharmacological treatments (Boelig et al., 2018). Additionally, many systematic reviews focus on a limited subset of interventions, leaving gaps in comparative effectiveness research. A comprehensive evaluation of existing evidence is necessary to guide clinical practice and inform future research priorities in NVP management.

6. OBJECTIVES

6.1. Study I. – Esketamine reduces the risk of postpartum depression in women undergoing cesarean section: a systematic review and meta-analysis

We aimed to systematically evaluate the efficacy and safety of perioperative esketamine administration in reducing the risk of PPD in women undergoing cesarean C-section. Through a comprehensive systematic review and meta-analysis of RCTs, we sought to determine whether esketamine could lower PPD rates and EPDS scores in the early postpartum period (days 3-7 and 28-42). Additionally, we aimed to assess adverse effects associated with esketamine use to provide evidence-based insights for clinical practice and future guidelines in PPD prevention.

6.2. Study II. – Comparative Effectiveness of Pharmacological and Non-Pharmacological Interventions for Nausea and Vomiting in Pregnancy: A Systematic Review and Network Meta-Analysis

Our objective was to conduct a systematic review and network meta-analysis of RCTs to compare the effectiveness and safety of pharmacological and non-pharmacological treatments for NVP. We evaluated interventions including vitamin B6, ginger, acupressure, acupuncture, dimenhydrinate, and doxylamine-pyridoxine, using validated scales to measure symptom severity, while also assessing adverse effects to inform clinical practice and future guidelines.

7. METHODS

This work was carried out as part of the Systems Education Program at Semmelweis University (Hegyi & Varro, 2024) and conducted within the Translational Medicine (TM) Cycle Framework by the Academia Europaea (Hegyi et al., 2020).

We report our systematic review and meta-analyses based on the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021) (Supplementary Table S1), while following the Cochrane Handbook (Higgins JPT, 2023). The study protocols were registered on PROSPERO (CRD42024548049), and we fully adhered to its guidelines (Booth et al., 2013; Lőrinc Frivaldszky, 2023, 2024).

7.1. Study I.

7.1.1. *Eligibility Criteria*

The following population–intervention–control–outcome (PICO) framework was used: population: women undergoing C-section; intervention: perioperative esketamine; control: placebo or standard of care; outcome: PPD rates, Edinburgh Postnatal Depression Scale (EPDS) scores, adverse effects. (Munn et al., 2018) Studies on patients undergoing cesarean section were included in our analysis if they provided data on the efficacy and safety of esketamine on PPD. Trials, cohort studies, cross-sectional studies, non-randomized controlled trials, and randomized controlled trials (RCTs) were included. Case series, case reports, and reviews were excluded.

7.1.2. *Information Sources and Search Strategy*

Our systematic search was conducted on the 12th of January 2025 in the following databases: CENTRAL, PubMed, EMBASE, Scopus, and Web of Science. Additional studies were searched by citation chasing in the reference lists of selected articles. (Haddaway, 2021) The authors were contacted if we needed further information. For a detailed search key, see Appendix S1.

7.1.3. Study Selection and Data Extraction

Two independent reviewers (LF and KL) screened all titles and abstracts to identify potentially eligible articles. They independently applied the eligibility criteria for final selection with the help of EndNote and Rayyan software tools. (Ouzzani et al., 2016) When discrepancies arose between the two reviewers about the inclusion of articles, they discussed and named the reasons for including or excluding the articles and then made the final decision. Cohen's kappa coefficient was reported to assess inter-rater agreement during the selection and extraction processes. Two independent reviewers (LF and KL) conducted the selection and extraction (using Excel sheet - Office 365, Microsoft, Redmond, WA, USA), and a third independent reviewer (JH) helped to resolve any disagreements. The following data were extracted: (1) study characteristics: first author, year of publication, study design, study population (number, age, BMI, preoperative EPDS scores, operation time, intraoperative blood loss), study period, study country; (2) intervention details (single-infusion dosage, PCIA dosage, time, volume, bolus volume, lockout interval), other drugs in intervention or control groups; (3) main outcomes: PPD rates, EPDS scores; (4) safety outcomes: incidence of adverse effects (nausea and vomiting, dizziness, skin pruritus, hallucinations, nightmares etc.). If not available in written form, data estimates from visual sources were collected using WebPlotDigitizer software. (Rohatgi, 2022)

7.1.4. Risk of Bias and Quality of Evidence Assessment

The risk of bias was assessed with the RoB2 tool and visualized with the ROBVIS tool. (Higgins JPT, 2023; McGuinness & Higgins, 2021; Sterne et al., 2019) Two independent reviewers (LF and KL) performed the assessment, and an independent third investigator resolved disagreements (MK). Small study publication bias was assessed by visual inspection of the funnel plots for more than ten studies, and a modified Egger's test was conducted when appropriate. Quality assessment of the included studies was performed using GRADE-Pro, as recommended by the Cochrane Collaboration. (Higgins JPT, 2023; Schünemann H, 2013)

7.1.5. Data Synthesis and Analysis

Both qualitative and quantitative synthesis of the data was performed. The minimum number of studies required to conduct a meta-analysis was three. As considerable

between-study heterogeneity was assumed in all cases, a random-effects model was used to pool effect sizes.

For dichotomous outcomes (post-partum depression prevalence at different follow-up times and adverse events), odds ratios (OR) with a 95% confidence interval (CI) were used as effect size measures. To calculate study odds ratios and pooled odds ratios, the number of patients and those with the event of interest in each group separately (hereafter referred to as “raw data”) was extracted or calculated from the studies where available. The results show the odds of an event of interest in the experimental group compared with the odds of an event of interest in the control group. In addition, absolute rates of adverse events were calculated by pooling reported event rates using random intercept logistic regression models. The potential effect of the way of esketamine administration was explored by means of subgroup analysis.

The Pooled OR calculation based on raw data was performed using the Mantel-Haenszel method. (Mantel & Haenszel, 1959; Robins et al., 1986) The exact Mantel-Haenszel method was used to manage zero-cell counts (Cooper, 2009). For a cell count of 0, an individual study OR with a 95% CI was calculated by adding 0.5 as a continuity correction (it was used only for visualization on a forest plot). The inverse variance weighting method was used to calculate the pooled OR (based on directly given OR without raw data). To estimate the heterogeneity variance measure (τ^2), the Paule-Mandel method (Paule & Mandel, 1989), recommended by Veroniki et al. (Veroniki et al., 2016), was used with the Q profile method for confidence intervals.

For continuous outcomes (EPDS scores at different follow-up times), the mean difference (MD) between intervention and control was used as an effect size measure with a 95% CI. To calculate study MDs and pooled MDs, the sample size, the mean, and the corresponding standard deviation (SD) were extracted from each study (for each group separately). If only quartiles were reported, we estimated the mean and SD, assuming normality. If the SD was not provided, but the SEM was available instead, the SD was calculated as SEM multiplied by the square root of the sample size. The mean values of the control group were subtracted from the mean values of the experimental group. The inverse variance weighting method was used to calculate the pooled MD. To estimate the heterogeneity variance measure (τ^2), we used the restricted maximum-likelihood estimator with the Q profile method for CIs (Harrer et al., 2021;

Veroniki et al., 2016). The t-distribution-based method was used for the CI of MD calculation of individual studies.

Results were considered statistically significant if the pooled CI did not contain the null effect value. We summarized the findings of the meta-analysis on forest plots. Where applicable, and where the study number was sufficiently large and not too heterogeneous. We also reported the prediction intervals of the results (i.e., the expected range of effects of future studies). In addition, between-study heterogeneity was described by Higgins & Thompson's I^2 statistics (Higgins & Thompson, 2002). Small study publication bias was assessed by visual inspection of Funnel-plots and by calculating Peters (modified Egger's) test p-value (Peters et al., 2006) for raw data OR and classic Egger's test p-value (Egger et al., 1997) for MD. We kept in mind that the test had limited diagnostic assessment below 10 studies. Potential outlier publications were explored using different measures of influence and plots as recommended by Harrer et al. (Harrer et al., 2021).

All statistical analyses were performed with R (R Core Team 2021, v4.1.2) using the meta (Schwarzer, 2007) package for basic meta-analysis calculations and plots and the dmetar (Harrer, 2019) package for additional influential analysis calculations and plots. Lou and Shi methods were used (Luo et al., 2018; Shi et al., 2020) to estimate the mean and SD from quartiles. We used a Hartung-Knapp correction (IntHout et al., 2014; Knapp & Hartung, 2003) for CIs. This correction was applied only when it was more conservative than the classic one (as recommended by Jackson et al., 2017).

7.2. Study II.

7.2.1. Eligibility Criteria

The study followed a population–intervention–control–outcome (PICO) (Munn et al., 2018) framework—population: pregnant women with NVP; intervention: different pharmacological and non-pharmacological interventions against NVP; control: placebo; outcome: efficacy measures [Pregnancy-Unique Quantification of Emesis (PUQE) scores—assessing the severity of nausea and vomiting symptoms; Visual-Analog Scale (VAS) scores—assessing subjective symptom severity; Nausea and Vomiting in Pregnancy Quality Of Life (NVPQOL) scores—assessing the impact of symptoms on quality of life; Rhodes-index scores, number of vomiting episodes] and adverse effects.

Studies reported different pharmacological and non-pharmacological interventions for NVP, comprising RCTs. Excluded were cohort studies, cross-sectional studies, non-randomized controlled trials, case series, case reports, animal studies, conference abstracts, and reviews.

7.2.2. Information Sources and Search Strategy

Our systematic search was conducted in Cochrane Central Register of Controlled Trials (CENTRAL), Medline (via PubMed), and Embase on the 28 May 2024. No filters or other restrictions were applied. For detailed search terms (see Supplementary S1). Our search key consisted of three domains regarding clinical condition, population, and study type.

7.2.3. Study Selection and Data Extraction

Two independent reviewers (ZK and CK) screened titles and abstracts for eligibility using EndNote (EndNote 20, 2013, Clarivate, PA, USA) and Rayyan software (Ouzzani et al., 2016). Discrepancies were resolved by a third reviewer (LF), and Cohen's kappa coefficient was reported to assess inter-rater agreement.

