

Association Between Depression and the Risk of Hyperemesis Gravidarum: A Systematic Review and Meta-Analysis

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Background: Hyperemesis gravidarum (HG) is a severe pregnancy-related condition that may be influenced by maternal psychological factors. This meta-analysis aimed to evaluate the association between maternal depression and the risk of HG and to explore whether this association varies by maternal or study characteristics.

Methods: A systematic search was conducted in PubMed, Embase, and Web of Science databases up to May 2, 2025, to identify observational studies examining the association between depression, assessed either prior to or during pregnancy, and HG. Heterogeneity was evaluated using the Cochrane Q test and I^2 statistic. Odds ratios (ORs) with 95% confidence intervals (CIs) were pooled using a random-effects model, incorporating the influence of heterogeneity. Subgroup analyses were conducted by maternal age, timing of depression assessment, diagnostic tools, timing of HG diagnosis, adjustment for gravidity or parity, and study quality.

Results: Totally, 13 case-control studies involving 95,249 pregnant women were included. Maternal depression was associated with a significantly higher risk of HG (OR: 5.08, 95% CI: 2.71–9.52; $p < 0.001$; $I^2 = 93\%$). The association was stronger among women who were younger than 27 years (OR: 11.64) than in those who aged 27 years or older (OR: 2.86; p (for subgroup difference) = 0.02). Depression assessed at the time of HG diagnosis showed a stronger association (OR: 6.04) than when assessed before diagnosis (OR: 2.11; p (for subgroup difference) = 0.04). Studies using the Beck Depression Inventory or Edinburgh Postnatal Depression Scale reported stronger associations than those using the Hospital Anxiety and Depression Scale (p (for subgroup difference) = 0.009).

Conclusion: Maternal depression is associated with the occurrence of HG; however, this association does not imply causation, and depressive symptoms may reflect the psychological impact of this severe condition.

Keywords: hyperemesis gravidarum, pregnancy, depression, risk factor, meta-analysis

Introduction

Hyperemesis gravidarum (HG) is a severe manifestation of nausea and vomiting during pregnancy that exceeds the intensity and duration of typical morning sickness.^{1,2} HG is globally defined by the Windsor criteria, which characterize the condition by severe nausea and vomiting, an inability to maintain adequate oral intake, significant functional impairment, and the presence of ketonuria or dehydration.³ It affects approximately 0.3–3% of pregnancies, although prevalence estimates vary by population and diagnostic criteria.⁴ HG not only contributes to significant maternal morbidity (eg, weight loss, anxiety, postpartum depression, and prolonged hospitalization), but is also associated with adverse perinatal outcomes, such as low birth weight, preterm delivery, and impaired fetal growth.^{5,6} Although the etiology of HG remains incompletely understood, emerging evidence shows that growth differentiation factor-15 (GDF-15) serves as a key hormonal mediator, playing a central role in the pathophysiology of the condition by contributing to the severe nausea, vomiting, and metabolic disturbances that are primary features of HG.⁷ Despite extensive clinical

attention, the precise etiology of HG remains elusive, and current management strategies primarily aim to alleviate symptoms rather than prevention of the condition.^{6,8} Identifying modifiable risk factors is essential for the early intervention and improved outcomes.

Depression is one of the most frequent mental health conditions during pregnancy, influencing up to 20% of women, with the highest prevalence observed in the first trimester.^{9,10} Several biological and psychological mechanisms may link depression to HG, including dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis,¹¹ increased sensitivity to hormonal changes,¹² and alterations in neuroimmune pathways.¹³ Beyond biological links, HG itself can precipitate significant psychological distress because of its prolonged, debilitating symptoms. A large-scale systematic review by Mitchell-Jones et al¹⁴ demonstrated that patients with HG have significantly higher levels of anxiety and depressive symptoms, supporting a bidirectional relationship in which HG may contribute to the onset or worsening of depression. Several psychological mechanisms may also explain why depressive symptoms are frequently observed in patients with HG.¹⁵ The condition is profoundly debilitating, with persistent nausea, vomiting, dehydration, and functional impairment often leading to significant emotional distress. Multiple studies have demonstrated elevated levels of anxiety and depressive symptoms among patients with HG.^{14,15} While previous studies have explored the association between depression and HG, findings have been inconsistent, which could arise from differences in study design, timing of depression assessment, diagnostic tools, and adjustment for confounders.^{14,16} Studies have demonstrated that women with a history of depression or depressive symptoms during early pregnancy may be at a greater risk of developing HG,^{17–27} while others have found no significant association.^{28,29} While depressive symptoms frequently co-occur with HG, current evidence demonstrates that they are more likely a psychological response to the intense and debilitating nature of the condition rather than a contributing cause.¹⁵ Nevertheless, a comprehensive summary of the current evidence regarding the association between depression and HG is needed. Therefore, this systematic review and meta-analysis was conducted to examine the association between maternal depression and the risk of HG, and to explore the influence of patients' characteristics on this relationship.

Methods

This study adhered to the PRISMA 2020 guidelines^{30,31} and the Cochrane Handbook for Systematic Reviews of Interventions,³² involving all aspects of study design, data collection, statistical analysis, and interpretation of findings. The study protocol was also registered in the PROSPERO database (Registration No. CRD420251088343).

Database Search

To identify studies pertinent to this meta-analysis, comprehensive searches were conducted in the PubMed, Embase, and Web of Science databases using the following combined terms: (1) “hyperemesis gravidarum,” “nausea and vomiting in pregnancy,” or “pregnancy-related nausea and vomiting”; and (2) “depression,” “depressive,” “mood,” or “affective disorder.” The search was limited to human studies and included only full-length, peer-reviewed articles published in English. Additionally, the reference lists of relevant original and review articles were manually screened to identify further eligible studies. The search included all records from each database inception through May 02, 2025.

Study Selection

The PICOS framework was applied to define the inclusion criteria:

- **P (Population):** Pregnant women, regardless of gestational age, age, or other demographic characteristics.
- **I (Exposure):** Presence of depression, including self-reported depressive symptoms, clinical diagnosis, or assessment via validated depression scales, occurring before or at the time of HG diagnosis.
- **C (Comparison):** Pregnant women without depressive symptoms prior to or at the diagnosis of HG served as the control group.
- **O (Outcome):** Occurrence of HG, as defined by clinical diagnosis, hospitalization records, or other diagnostic criteria used in the included studies.
- **S (Study design):** Observational studies, including cohort, case-control, and cross-sectional designs.

Exclusion criteria involved reviews, editorials, other meta-analyses, studies not including pregnant populations, studies that did not assess depression as an exposure, studies evaluating depression only after HG diagnosis, and those lacking HG outcome data. In cases of overlapping populations, the study with the largest sample size was retained for analysis.

Study Quality Evaluation

Two authors independently performed the literature search, study selection, quality assessment, and data extraction. Disagreements in study selection or data extraction were resolved through consultation with the corresponding author. The quality of included studies was evaluated using the Newcastle-Ottawa Scale (NOS),³³ assessing selection of participants, control for confounding variables, and outcome assessment. Scores range from 1 to 9, and a total score of 7 or above indicates high methodological quality.

Data Collection

The collected data included the study details (the first author's name, year of publication, country of origin, and study design), participants' characteristics (eg, sample size, inclusion criteria, and mean age), details of depression analysis (timing and tools used for evaluating depressive symptoms, and number of women with depression), and outcomes (timing for diagnosis of HG, number of women who developed HG, and covariates adjusted or matched in the analytic models).

Statistical Analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the association between depression and the risk of HG among pregnant women by comparing the prevalence of HG in those with and without depression. ORs and standard errors were either directly extracted or calculated from reported 95% CIs or p-values, and then log-transformed to stabilize variance and approximate normality.³² When multiple ORs were available from different models, the estimate with the most comprehensive adjustment for confounders was selected. Heterogeneity across studies was assessed using the Cochrane Q test and the I^2 statistic,³⁴ with a p value < 0.10 indicating significant heterogeneity and I^2 values of < 25%, 25–75%, and > 75% representing low, moderate, and high heterogeneity, respectively. A random-effects model was utilized to pool the data, accounting for heterogeneity among studies.³² Sensitivity analyses were performed by sequentially excluding individual studies to assess the robustness of the findings. Predefined subgroup analyses were conducted based on participants' mean age, timing of depression assessment (prior to vs at the time of HG diagnosis), instruments used to evaluate depression, timing of HG diagnosis (limited to the first trimester vs not restricted), adjustment for gravidity and/or parity, and the NOS scores of the included studies. Since not all included studies diagnosed HG within the first 16 weeks, particularly earlier studies published prior to the widespread adoption of the Windsor criteria, subgroup analysis was conducted based on whether the HG diagnosis was explicitly restricted to the first trimester. This approach enabled an evaluation of whether variation in diagnostic timing contributed to the observed heterogeneity across studies. Because some studies assessed depression prior to HG diagnosis while others evaluated depressive symptoms at the time of HG diagnosis, the timing of assessment may influence the observed association. To account for this variability, subgroup analysis was carried out to examine whether studies measuring pre-existing depression differed from those assessing depressive symptoms during active HG. Medians of continuous variables were used to ensure balanced subgroup stratification. Publication bias was visually evaluated through funnel plot asymmetry and assessed statistically using Egger's test.³⁵ All analyses were performed using RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata (Version 12.0; Stata Corporation, College Station, TX, USA) software.