Data selection and extraction were performed by two independent reviewers (ZK and CK) using Excel (Office 365, Microsoft, Redmond, WA, USA), with a third reviewer (FL) resolving disagreements. Extracted data included: (1) study characteristics: author, year, country of origin, population details (number, age, BMI, parity, gestational week); (2) intervention details (intervention type, dosage, time) and other drugs; (3) primary outcomes: PUQE, VAS, NVPQOL, Rhodes-index scores, number of vomiting episodes; and (4) safety outcomes: adverse effects. Data from visual sources were estimated using WebPlotDigitizer software (Rohatgi, 2022). All scales used in our final analysis (PUQE, VAS, Rhodes-index) were subjective assessment questionnaires measuring the intensity of NVP symptoms, with lower scores indicating less severe symptoms and higher scores indicating more severe symptoms. Minimum and maximum of scores were: PUQE (3–15), VAS (0–10), Rhodes-index (0–32) (Laitinen et al., 2022; Meek et al., 2009; Yamada et al., 2022; Zhou et al., 2001).

7.2.4. Risk of Bias and Quality of Evidence Assessment

The risk of bias was assessed using the RoB2 tool and visualized with the Risk-of-bias VISualization (ROBVIS) tool (Higgins JPT, 2023; McGuinness & Higgins, 2021;

Sterne et al., 2019). Two reviewers (LF and CK) conducted assessments, with a third reviewer (MO) resolving disagreements. The CINEMA (Confidence in Network Meta-Analysis) assessment was used to evaluate the certainty of evidence in network meta-analyses (Nikolakopoulou et al., 2020; Papakonstantinou et al., 2020).

7.2.5. Data Synthesis and Analysis

The different scales used to report nausea and vomiting scores shared similar definitions of minimum and maximum scores, which made it possible to harmonize all scores onto a 0–10 scale, where 0 indicated no discomfort and 10 the worst nausea imaginable.

This enabled the use of mean differences (MDs) as the effect size for antiemetic treatment efficiency. Also, we grouped the reduction in nausea scores by follow-up time into “one-week follow-up” and “one-month follow-up”.

Control conditions were categorized as placebo, sham intervention, or no intervention and modeled as separate nodes, as these comparators were considered to differ in both contextual (expectation-related) and potential physiological effects.

The inclusion of only RCTs allowed us to perform a network meta-analysis using a frequentist approach. Network meta-analysis enables the comparison of multiple interventions by integrating direct and indirect evidence across a connected network of interventions. For each pairwise comparison, we calculated MDs and their 95% confidence intervals (CIs). We used random-effects modeling since we expected considerable between-study heterogeneity. The variance component was estimated using restricted maximum likelihood (REML).

To evaluate the transitivity assumption, we systematically compared the distribution of key clinical and methodological effect modifiers—including symptom severity, gestational age, and intervention protocols—across all included studies. This qualitative assessment ensured that the studies were sufficiently comparable in terms of population characteristics, interventions, and outcomes, thereby supporting the validity of indirect comparisons in our network meta-analysis.

Multi-arm studies were included using multi-arm correction methods to ensure accurate variance estimates. Treatments were ranked using the P-score metric, which quantifies the certainty that an intervention is better than another based on point estimates and standard errors (Rucker & Schwarzer, 2015).

Diagnostics for consistency and reliability included netsplit analysis, direct evidence proportion plots, minimal parallelism plots, and mean path length plots. These methods evaluated the robustness of the effect size estimates by distinguishing between direct and indirect evidence. Small study publication bias was assessed using funnel plots and a modified Egger's test.

The results were visualized using forest plots (where interventions are compared to a reference, in our case, "placebo"), league tables (where the upper triangle shows direct pairwise comparisons, while the lower triangle shows the results of network meta-analysis), network graphs (where circles at the vertices represent intervention arms, and edges represent direct comparisons), and rank plots (where treatments are ranked based on the aforementioned P-score metric), providing a comprehensive summary of the intervention comparisons. Netpairwise plots were used to visualize all direct comparisons, with pooled estimates for comparisons involving at least three studies. All analyses were performed in R using the meta (Guido Schwarzer, 2015), netmeta (Balduzzi S, 2023), and dmetar (Harrer et al., 2021) packages.

8. RESULTS

8.1. Study I

8.1.1. *Study Search and Selection*

Altogether, 2681 studies were found in our systematic search. After duplicate removal, 1336 records were screened based on the abstract. We excluded 1320 records and retrieved 16 reports to be assessed based on their full texts. (Baiqing et al., 2023; Chen et al., 2024; Gu Pan, 2021; Guo et al., 2023; Han et al., 2022; Hui et al., 2023; Li, Zhuo, et al., 2024; Liu et al., 2023; Shen et al., 2022; Wan et al., 2024; Q. Wang et al., 2022; Wang et al., 2023; W. Wang et al., 2022; Xu et al., 2024; Yang et al., 2023; Zhang et al., 2021) Out of 16 reports, we found 14 eligible articles; 2 were excluded (one retracted article (Q. Wang et al., 2022), one inappropriate data reporting and high risk of bias (Shen et al., 2022)). Furthermore, we identified three eligible studies through citation chasing. (Chi et al., 2022; Gao et al., 2022; Haddaway, 2021; Shao, 2023) A summary of the selection process is shown in Figure S1. Cohen's kappa values were 0,9 and 1, respectively.

8.1.2. *Basic Characteristics of Studies Included*

The baseline characteristics of the analyses included are detailed in Table S1. All studies analyzed were from China. They used single-infusion (Chi et al., 2022; Gao et al., 2022; Gu Pan, 2021; Shao, 2023; Wan et al., 2024; Wang et al., 2023; Xu et al., 2024; Zhang et al., 2021) or patient-controlled intravenous analgesia (Guo et al., 2023; Han et al., 2023; W. Wang et al., 2022) to administer esketamine perioperatively; some used both (Baiqing et al., 2023; Chen et al., 2024; Liu et al., 2023; Yang et al., 2023). In some studies, other pharmacological agents were administered with esketamine, including tramadol (Guo et al., 2023; Wan et al., 2024), sufentanil (Baiqing et al., 2023; Chen et al., 2024; Chi et al., 2022; Gu Pan, 2021; Han et al., 2022; Hui et al., 2023; Li, Zhuo, et al., 2024; Liu et al., 2023; Wan et al., 2024; W. Wang et al., 2022; Xu et al., 2024; Yang et al., 2023), ropivacaine (Zhang et al., 2021), tropisetron (Chi et al., 2022; Han et al., 2022; Li, Zhuo, et al., 2024), ondansetron (Baiqing et al., 2023; Hui et al., 2023; Liu et al., 2023), palonosetron (Chen et al., 2024), butorphanol (Gu Pan, 2021; Guo et al., 2023; Shao, 2023), metoclopramide (Gu Pan, 2021) or totanisoltron (W. Wang et al., 2022). Esketamine dosages ranged from 0.2 mg/kg to 2 mg/kg. In addition, biometric

data (age, BMI) and other important confounding factors, such as preoperative EPDS scores, operation times, and blood loss, were collected (see Table S1).

8.1.3. Primary Outcome – Rate of Depression

Twelve studies reported rates of depression on at least one follow-up date. On postpartum days 3-7, patients receiving esketamine had significantly lower rates of PPD, see Figure 1 (OR = 0.43; 95% CI: 0.31-0.59; $p < 0.001$; $I^2 = 11\%$). Subgroups receiving esketamine in single-dose or single-dose combined with PCIA had significantly lower rates of PPD on postpartum days 3-7 (OR = 0.45; 95% CI: 0.26-0.79; $p = 0.015$; $I^2 = 17\%$; and OR = 0.44; 95% CI: 0.25-0.79; $p = 0.021$; $I^2 = 0\%$; respectively). On postpartum day 14, no significant differences could be observed, see Figure S2 (OR = 0.55; 95% CI: 0.17-1.74; $p = 0.156$; $I^2 = 37\%$). On postpartum days 28-42, patients in the intervention group had significantly lower rates of PPD, see Figure 2 (OR = 0.59; 95% CI: 0.39-0.87; $p = 0.014$; $I^2 = 33\%$). Only one study reported data on further follow-up dates. (Liu et al., 2023) Sensitivity analysis showed no clear outliers in this outcome; see Figures S3-S5.

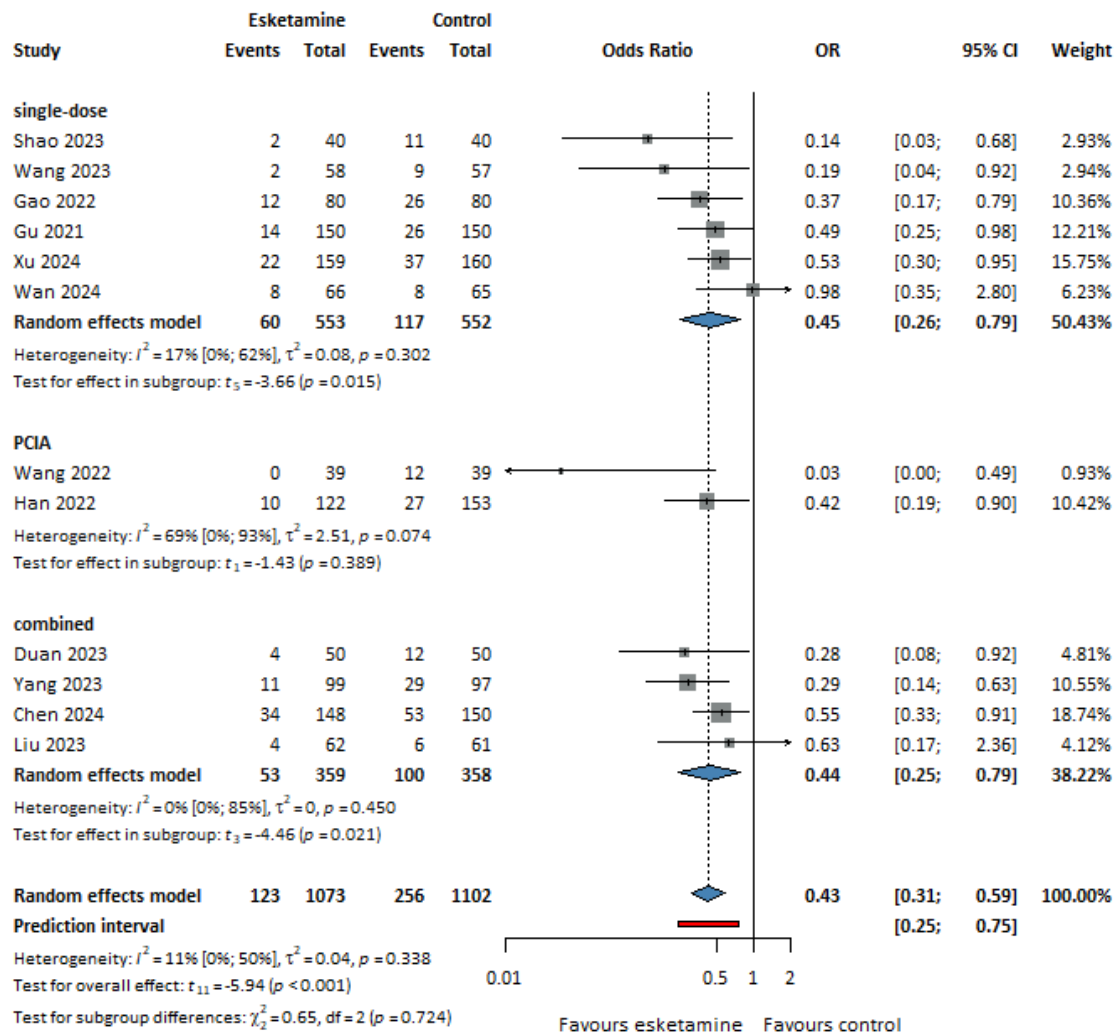


Figure 1. Odds ratio for PPD in women undergoing CS receiving esketamine vs. controls, days 3-7 (PPD: postpartum depression; CS: cesarean section; PCIA: patient-controlled intravenous analgesia; OR: odds ratio; CI: confidence interval)