Results

Study Inclusion

The study selection process is shown in [Figure 1](#). A total of 433 records were initially retrieved from the three databases. After excluding 91 duplicates, 342 unique articles remained for title and abstract screening. Among them, 315 were excluded for not meeting the objectives of the meta-analysis. The full texts of the remaining 27 articles were reviewed by two independent authors, and 14 were excluded for various reasons ([Figure 1](#)). Ultimately, 13 studies were included in the quantitative analysis.^{17–29}

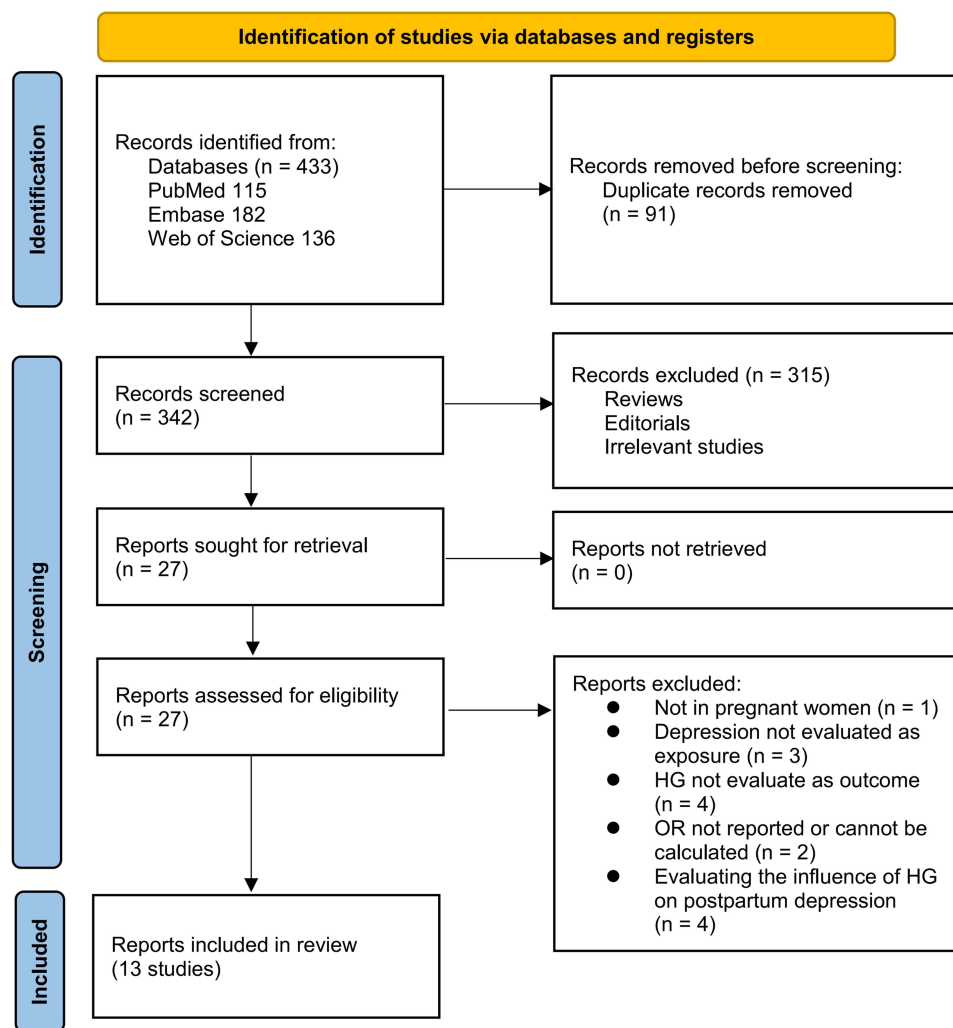


Figure 1 Flowchart of database search and study inclusion.