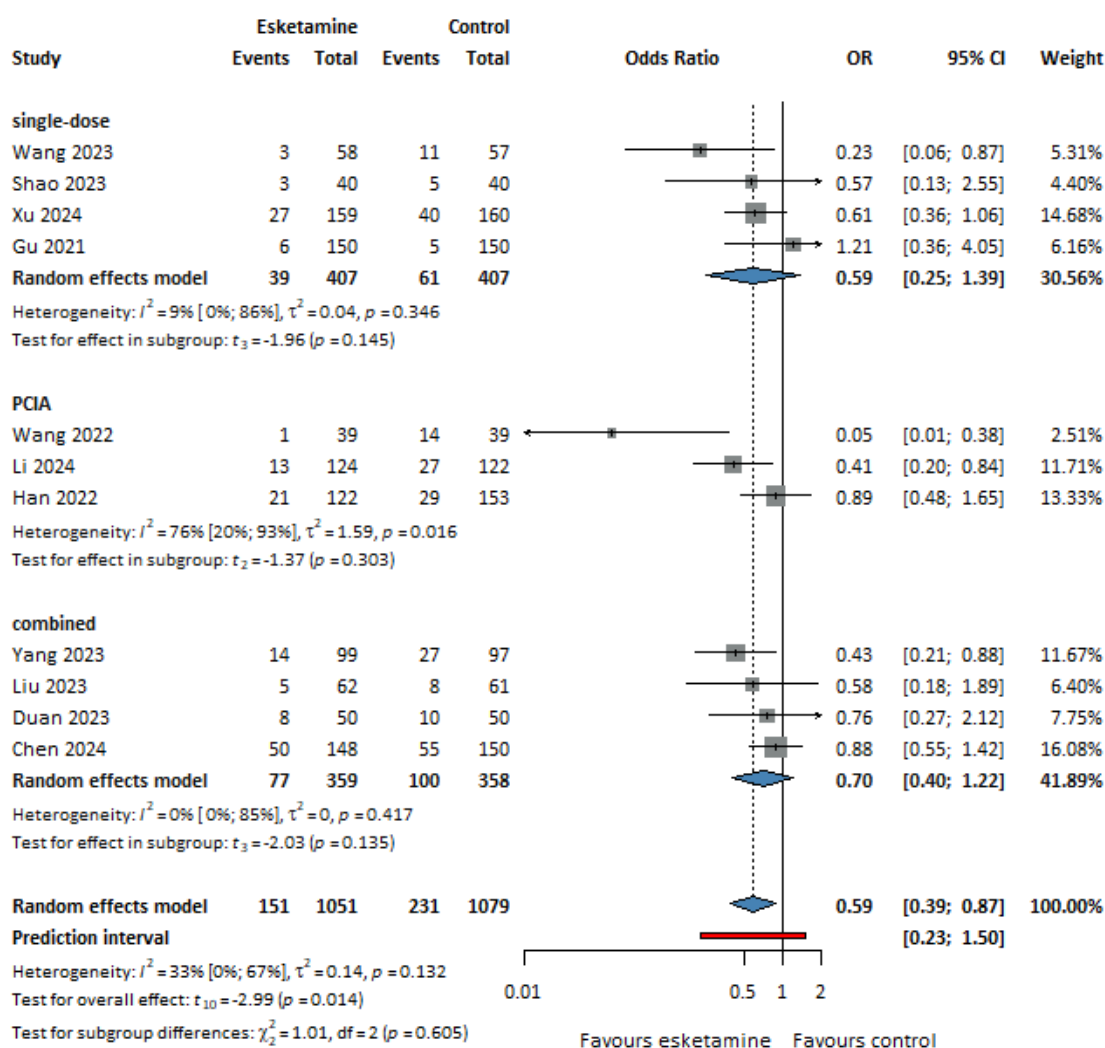


Figure 2. Odds ratio for PPD in women undergoing CS receiving esketamine vs. controls, days 28-42 (PPD: postpartum depression; CS: cesarean section; PCIA: patient-controlled intravenous analgesia; OR: odds ratio; CI: confidence interval)

8.1.4. Secondary Outcome – EPDS Scores

Nine studies reported scores on the Edinburgh Postnatal Depression Scale. Patients receiving esketamine had significantly lower scores on postpartum days 3-7; see Figure 3 (MD = -1.32; 95% CI: -1.84 - -0.80; $p < 0.001$; $I^2 = 80\%$). An explicit time dependence could be described based on this outcome as EPDS scores on postpartum days 28-42 did not significantly differ (MD = -0.93; 95% CI: -2.02 – 0.16; $p = 0.078$; $I^2 = 88\%$); see Figure S6. Only one study reported data on further follow-up dates. (Liu et al., 2023) Sensitivity analysis showed no clear outliers in this outcome; see Figures S7-S8.

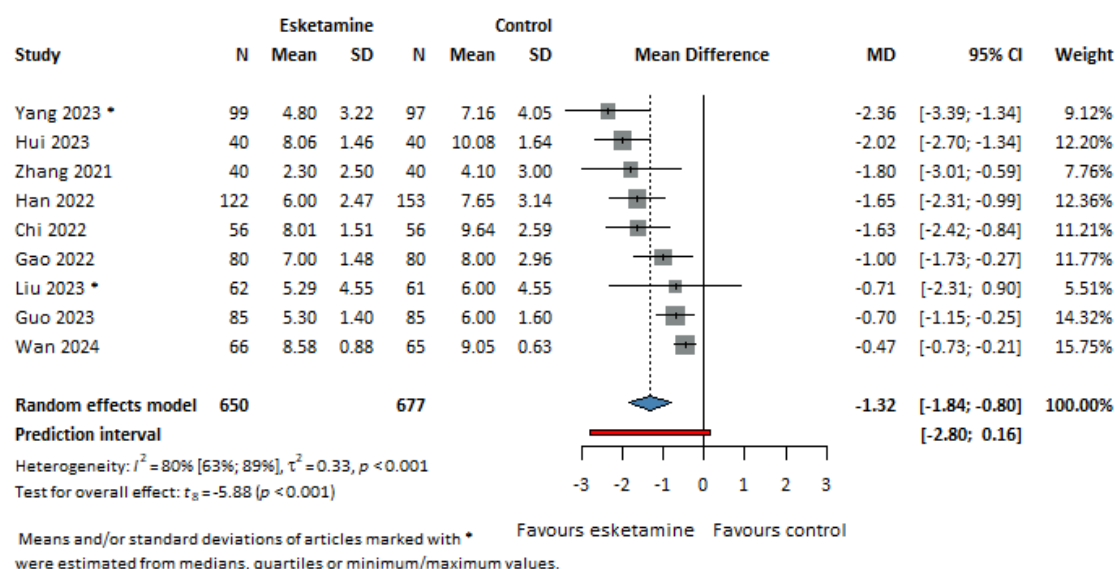


Figure 3. Mean differences for EPDS in women undergoing CS receiving esketamine vs controls, days 3-7 (EPDS: Edinburgh Postnatal Depression Scale; CS: cesarean section; MD: mean difference; CI: confidence interval)

8.1.5. Secondary Outcome – Adverse Effects

All studies analyzed reported specific intraoperative and postoperative adverse effects. Meta-analysis could be performed for nine of them (see Figure 4): nausea and vomiting (OR = 0.65; 95% CI: 0.32-1.30; $p = 0.205$; $I^2 = 68\%$), dizziness (OR = 3.66; 95% CI: 1.24-10.82; $p = 0.022$; $I^2 = 78\%$), skin pruritus (OR = 0.58; 95% CI: 0.31-1.06; $p = 0.064$; $I^2 = 0\%$), shivers (OR = 0.68; 95% CI: 0.01-42.98; $p = 0.726$; $I^2 = 52\%$), hallucinations (OR = 6.41; 95% CI: 2.07-19.82; $p = 0.006$; $I^2 = 0\%$), nightmares (OR = 0.95; 95% CI: 0.33-2.74; $p = 0.893$; $I^2 = 0\%$), headache (OR = 1.16; 95% CI: 0.26-5.14; $p = 0.702$; $I^2 = 0\%$), drowsiness (OR = 2.61; 95% CI: 0.70-9.72; $p = 0.131$; $I^2 = 43\%$) and diplopia (OR = 3.87; 95% CI: 0.05-274.75; $p = 0.305$; $I^2 = 0\%$), respectively. Dizziness and hallucinations were the only adverse effects that appeared at a significantly higher rate in women receiving esketamine. However, their proportion was low overall in the intervention group (0.13 and 0.03, respectively), see Figures S9-S35. No subgroup differences regarding adverse effects could be observed.

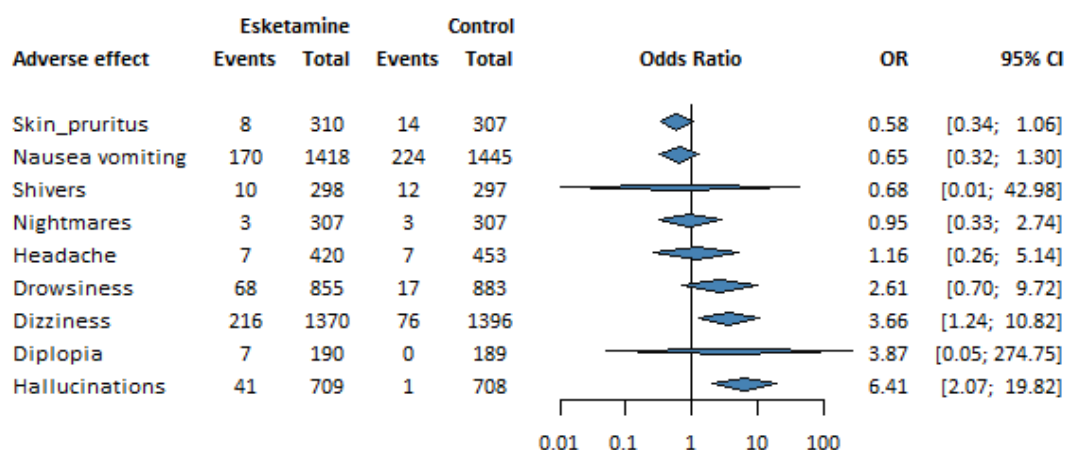


Figure 4. Odds ratios for adverse effects in women undergoing CS receiving esketamine vs. controls (CS: cesarean section; OR: odds ratio; CI: confidence interval)

8.1.6. Risk of Bias Assessment

Most of the outcomes of the studies included in the meta-analysis were rated as having a low or moderate risk of bias. The risk of bias was low for one and moderate for two outcomes of studies included in the meta-analysis. Most concerns emerged in the domains related to outcome measurement and reporting, mainly due to varying definitions of PPD. The risk of bias assessment of our primary outcome is shown in Figure 5; for all other outcomes, see Figures S36-S37.

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Han 2022	+	+	+	-	-	-
	Liu 2023	+	+	+	-	-	-
	Wang 2022	+	+	+	-	-	-
	Wang 2023	+	+	+	-	-	-
	Yang 2023	+	-	+	-	+	-
	Chen 2024	+	+	+	-	-	-
	Xu 2024	+	-	+	-	-	-
	Gu 2021	+	+	+	-	-	-
	Gao 2022	+	+	+	+	+	+
	Shao 2023	+	-	+	-	-	-
	Duan 2023	+	+	+	-	-	-
	Wan 2024	+	+	+	+	+	+
Domains:							Judgement
D1: Bias arising from the randomization process.							- Some concerns
D2: Bias due to deviations from intended intervention.							+
D3: Bias due to missing outcome data.							Low
D4: Bias in measurement of the outcome.							
D5: Bias in selection of the reported result.							

Figure 5. Results of risk of bias assessment of primary outcome (postpartum depression rates)

8.1.7. Publication Bias and Heterogeneity

Due to the low number of studies included per subgroup, publication bias was only investigated by visual inspection. Significant publication bias could not be observed in any analyzed outcomes, see Figures S38-S42. Heterogeneity was relatively high for all outcomes due to differences in baseline characteristics of study participants, differences in interventions, or differences in definitions and measurements of outcomes.

8.1.8. *Quality of Evidence*

The quality of evidence for all outcomes was rated as moderate; see Table S2. As our analysis relied on RCTs, the risk of bias was relatively low. However, it is essential to note that the generalizability of our findings is limited, as the studies analyzed included only Chinese centers. Therefore, drawing conclusions for the global population may be challenging. In addition, different definitions and cut-off values for PPD assessment may be of concern.

8.2. Study II

8.2.1. Search and Selection

A total of 9844 studies were identified in our systematic search. After duplicate removal, 7900 records were screened based on the title and abstract. We excluded 7715 records and retrieved 185 reports to be assessed based on their full texts. Out of 185 reports, we found 24 eligible articles; 161 were excluded, mainly due to not matching PICO, ineligible study type, or inappropriate data reporting. A summary of the selection process is shown in Figure 6. Cohen's kappa values were 0.91 and 0.99.

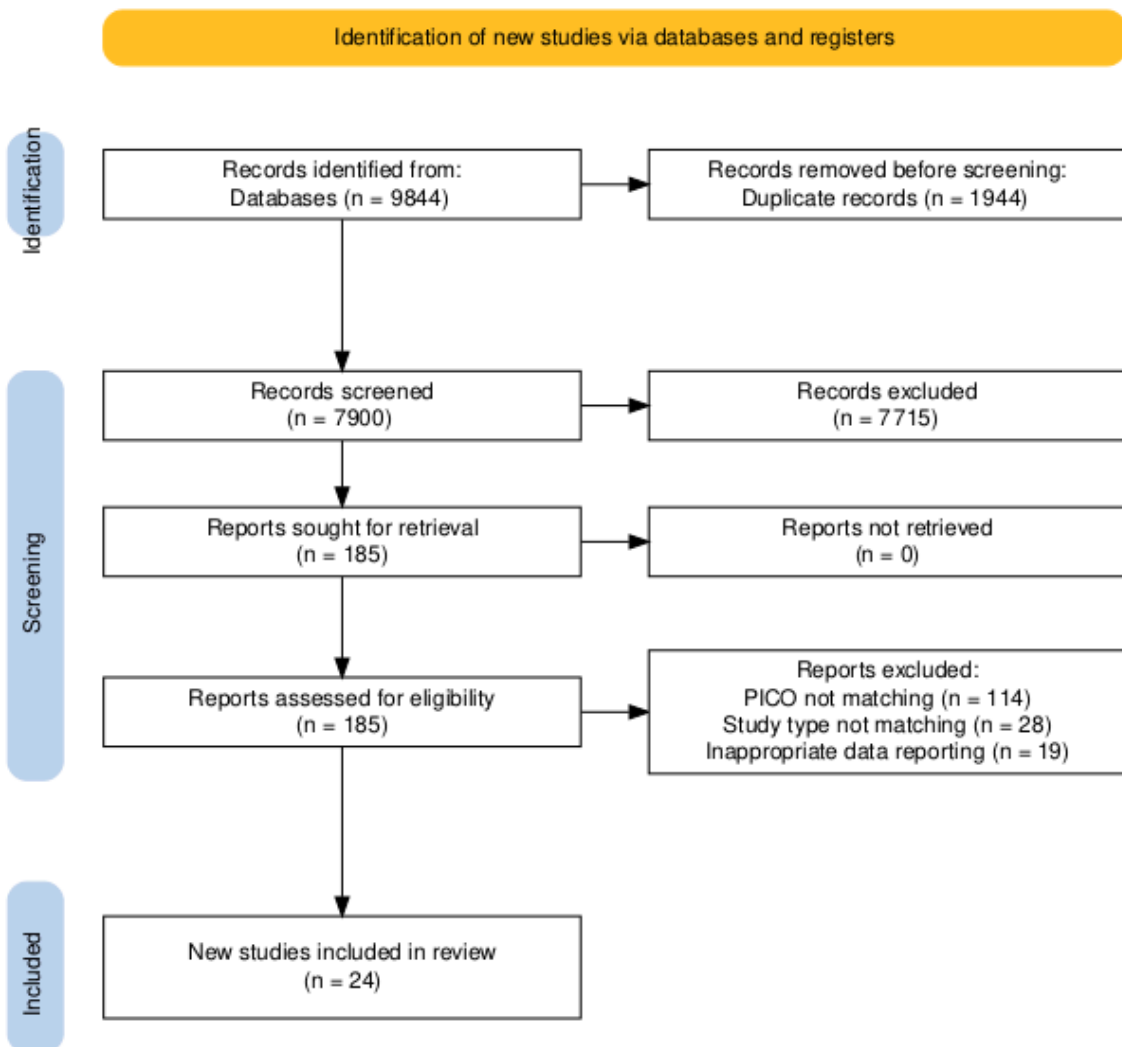


Figure 6. PRISMA flowchart of the selection process

1.2.1. Basic Characteristics of Studies Included

Our review encompassed 24 studies involving a total of 3017 patients. Study arms were grouped by their intervention types into the following 16 intervention categories: B6 (Abdolhosseini et al., 2017; Babaei & Foghaha, 2014; Chittumma et al., 2007; Firouzbakht et al., 2014; Jafari-Dehkordi et al., 2017; Jamigorn & Phupong, 2007; Sharifzadeh et al., 2018), B6 and pomegranate and mint (Abdolhosseini et al., 2017), acupressure KID21 (Galeshi et al., 2020), acupressure P6 (Adlan et al., 2017; Galeshi et al., 2020; Jamigorn & Phupong, 2007; Saberi et al., 2013; Solt Kirca & Kanza Gul, 2020; Yilmaz et al., 2023), acupuncture and doxylamine–pyridoxine (Wu et al., 2023), acupuncture (Fróes et al., 2024; Negar et al., 2020; Smith et al., 2002; Wu et al., 2023), dimenhydrinate (Babaei & Foghaha, 2014), doxylamine–pyridoxine (Biswas et al., 2011; Koren et al., 2016; Wu et al., 2023), essential oil (Joulaeerad et al., 2018; Pasha et al., 2012; Safajou et al., 2020; Yavari Kia et al., 2014), ginger (Basirat et al., 2009; Biswas et al., 2011; Chittumma et al., 2007; Firouzbakht et al., 2014; Mohammadbeigi et al., 2011; Saberi et al., 2013; Sharifzadeh et al., 2018), metoclopramide (Mohammadbeigi et al., 2011), quince (Jafari-Dehkordi et al., 2017), no intervention (Smith et al., 2002), placebo (Adlan et al., 2017; Basirat et al., 2009; Firouzbakht et al., 2014; Fróes et al., 2024; Joulaeerad et al., 2018; Koren et al., 2016; Mohammadbeigi et al., 2011; Negar et al., 2020; Pasha et al., 2012; Saberi et al., 2013; Safajou et al., 2020; Sharifzadeh et al., 2018; Yavari Kia et al., 2014; Yilmaz et al., 2023), sham acupressure (Solt Kirca & Kanza Gul, 2020), and sham acupuncture (Smith et al., 2002; Wu et al., 2023). Included studies originated from Iran (14), Australia (1), India (1), Malaysia (1), Brazil (1), Turkey (2), Thailand (2), Canada (1), and China (1). All studies included patients in the first and the early second trimester, as NVP symptoms are most prevalent in this timeframe. The duration of most treatments ranged from 3 to 7 days; in exceptional cases, interventions lasted up to 2 to 3 weeks. Further study characteristics, including countries of origin, assessment scale preferences, number of included patients, treatment durations, intervention details, drug dosages, BMI values, parity, and gestational age of included patients, are detailed in Supplementary Table S2.