Summary of Study Characteristics

Table 1 summarizes the key characteristics of the 13 studies included in the meta-analysis,^{17–29} involving a total of 95,249 pregnant women from various countries, such as the USA, Turkey, Norway, the UK, Malaysia, Ethiopia, and India. All studies adopted a case-control design. Participants' mean age was reported between 24.5 and 31.6 years. Depression was assessed either prior to or during pregnancy, primarily in the first trimester, using validated assessment tools, such as the International Classification of Diseases, 9th Revision (ICD-9), the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinical Version (SCID-I/CV), the Beck Depression Inventory (BDI), the Beck Depression Inventory-II (BDI-II), the Hospital Anxiety and Depression Scale–Depression subscale (HADS-D), the Edinburgh Postnatal Depression Scale (EPDS), the Symptom Checklist-90-Revised (SCL-90-R), the Patient Health Questionnaire-9 (PHQ-9), and the Kendler Lifetime Depression Scale (KLTDs). Accordingly, 18,426 (19.3%) women were diagnosed with depression. In two studies, this assessment was made prior to the diagnosis of HG,^{17,22} while in all other studies, depression was evaluated at the time of HG diagnosis.^{18–21,23–29} HG was diagnosed clinically in 12 studies^{18–29} and using ICD-9 codes in another study,¹⁷ in which most diagnoses were made during the first trimester.^{18–21,23,25,29} The number of HG cases per study ranged from 41 to 208. Accordingly, 2,076 (2.2%) women developed HG. The majority of studies adjusted or matched for potential confounding factors, including maternal age, gestational age (GA), parity, body mass index (BMI), gravidity, educational level, smoking status, socio-economic status, ethnicity, *Helicobacter pylori* infection, and family history of HG to a varying degree. However, one study¹⁷ did not report any adjustments for confounders.

Table 1 Characteristics of the Included Studies

Study	Country	Design	Participant Characteristics	No. of Pregnant Women	Mean Age (Years)	Timing of Depressive Symptom Assessment	Methods for Validating Depression	No. of Women with Depression	Methods for Validating the Diagnosis of HG	Timing for the Diagnosis of HG	No. of Women with HG	Variables Adjusted or Matched
Seng 2007 ¹⁷	USA	CC	Women gave birth to live singletons	11016	29.7	Within the years preceding pregnancy	ICD-9 codes	347	ICD-9 codes	NR	208	None
Uguz 2012 ²⁰	Turkey	CC	Pregnant women with no severe medical illnesses, gestational problems, or multiple fetus	142	26.6	At the diagnosis of HG	SCID-I/CV	12	Clinical diagnosis	1st trimester (mean GA: 9.1 weeks)	52	GA
Hizli 2012 ¹⁸	Turkey	CC	Pregnant women without known thyroid disease, multiple gestations, gestational trophoblastic disease, and psychological and gastrointestinal disorders	400	24.5	At the diagnosis of HG	BDI-II	168	Clinical diagnosis	1st trimester (mean GA: 8.5 weeks)	200	Age, parity, and GA
Simsek 2012 ¹⁹	Turkey	CC	Women with a singleton pregnancy without pre-existing medical or psychiatric comorbid condition	86	28.6	At the diagnosis of HG	BDI	39	Clinical diagnosis	1st trimester (mean GA: 10.0 weeks)	41	Age, parity, GA, and BMI
Ezberci 2014 ²⁸	Turkey	CC	Women with a singleton pregnancy without pre-existing severe medical illness, gestational problems, multiple fetuses, or psychotic diseases	200	27.4	At the diagnosis of HG	HADS-D	92	Clinical diagnosis	NR	100	Age, parity, GA, and BMI
Aksoy 2015 ²¹	Turkey	CC	Women with a singleton pregnancy without pre-existing medical or psychiatric disorders	160	25.9	At the diagnosis of HG	BDI	92	Clinical diagnosis	1st trimester (mean GA: 8.4 weeks)	78	Age, parity, GA, and BMI

(Continued)

Table 1 (Continued).