1.2.2. Primary Outcome – Efficacy assessment

Our primary outcome analysis results include a network of 24 studies, including 18 two-arm studies and six multi-arm studies (see Figure 7). Outcome data were reported

at 1-week follow-up and standardized to a scale of 0–10. The total number of patients examined in the network was 3017. P-scores indicated that quince administration is likely to result in the most considerable reduction in NVP scores, followed by B6 and pomegranate and mint, acupressure P6, dimenhydrinate, and acupuncture and doxylamine–pyridoxine (see Figure 8). The league table for the primary outcome (Table 1) shows the pairwise comparisons of different techniques; most comparisons were results of indirect estimates, meaning that the ranking of different interventions should be interpreted with caution. Compared to the placebo, most included interventions showed a statistically significant reduction in NVP scores (see Figure 9). The consistency analysis showed that the comparisons in the network were consistent (Figure S2). Further sensitivity analyses were conducted excluding single-study nodes and digitized outcomes or based on SMD calculations to ensure robustness (see Supplementary Figures S4–S8). Regarding 1-month follow-up data, no network meta-analysis could be conducted because the data was particularly sparse, even compared with 1-week follow-up outcomes.

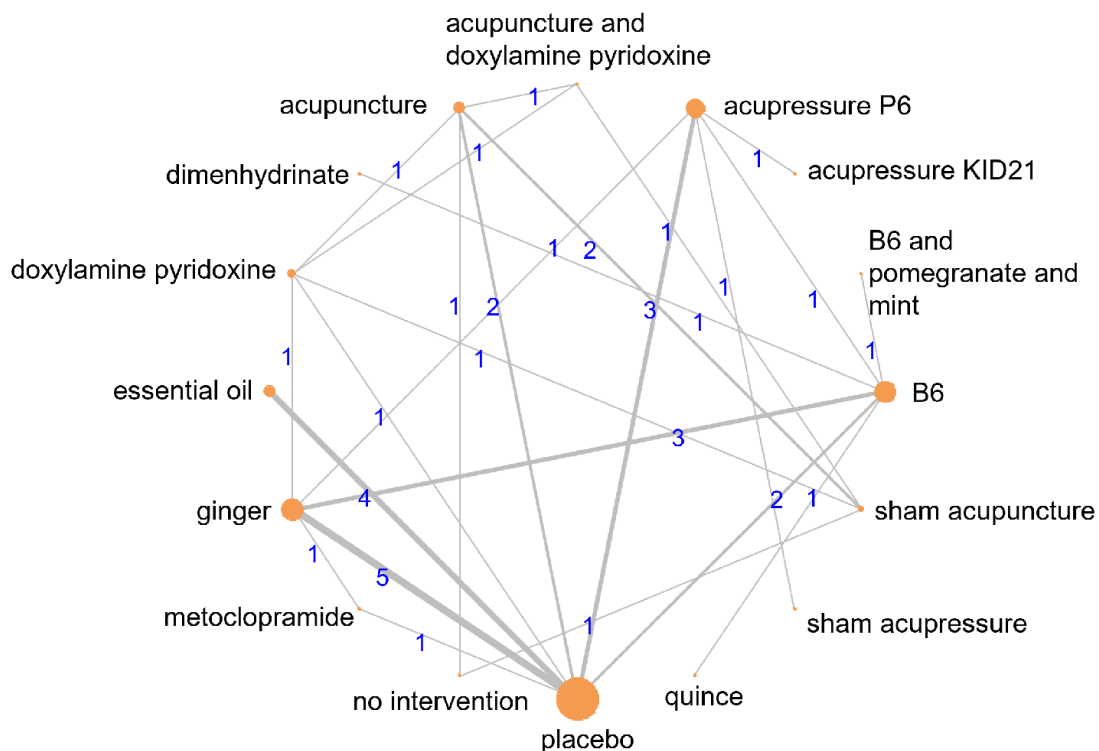


Figure 7. Network plot of efficacy analysis. The numbers above the connecting lines indicate the count of studies comparing the two linked interventions, while the size of

each node (dot) reflects the total number of studies associated with that specific intervention.

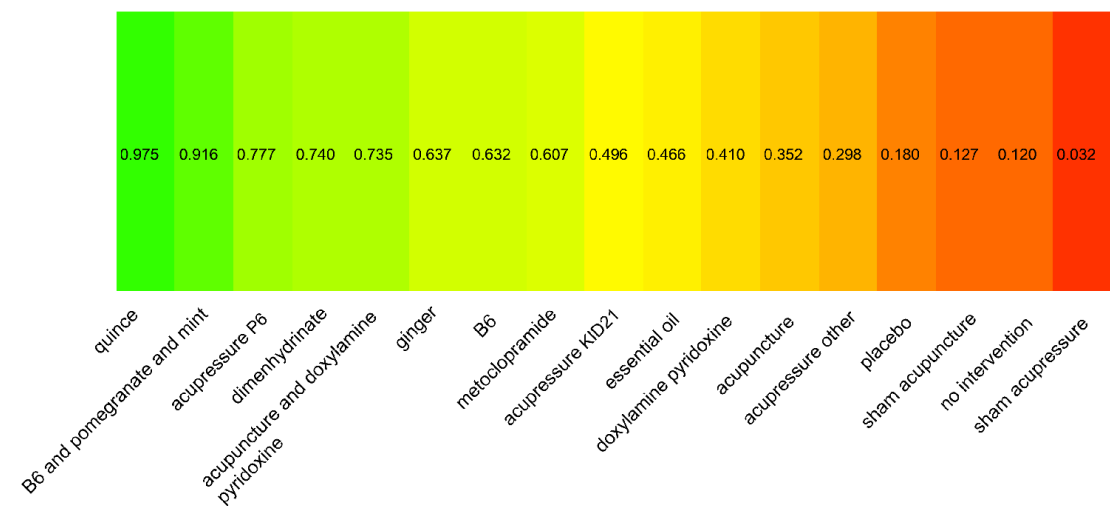


Figure 8. P-scores of interventions—efficacy assessment

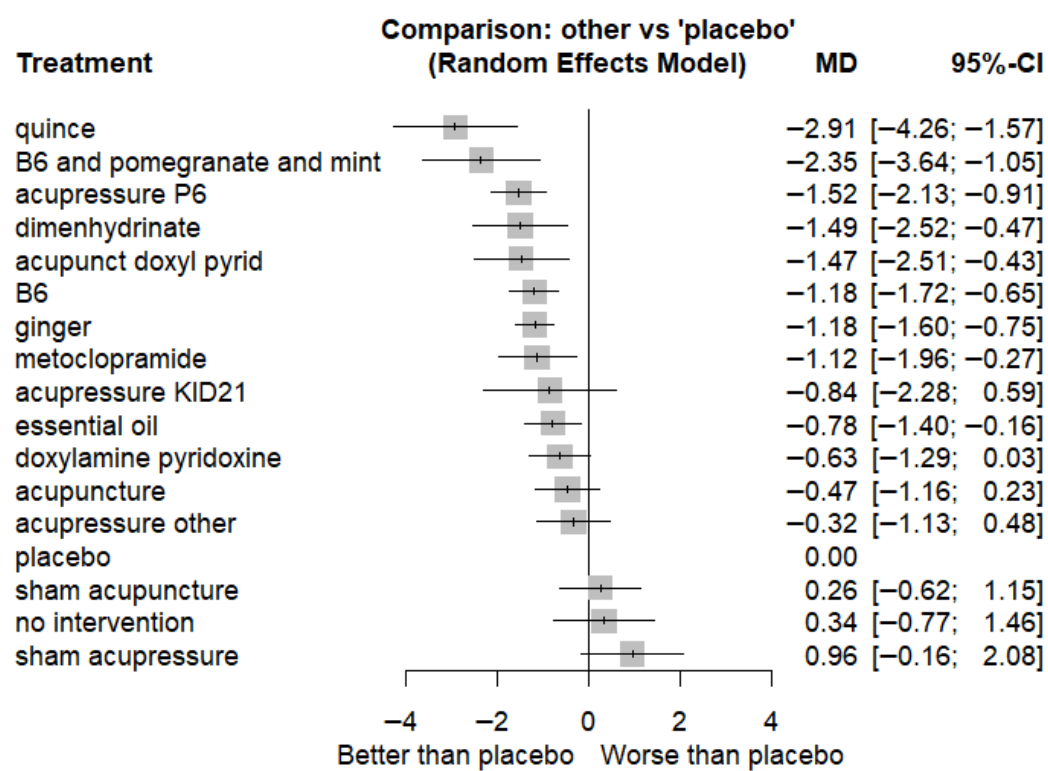


Figure 9. Forest plot with placebo reference—mean differences in NVP symptom score reductions. MD: mean differences; CI: confidence interval

Table 1. League table of efficacy analysis. Mean difference of score reductions, direct and indirect comparisons (with 95% confidence intervals)

V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17
quince	.	.	.	.	.	-1.73 [-2.97; -0.50]	.	.	.	.	.	.	.	.	.	.
-0.57 [-2.27; 1.14]	B6 and pomegranate and mint	.	.	.	.	-1.17 [-2.34; 0.01]	.	.	.	.	.	.	.	.	.	.
-1.39 [-2.78; 0.00]	-0.82 [-2.16; 0.52]	acupressure P6	.	.	.	-0.37 [-1.23; 0.49]	.	-0.68 [-1.98; 0.62]	.	.	.	.	-1.50 [-2.25; -0.76]	.	.	-2.49 [-3.42; -1.55]
-1.42 [-2.93; 0.09]	-0.85 [-2.32; 0.61]	-0.03 [-1.11; 1.05]	dimenhydrinate	.	.	-0.31 [-1.18; 0.56]	.	.	.	.	.	.	.	.	.	.
-1.44 [-3.13; 0.24]	-0.88 [-2.52; 0.77]	-0.05 [-1.25; 1.14]	-0.02 [-1.46; 1.42]	acupuncture doxylamine-pyridoxine	.	.	.	.	.	-0.92 [-1.92; 0.09]	-0.75 [-1.77; 0.27]	.	.	-1.92 [-2.95; -0.89]	.	.
-1.74 [-3.07; -0.41]	-1.17 [-2.45; 0.11]	-0.35 [-1.02; 0.33]	-0.32 [-1.32; 0.68]	-0.30 [-1.39; 0.80]	ginger	-0.17 [-0.73; 0.38]	0.09 [-0.83; 1.01]	.	.	-0.21 [-1.47; 1.05]	.	-0.85 [-1.74; 0.03]	-1.15 [-1.62; -0.69]	.	.	.
-1.73 [-2.97; -0.50]	-1.17 [-2.34; 0.01]	-0.34 [-0.98; 0.30]	-0.31 [-1.18; 0.56]	-0.29 [-1.44; 0.86]	0.01 [-0.49; 0.50]	B6	.	.	.	.	.	.	-1.90 [-2.70; -1.11]	.	.	.

-1.80 [-3.35; -0.24]	-1.23 [-2.74; 0.28]	-0.41 [-1.42; 0.61]	-0.38 [-1.66; 0.91]	-0.35 [-1.68; 0.97]	-0.06 [-0.90; 0.78]	-0.06 [-1.00; 0.88]	metoclopramide	.	.	.	.	.	.	-0.95 [-1.89; -0.01]	.	.	.
-2.07 [-3.98; -0.17]	-1.50 [-3.37; 0.37]	-0.68 [-1.98; 0.62]	-0.65 [-2.34; 1.04]	-0.63 [-2.40; 1.14]	-0.33 [-1.80; 1.14]	-0.34 [-1.79; 1.11]	-0.27 [-1.93; 1.38]	acupressure	.	.	.	.	.	.	.	.	.
-2.14 [-3.62; -0.66]	-1.57 [-3.00; -0.14]	-0.75 [-1.61; 0.12]	-0.72 [-1.91; 0.48]	-0.69 [-1.90; 0.52]	-0.40 [-1.15; 0.35]	-0.40 [-1.22; 0.42]	-0.34 [-1.39; 0.71]	-0.07 [-1.63; 1.50]	essential oil	.	.	.	.	-0.78 [-1.40; -0.16]	.	.	.
-2.28 [-3.76; -0.81]	-1.72 [-3.15; -0.29]	-0.89 [-1.78; -0.01]	-0.86 [-2.05; 0.33]	-0.84 [-1.79; 0.11]	-0.55 [-1.26; 0.17]	-0.55 [-1.36; 0.26]	-0.49 [-1.54; 0.56]	-0.21 [-1.79; 1.36]	-0.15 [-1.05; 0.76]	doxylamine-pyridoxine	0.17 [-0.83; 1.16]	.	.	-0.58 [-1.53; 0.36]	-1.00 [-2.00; 0.00]	.	.
-2.45 [-3.95; -0.94]	-1.88 [-3.34; -0.42]	-1.06 [-1.98; -0.14]	-1.03 [-2.25; 0.20]	-1.01 [-1.92; -0.09]	-0.71 [-1.50; 0.08]	-0.71 [-1.58; 0.15]	-0.65 [-1.74; 0.43]	-0.38 [-1.97; 1.22]	-0.31 [-1.24; 0.62]	-0.16 [-0.89; 0.56]	acupuncture	.	.	-0.35 [-1.21; 0.50]	-0.77 [-1.46; -0.07]	-0.66 [-1.63; 0.30]	.
-2.59 [-4.12; -1.06]	-2.03 [-3.51; -0.54]	-1.20 [-2.19; -0.22]	-1.17 [-2.43; 0.08]	-1.15 [-2.45; 0.15]	-0.85 [-1.65; -0.05]	-0.86 [-1.76; 0.05]	-0.80 [-1.92; 0.33]	-0.52 [-2.15; 1.11]	-0.46 [-1.47; 0.56]	-0.31 [-1.32; 0.71]	-0.14 [-1.20; 0.91]	acupressure other	.	-0.32 [-1.22; 0.57]	.	.	.
-2.91 [-4.26; -1.57]	-2.35 [-3.64; -1.05]	-1.52 [-2.13; -0.91]	-1.49 [-2.52; -0.47]	-1.47 [-2.51; -0.43]	-1.18 [-1.60; -0.75]	-1.18 [-1.72; -0.65]	-1.12 [-1.96; -0.27]	-0.84 [-2.28; 0.59]	-0.78 [-1.40; -0.16]	-0.63 [-1.29; 0.03]	-0.47 [-1.16; 0.23]	-0.32 [-1.13; 0.48]	placebo	.	.	.	.
-3.18 [-4.78; -1.58]	-2.61 [-4.17; -1.05]	-1.79 [-2.86; -0.72]	-1.76 [-3.10; -0.42]	-1.73 [-2.69; -0.78]	-1.44 [-2.39; -0.49]	-1.44 [-2.46; -0.43]	-1.38 [-2.59; -0.17]	-1.11 [-2.79; 0.58]	-1.04 [-2.12; 0.04]	-0.89 [-1.72; -0.06]	-0.73 [-1.41; -0.05]	-0.59 [-1.77; 0.60]	-0.26 [-1.15; 0.62]	sham acupuncture	-0.25 [-1.25; 0.75]	.	.
-3.26 [-5.00; -1.52]	-2.69 [-4.39; -0.99]	-1.87 [-3.13; -0.60]	-1.84 [-3.34; -0.33]	-1.81 [-3.04; -0.59]	-1.52 [-2.69; -0.35]	-1.52 [-2.75; -0.30]	-1.46 [-2.85; -0.07]	-1.19 [-3.00; 0.63]	-1.12 [-2.40; 0.15]	-0.97 [-2.08; 0.13]	-0.81 [-1.72; 0.10]	-0.66 [-2.03; 0.70]	-0.34 [-1.46; 0.77]	-0.08 [-1.01; 0.85]	no intervention	.	.
-3.88 [-5.55; -2.20]	-3.31 [-4.95; -1.67]	-2.49 [-3.42; -1.55]	-2.45 [-3.89; -1.02]	-2.43 [-3.95; -0.91]	-2.14 [-3.29; -0.98]	-2.14 [-3.28; -1.00]	-2.08 [-3.46; -0.69]	-1.81 [-3.41; -0.20]	-1.74 [-3.02; -0.46]	-1.59 [-2.88; -0.30]	-1.43 [-2.74; -0.11]	-1.28 [-2.64; 0.08]	-0.96 [-2.08; 0.16]	-0.70 [-2.12; 0.72]	-0.62 [-2.19; 0.96]	sham acupressure	.

1.2.3. Secondary Outcome – Safety Assessment

The reporting of safety outcomes was sparse in the included studies. Thus, no meta-analysis could be performed for this outcome. Overall, studies have found low occurrence of adverse effects, especially in the case of non-pharmacological interventions (see Supplementary Table S3). Patients taking ginger supplements reported loose stools (2.94%) (Biswas et al., 2011), heartburn (12.1%), sedation (11.1%), and arrhythmia (1.6%) (Chittumma et al., 2007), as well as dizziness (3.12%) and heartburn (3.2%) (Basirat et al., 2009). Regarding the administration of doxylamine–pyridoxine, hyperacidity (6.89%) was reported (Biswas et al., 2011). Certain patients receiving B6 supplements experienced heartburn (3.2%), sedation (17.5%), headache (3.1%) (Chittumma et al., 2007), or drowsiness (4.46%) (Babaei & Foghaha, 2014). One study reported that 52.94% of patients taking dimenhydrinate experienced drowsiness (Babaei & Foghaha, 2014). Acupressure was associated with irritation in one case (3.03%) (Jamigorn & Phupong, 2007). Patients inhaling peppermint oil reported headache (3.57%), dizziness (1.79%), and shortness of breath (1.79%) in one study (Joulaeerad et al., 2018).

1.2.4. Risk of Bias Assessment

Most of the outcomes of the studies included in the meta-analysis were rated as having a low or moderate risk of bias. Most concerns emerged in the domains related to outcome measurement and reporting, mainly due to the subjective matter of the measurement scales used. The risk-of-bias assessment for our primary outcome is shown in Figure S1.

1.2.5. Publication Bias and Heterogeneity

Publication bias was assessed using comparison-adjusted funnel plots, which are recommended in the context of network meta-analysis to account for multiple comparisons and differing reference groups. However, several important limitations should be considered when interpreting these plots. First, visual assessment of funnel plot asymmetry is inherently subjective and may be particularly challenging in complex networks. Second, comparison-adjusted funnel plots may be difficult to interpret when the number of studies per comparison is small, as is the case in parts of our network, limiting their ability to reliably detect small-study effects. Third, observed asymmetry may arise not only from publication bias but also from clinical or methodological

heterogeneity, differences in study precision, or chance. However, the funnel plot showed no asymmetry. A potential source of further publication bias may stem from the limited coverage of regional databases, especially for Chinese and Arabic literature. Heterogeneity was relatively high for all outcomes due to differences in baseline characteristics of study participants (tau-squared: 0.1774, network-level I-squared: 68.6% (95% CI: 47.3%; 81.3%), differences in interventions, or differences in definitions and measurements of outcomes.

1.2.6. Quality of Evidence

Using the CINeMA tool, the overall quality of evidence was rated as low to moderate. The major data quality concerns for all outcomes were due to high imprecision, incoherence, and heterogeneity. Imprecision was reflected in the wide range of CIs and the limited number of patients in certain studies. Additionally, incoherence arose from significant heterogeneity in certain methodological and clinical domains across the reported studies. The result of the certainty-of-evidence analysis is detailed in Supplementary Table S4.

2. DISCUSSION

9.1. Summary of Findings

9.1.1. Study I.

Our comprehensive study provides evidence that perioperative administration of esketamine, including single-dosage infusion and patient-controlled intravenous analgesia, can significantly reduce rates of PPD in women undergoing cesarean section on postpartum days 3-7. Furthermore, we observed a clinically relevant reduction in PPD rates on postpartum days 28-42 in favor of esketamine. We observed similar trends in EPDS scores, which were significantly lower in women receiving esketamine on postpartum days 3-7. These changes underscore the validity of our hypothesis that esketamine is effective in preventing PPD in this population.