Study	Country	Design	Participant Characteristics	No. of Pregnant Women	Mean Age (Years)	Timing of Depressive Symptom Assessment	Methods for Validating Depression	No. of Women with Depression	Methods for Validating the Diagnosis of HG	Timing for the Diagnosis of HG	No. of Women with HG	Variables Adjusted or Matched
Kjeldgaard 2017 ²²	Norway	CC	Women with a singleton pregnancy	81786	30.3	Depression history, before the diagnosis of HG	KLTDS	17351	Clinical diagnosis	Before the 25th week of GA	731	Age, parity, GA, sex of the child, socio-economic status, BMI and smoking, education, pre-pregnancy BMI, and pelvic girdle pain
Senturk 2017 ²³	Turkey	CC	Women with a singleton pregnancy without pre-existing medical or psychiatric disorders	384	26.3	At the diagnosis of HG	SCL-90-R	110	Clinical diagnosis	1st trimester (mean GA: 6.6 weeks)	207	Age and gravid
Topal Ahmetoğlu 2017 ²⁴	Turkey	CC	Women with a singleton pregnancy without pre-existing medical or psychiatric disorders	200	25.5	At the diagnosis of HG	BDI	70	Clinical diagnosis	Before the 20th week of GA	100	Age, parity, gravid, and GA
Mitchell-Jones 2020 ²⁵	UK	CC	Pregnant women without concurrent mental health condition	214	31.6	At the diagnosis of HG	EPDS	45	Clinical diagnosis	1st trimester (mean GA: 9.4 weeks)	106	BMI and gravid
Azlan 2022 ²⁹	Malaysia	CC	Pregnant women without concurrent mental health condition	117	NR	At the diagnosis of HG	HADS-D	14	Clinical diagnosis	1st trimester (mean GA < 12 weeks)	55	Age, ethnicity, and GA
Asrade 2023 ²⁶	Ethiopia	CC	Pregnant women without concurrent mental health condition or critical illness	444	27.9	At the diagnosis of HG	EPDS	42	Clinical diagnosis	1st to 3rd trimesters	148	GA, gravidity, HP infection, family history of HG, type of gestation, and residency
Dutta 2023 ²⁷	India	CC	Women with a singleton pregnancy without pre-existing medical or psychiatric disorders	100	NR	At the diagnosis of HG	PHQ-9	44	Clinical diagnosis	1st or 2nd trimesters	50	Age, gravid, and GA

Abbreviations: NR, not reported; CC, case-control; GA, gestational age; ICD-9, International Classification of Diseases, 9th Revision; SCID-I/CV, Structured Clinical Interview for DSM-IV Axis I Disorders, Clinical Version; BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II; HADS-D, Hospital Anxiety and Depression Scale – Depression subscale; KLTDS, Kendler Lifetime Depression Scale; SCL-90-R, Symptom Checklist-90-Revised; EPDS, Edinburgh Postnatal Depression Scale; PHQ-9, Patient Health Questionnaire-9; HG, hyperemesis gravidarum; BMI, body mass index; HP, Helicobacter pylori.

Study quality was assessed using the NOS score (Table 2), and total scores ranged from 5 to 9, indicating overall moderate to high methodological quality. Four studies^{18,21,26,28} received the maximum score of 9, reflecting clearly defined case and control groups, robust exposure ascertainment, and adequate adjustment for major confounding variables. The study by Seng et al¹⁷ scored the lowest (5 points), primarily due to inadequate case definition, lack of control for confounders, and insufficient exposure assessment. The majority of studies ($n = 11$) scored ≥ 7 ,^{18–29} indicating generally acceptable quality with consistent ascertainment methods and minimal non-response bias.

Association Between Depression and the Risk of HG

A total of 13 case-control studies^{17–29} reported the association between depression and the risk of HG in pregnant women. Significant heterogeneity was found (p for Cochrane Q test < 0.001 ; $I^2 = 93\%$). Pooled analysis using a random-effects model indicated that in the overall analysis, women with depression had higher odds of being classified in the HG group than in the control group (OR: 5.08, 95% CI: 2.71 to 9.52, $p < 0.001$; Figure 2). Because only two studies assessed depression before HG diagnosis and all others concentrated on depressive symptoms at the time of HG diagnosis, these findings should be interpreted primarily as evidence of a strong co-occurrence of depression and HG, rather than as proof that depression is a causal risk factor for HG. Sensitivity analyses, conducted by sequentially excluding individual studies, demonstrated consistent and robust results (OR: 3.99–5.71, p (for all) < 0.05).