Our results are parallel with existing literature, as previous studies have described similar reductions in EPDS scores and lower rates of maternal depression after administering esketamine. (Cao et al., 2024; Hung et al., 2024; Li et al., 2023; Li, Zhou, et al., 2024; Liang S., 2022; Lou et al., 2023; B. Ma et al., 2024; S. Ma et al., 2024; Nayyer et al., 2024; Parsaei et al., 2024; J. Wang et al., 2024; Wen et al., 2024; Wong et al., 2024) However, our study provides more detailed answers and higher-quality evidence for these questions. Lou et al. found that esketamine administered during cesarean section stabilized vital signs, reduced pain, and improved mental well-being in puerperae without affecting newborns. (Lou et al., 2023) In the absence of up-to-date guidelines for the prevention of PPD, we provide further evidence along with these previous studies to seriously consider esketamine as a viable option for PPD prevention. Compared to previous meta-analyses, our research demonstrates greater methodological rigor and comprehensiveness. (Cao et al., 2024; Hung et al., 2024; Li, Zhou, et al., 2024; B. Ma et al., 2024; S. Ma et al., 2024; Nayyer et al., 2024; Parsaei et al., 2024; J. Wang et al., 2024; Wen et al., 2024; Wong et al., 2024) We provide a broader and more robust evidence base by including more studies and more patients than any previous meta-analysis and focusing solely on RCTs. We included additional safety outcomes, follow-up dates, and subgroup analyses. Furthermore, our use of prediction intervals and leave-one-out analyses enhances the reliability and generalizability of our findings. Combined with a thorough assessment of publication bias using Funnel plots, these

methodological strengths set our study apart as a more detailed and systematic contribution to the field.

When comparing PPD rates on days 3-7 versus 28-42, we observed an explicit time dependence similar to the EPDS scores on postpartum days 3-7 versus 28-42. The preventive effects of esketamine were reduced when measured on later postpartum days. This trend can be explained by the fact that esketamine was administered as a one-time intervention. As the metabolism of esketamine progresses, its effects fade over time. The half-life of ketamine is around 2-3 hours; in addition, esketamine has an even higher clearance. (Johnston et al., 2023)

There is limited literature on which dosage regimens and administration types are optimal for achieving the most positive effects of perioperative esketamine administration; Li et al. used traditional logistic regression and machine learning models and found that high-dosage regimens were most effective in preventing PPD. (Li et al., 2023) Further studies are needed to evaluate which dosage and administration are optimal for PPD prevention with minimal side effects.

We also analyzed nine crucial adverse effects associated with esketamine administration. We found that only two adverse effects (dizziness and hallucinations) appeared at a significantly higher rate in women receiving esketamine. However, their proportion was low overall in the intervention group. Thus, we can conclude that esketamine is a safe intervention for PPD prevention, although it requires careful monitoring for specific adverse effects. Our results are parallel to those of the existing literature. Johnston et al. have described that the most common adverse events associated with ketamine and esketamine include dissociation, nausea, vertigo, dizziness, and a metallic taste in the mouth, most of which are associated with NMDAR antagonism. (Johnston et al., 2023) Previous studies have also found that adverse events related to perioperative esketamine administration occurred at low rates when used to prevent PPD in women undergoing cesarean section. (Li et al., 2023; Liang S., 2022; Lou et al., 2023)

Although esketamine might be safe and effective in preventing PPD and improving postpartum life quality, a complex problem such as PPD requires a complex answer. The intricate interplay of genetic, biological, and environmental factors that contribute to depression needs a wide range of interventions and treatment alternatives. (Werner et

al., 2016) This solution should not only include pharmacological preventive methods, such as esketamine or existing psychological interventions, but also a holistic approach that provides a more nuanced and personalized strategy for future mothers, especially those at higher risk for PPD. Such an approach should consist of lifestyle recommendations (e.g., regular exercise), psychoeducation, evidence-based caregiving techniques, and traditional psychotherapy methods and medical solutions. (Coll et al., 2019; Lewis et al., 2021; Meng et al., 2022; Sangsawang et al., 2019)

9.1.2. Study II.

This systematic review and network meta-analysis evaluated the efficacy of both pharmacological and non-pharmacological interventions for NVP. The analysis synthesized data from 24 RCTs, encompassing 3017 participants. The findings highlighted the effectiveness of specific dietary supplements, such as vitamin B6, quince, ginger, mint, and pomegranate, as well as acupressure and acupuncture in alleviating NVP symptoms. Among pharmacological treatments, dimenhydrinate, doxylamine–pyridoxine, and metoclopramide, often combined with non-pharmacological approaches, also demonstrated clinically meaningful benefits. However, ranking these interventions remains challenging due to high heterogeneity, limited study and participant numbers, and insufficient safety data, which collectively hinder definitive comparative conclusions. Further uncertainty arises from differences in baseline symptom severity, age, BMI, gestational age, intervention duration, and treatment dosage regimens, as these factors may affect treatment outcomes, particularly when ranking interventions. Certain interventions might have different effects depending on baseline symptom levels, treatment durations, and dosages, while age and BMI might influence the pharmacodynamics and pharmacokinetics of drugs and dietary supplements, and even modify how non-pharmacological interventions affect NVP symptoms.

The American College of Obstetricians and Gynecologists (ACOG) practice bulletin recommends vitamin B6 alone or combined with doxylamine as a safe and effective first-line pharmacotherapy for NVP (Committee on Practice, 2018). Our findings align with these guidelines, demonstrating clinically relevant improvements in NVP symptoms following the administration of combined doxylamine–pyridoxine. Additionally, the existing literature consistently supports the safety profile of

doxylamine–pyridoxine and doxylamine alone, indicating no increased risk of adverse pregnancy outcomes (Biffi et al., 2021; Chin et al., 2014; Madjunkova et al., 2014). Some studies further suggest that specific delayed-release formulations of this combination may offer the best efficacy in managing NVP (Madjunkova et al., 2014). Multiple systematic reviews and meta-analyses also recognize vitamin B6 administration as a safe and effective treatment for NVP (Hu et al., 2022; Jayawardena et al., 2023). Metoclopramide is effective in reducing symptoms of NVP; however, it is associated with a high rate of adverse effects—31% of pregnant women reported discontinuing its use due to these side effects (Wills et al., 2025). Dimenhydrinate was also associated with improved NVP symptoms, even when compared to vitamin B6 or ginger (Babaei & Foghaha, 2014; Pongrojpaew et al., 2007).

Several reviews suggest that ginger may help reduce nausea symptoms during pregnancy, though the evidence is limited by the small number of studies, inconsistent outcome reporting, and overall low quality (Hu et al., 2022; Sridharan & Sivaramakrishnan, 2018; Thomson et al., 2014; Viljoen et al., 2014). Our findings also support the beneficial effects of ginger. However, the variability in administration methods and dosages of ginger supplements poses challenges to standardizing treatment regimens. Importantly, according to the available literature, ginger has not been associated with side effects or adverse events in pregnancy (Viljoen et al., 2014). Based on the evidence from these systematic reviews, ginger could be considered a safe and potentially effective alternative for women experiencing NVP, even compared to other interventions such as vitamin B6 administration (Hu et al., 2022; Sridharan & Sivaramakrishnan, 2018; Tan et al., 2023). Essential oils and other dietary supplements, such as quince, pomegranate, or mint products, have also been evaluated as safe and effective interventions for managing NVP (Gergo et al., 2025; Khorasani et al., 2020; Nassif et al., 2022). However, regarding inhalative agents, different products and delivery methods can result in different outcomes; thus, further research is needed in this area to inform clinical choices. Lastly, it is important to note that the availability of certain dietary supplements or products is highly influenced by geographical or cultural factors; thus, practitioners must take these factors into account when interpreting study results for clinical practice.

A substantial body of literature, particularly from trials and reviews conducted in China, supports the efficacy of acupoint-based techniques, including acupuncture and acupressure, in managing NVP (Gong et al., 2024; Jin et al., 2024; Tan et al., 2023; Van den Heuvel et al., 2016; X. Wang et al., 2024). A systematic review and meta-analysis comparing acupuncture to Western Medicine (WM) found that combining acupuncture with WM may enhance treatment effectiveness for NVP compared to WM alone. Additionally, this approach has been demonstrated to be safe (Jin et al., 2024). Other reviews indicate that acupressure may have a potentially beneficial effect in treating NVP. However, robust supportive data are currently lacking (Gong et al., 2024; X. Wang et al., 2024). While some evidence suggests that acustimulation may help alleviate nausea, vomiting, or hyperemesis during pregnancy, the results remain inconclusive (Van den Heuvel et al., 2016). Furthermore, the absence of standardized guidelines and the limited accessibility of acupoint-based interventions hinder their integration into routine clinical practice.

Although our analysis incorporates the latest developments and trials on the efficacy of available treatments for NVP, comparative assessments of these interventions remain challenging, given that most comparisons are indirect and we identified high heterogeneity due to differences in study characteristics, along with low-to-moderate quality of evidence and sparse reporting of adverse effect profiles. This is primarily due to the lack of high-quality, head-to-head comparative trials with large patient populations and to the inadequate assessment of maternal and fetal complications. According to a 2015 Cochrane review, there is insufficient high-quality evidence to definitively endorse any specific intervention for NVP. This does not imply that the interventions studied are ineffective; rather, it reflects a lack of robust evidence to support the superiority of any single approach (Matthews et al., 2015). A previous network meta-analysis concluded that current evidence strongly supports the therapeutic benefits of ginger for treating NVP. While several other interventions also demonstrated promising results, the overall strength of the evidence remains very low; thus, the results of this analysis should be interpreted with considerable caution (Sridharan & Sivaramakrishnan, 2018). Our results align with previous studies in this area, as we also observed low-to-moderate quality of evidence and high heterogeneity in study design and population characteristics, even after including the latest studies with stricter

inclusion criteria and rigorous analytical methods. Ranking of treatments was also challenging, due to the dominance of indirect comparisons and the lack of safety data reporting.

9.2. Strengths

9.2.1. Study I.

The strength of this study lies in its extensive literature review, which includes a broad spectrum of studies on the administration of esketamine in cesarean section. It follows clear reporting standards, uses thorough assessments of risk of bias and evidence quality, and provides practical advice for clinical application. Together, these aspects strengthen the reliability and relevance of trial results in clinical practice.

9.2.2. Study II.

This study is strengthened by its strict adherence to internationally recognized guidelines, including PRISMA 2020 [11] and the Cochrane Handbook [12], which ensures methodological rigor and transparency throughout the research process. Furthermore, our analysis includes an extensive range of interventions, spanning pharmacological treatments like doxylamine–pyridoxine and metoclopramide, as well as non-pharmacological approaches such as acupuncture, acupressure, ginger, and dietary supplements, offering a holistic evaluation of available options for managing NVP. Additionally, applying advanced analytical techniques, such as a frequentist network meta-analysis and the CINEMA framework, allows for a comprehensive and nuanced comparison of pharmacological and non-pharmacological interventions, providing clinicians with a robust evidence base for decision-making.

9.3. Limitations

9.3.1. Study I.

The diversity of screening definitions for postpartum depression (PPD) across studies creates variability in identifying affected individuals, which can lead to inconsistencies in prevalence rates and outcomes. Furthermore, the exclusive focus on Chinese populations in this research presents a significant limitation in terms of generalizability. Cultural, genetic, and healthcare system differences between Chinese populations and

other demographic groups may influence both the manifestation of PPD and responses to treatment, including esketamine.

Additionally, the relatively short duration of follow-up in the analyzed studies may not adequately capture the long-term efficacy, safety, and sustainability of esketamine as a preventive or therapeutic intervention for PPD. Postpartum depression can persist for months or even years if untreated, and the potential for relapse or the emergence of late-onset symptoms remains unclear in the absence of extended observation. (Miguez & Vazquez, 2023; Xiong et al., 2022)

9.3.2. Study II.

A primary limitation of this study is the considerable heterogeneity observed among the included trials, which arises from differences in participant demographics, intervention protocols, and outcome definitions, thereby complicating the interpretation of comparative effectiveness. While we observed some variability in baseline characteristics or study design, our qualitative assessment of effect modifiers indicated that the included studies were broadly comparable in terms of population characteristics and intervention protocols. This supports the assumption of transitivity for our network meta-analysis. However, we acknowledge that unmeasured or unreported effect modifiers may introduce residual heterogeneity, and we urge cautious interpretation of the findings in light of this potential limitation. The limited reporting of safety outcomes in the primary studies also restricts the ability to conduct a thorough meta-analysis of adverse effects, particularly for pharmacological treatments, where long-term maternal and fetal safety remain a critical concern. Furthermore, the relatively small number of RCTs and participants included in the analysis may limit the generalizability of the findings, especially across diverse populations and clinical settings. Also, the subjective nature of specific outcome measures, such as quality-of-life assessments, introduces potential bias. At the same time, the lack of standardized protocols for non-pharmacological interventions (e.g., acupuncture, ginger dosage) poses challenges for consistent clinical implementation. Finally, the assumption of comparability across scales may introduce residual heterogeneity, and that linear rescaling may not fully account for differences in scale structure, item weighting, or responsiveness. These limitations should be considered when interpreting the pooled estimates.

10. CONCLUSIONS

Our first study demonstrates the significant potential benefits of perioperative esketamine administration, both as a single-dose infusion and as a patient-controlled intravenous analgesia, in reducing PPD rates in women undergoing cesarean section. (Frivaldszky et al., 2025)

The results of our second study show that specific pharmacological treatments (vitamin B6, metoclopramide, and dimenhydrinate) and non-pharmacological interventions (dietary supplements and acupoint-based techniques) are effective in reducing nausea and vomiting during pregnancy. The lack of available safety data warrants careful assessment of potential adverse effects and the development of carefully tailored treatment plans. (Frivaldszky et al., 2026)

Together, these studies emphasize the importance of integrating high-quality evidence into individualized clinical care, balancing efficacy with maternal and fetal safety, and considering women's experiences and preferences when selecting therapeutic interventions. Ultimately, this work contributes to the growing body of translational evidence aimed at optimizing perinatal care, promoting maternal well-being, and informing future clinical practice, research, and healthcare policy.

11. IMPLICATIONS FOR PRACTICE

11.1. Study I.

In the observed period, our findings suggest that perioperative esketamine administration is a safe and effective way to prevent PPD in women undergoing cesarean section, as it significantly reduces PPD rates and EPDS scores in this population. Additionally, no serious adverse effects were observed during this period, further supporting the safety profile of esketamine within the context of this study.

11.2. Study II.

Implementing scientific findings in practice is crucial (Hegyi et al., 2021; Hegyi et al., 2020). This review supports the effectiveness of vitamin B6, metoclopramide, dimenhydrinate, ginger, specific dietary supplements, acupuncture, and P6 acupressure in managing NVP, while indicating low-to-moderate quality of evidence. While other acupressure techniques and doxylamine–pyridoxine alone showed clinically relevant improvements, these improvements did not reach statistical significance compared with placebo. Furthermore, data on their long-term safety and cost-effectiveness remain limited (see Figure 10); thus, careful monitoring for adverse effects is warranted (Hegyi et al., 2025).

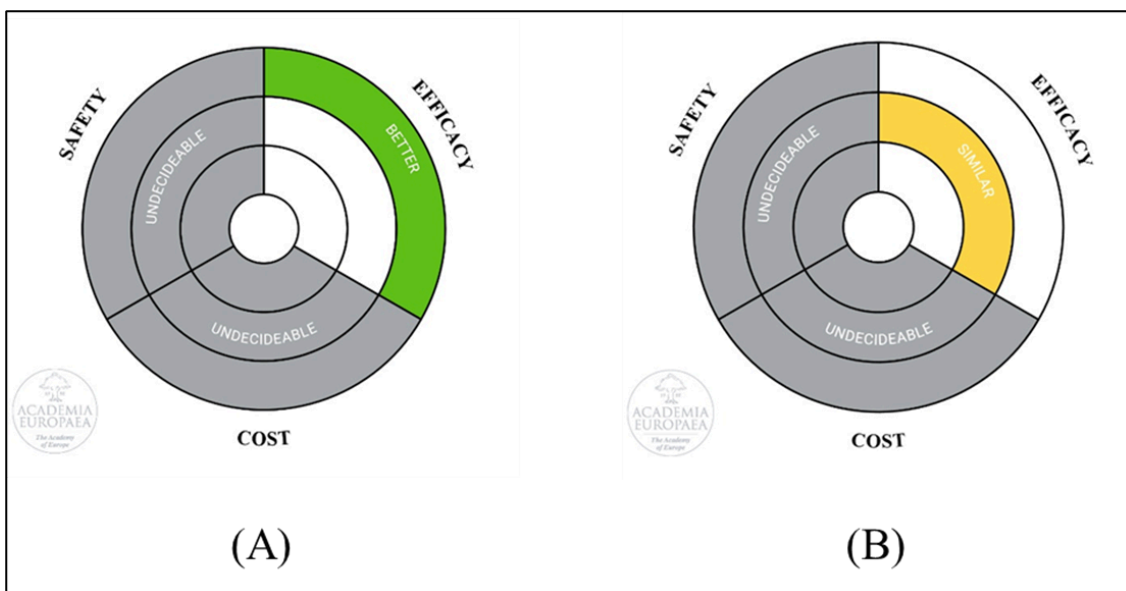


Figure 10. Academia Europaea's Ring Model for visualizing research implications in publication. (A) Comparison of vitamin B6, metoclopramide, dimenhydrinate,

ginger, quince, essential oils, acupuncture combined with doxylamine–pyridoxine, acupuncture, and P6 acupressure versus placebo. **(B)** Comparison of other acupressure techniques and doxylamine–pyridoxine versus placebo.

12. IMPLICATIONS FOR RESEARCH

12.1. Study I.

Several limitations emphasize the need for further research to enhance our understanding of esketamine's role in preventing postpartum depression. Future studies should prioritize more extensive and diverse samples to improve generalizability and adopt standardized definitions of PPD for consistency. More extended follow-up periods are essential to evaluate the sustained efficacy, safety, and potential long-term impacts of esketamine. Additionally, research should explore various dosage regimens and administration methods and rigorously address potential biases. A focused examination of neonatal and lactational outcomes is equally important to ensure comprehensive insights into this critical area of maternal and child healthcare.

It is crucial to note that although women undergoing cesarean section are particularly susceptible to PPD, all women are at risk of experiencing PPD regardless of their method of delivery. This underscores the need for comprehensive research to develop effective prevention strategies for all mothers.

12.2. Study II.

Future research should focus on large-scale, high-quality RCTs with standardized outcomes to address the heterogeneity and evidence gaps identified in this review. Prioritizing long-term safety assessments for pharmacological interventions and establishing consistent protocols for non-pharmacological approaches, such as ginger and acupuncture, will improve clinical guidance. Additionally, incorporating cost-effectiveness analyses and patient-centered outcomes can enhance the practical relevance of findings, ultimately informing more robust treatment guidelines for NVP. Careful assessment of maternal and fetal adverse effects is necessary in future studies examining treatments for NVP.

13. IMPLICATIONS FOR POLICY MAKERS

13.1. Study I.

The practical implementation of scientific findings is essential (Hegyi et al., 2021; Hegyi et al., 2020); therefore, we suggest that future clinical guidelines should consider the use of esketamine for the prevention of PPD in women undergoing cesarean section.

13.2. Study II.

While the examined interventions demonstrate clinical benefits, their application should be tailored to individual patient needs, considering symptom severity and preferences. However, due to high heterogeneity among studies and limited safety data, especially for pharmacological treatments, clinicians should remain cautious and prioritize shared decision-making. Standardized protocols and additional safety evaluations are necessary to enhance confidence in these recommendations.

14. FUTURE PERSPECTIVES

14.1. Study I.

Another aspect we need to address in PPD prevention is the importance of screening, e.g., through the help of the EPDS questionnaire. (Oliveira et al., 2022; Park & Kim, 2023; Ukatu et al., 2018) Extensive screening can contribute to an adequate risk assessment; thus, caregivers can identify individuals at higher risk of PPD and create personalized prevention strategies. Furthermore, they can evaluate who would benefit most from pharmacological interventions, such as esketamine. (Wells, 2023) Institutions and decision-makers should provide sufficient support for these screening programs to reach as many future mothers as possible and minimize the dangers of undetected and untreated PPD. (O'Connor et al., 2016) Health education programs should also address this issue to raise awareness of this critical public health domain. (Shimpuku et al., 2022) This can lead to significant improvements in postpartum life quality.

14.2. Study II.

Standardized symptom severity scores and outcome assessments are critical for advancing research and clinical practice in the management of NVP (Matthews et al., 2014). Consistent, validated tools, such as the PUQE scale, VAS, and NVP-specific quality-of-life measures, enable reliable comparison of interventions across studies, reducing heterogeneity and improving the robustness of meta-analyses (Koren et al., 2002; Lacasse et al., 2008). Without standardization, variations in outcome definitions and measurement methods can lead to inconsistent findings, complicating efforts to establish evidence-based guidelines. Additionally, uniform assessment tools facilitate better clinical decision-making by providing clear, comparable benchmarks for symptom severity, treatment efficacy, and patient response. Implementing these standardized measures in future research will enhance data quality and support the development of more precise, patient-centered treatment protocols for NVP.

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