Subgroup analyses revealed that the association between depression and the risk of HG was more significant among women with a mean age of < 27 years compared to those aged ≥ 27 years (OR: 11.64 vs 2.86, p for subgroup difference = 0.02; Figure 3A). The association was also stronger in studies where depression was assessed at the time of HG diagnosis rather than before diagnosis (OR: 6.04 vs 2.11, p (for subgroup difference) = 0.04; Figure 3B), which may largely reflect the psychological and functional influences of HG itself, rather than representing a preceding risk factor. In addition, the method used to evaluate depression could influence the strength of the association: studies utilizing BDI/BDI-II or EPDS reported higher effect estimates than those using HADS-D (OR: 13.38 and 5.48 vs 1.73, p (for subgroup difference) = 0.009; Figure 4A). In contrast, the timing of HG diagnosis (first trimester only vs not restricted to first trimester) did not significantly influence the association (p (for subgroup difference) = 0.05; Figure 4B). Finally, further subgroup analyses indicated similar results in studies with and without the adjustment of gravidity or parity (OR: 5.88 vs 3.17, p (for subgroup difference) = 0.17; Figure 5A), and in studies with NOS scores of 5–7 and 8–9 (OR: 6.37 vs 4.86, p (for subgroup difference) = 0.75; Figure 5B).

Publication Bias

Funnel plots for the meta-analysis of the association between depression and HG are illustrated in Figure 6. The plots appeared symmetrical, suggesting a low risk of publication bias. Egger's test also indicated no evidence of publication bias ($p = 0.31$).

Discussion

Main Findings

This meta-analysis demonstrated a significant association between maternal depression and an increased risk of HG, based on pooled data from 13 case-control studies, involving over 95,000 pregnant women. The findings remained robust in sensitivity analyses. Taken together, these results indicate that depressive symptoms are commonly associated with HG and are likely a reflection of the psychological and functional influences of this severe condition, rather than demonstrating that depression predisposes individuals to the development of HG. Although heterogeneity was high, subgroup analyses identified several key study- and patient-level characteristics that may partly explain this variation. Notably, the association was more significant in younger women, when depression was assessed concurrently with HG, and when specific depression screening tools, such as the BDI and the EPDS, were utilized. These findings support the relevance of both biological and psychosocial mechanisms linking depression to the pathogenesis of HG.

Several interconnected mechanisms may explain the abovementioned relationship. From a neuroendocrine perspective, depression is associated with dysregulation of the HPA axis, leading to elevated cortisol and altered stress responses.^{36,37}

Table 2 Study Quality Evaluation via the Newcastle-Ottawa Scale Scores

Studies	Adequate Case Definition	Representativeness of the Cases	Selection of Controls	Definition of Controls	Control for GA	Control for Other Confounding Factors	Ascertainment of Exposure	Same method of Ascertainment of Exposure	Non-Response Rate	Total
Seng 2007 ¹⁷	0	I	I	I	0	0	0	I	I	5
Uguz 2012 ²⁰	I	I	I	I	I	0	I	I	I	8
Hizli 2012 ¹⁸	I	I	I	I	I	I	I	I	I	9
Simsek 2012 ¹⁹	I	0	I	I	I	I	I	I	I	8
Ezberci 2014 ²⁸	I	I	I	I	I	I	I	I	I	9
Aksoy 2015 ²¹	I	I	I	I	I	I	I	I	I	9
Kjeldgaard 2017 ²²	I	0	I	I	I	I	I	I	I	8
Senturk 2017 ²³	I	I	I	I	0	I	I	I	I	8
Topalahmetoğlu 2017 ²⁴	I	0	I	I	I	I	I	I	I	8
Mitchell-Jones 2020 ²⁵	I	0	I	I	0	I	I	I	I	7
Azlan 2022 ²⁹	I	0	I	I	I	I	I	I	I	8
Asrade 2023 ²⁶	I	I	I	I	I	I	I	I	I	9
Dutta 2023 ²⁷	I	0	I	I	I	I	I	I	I	8

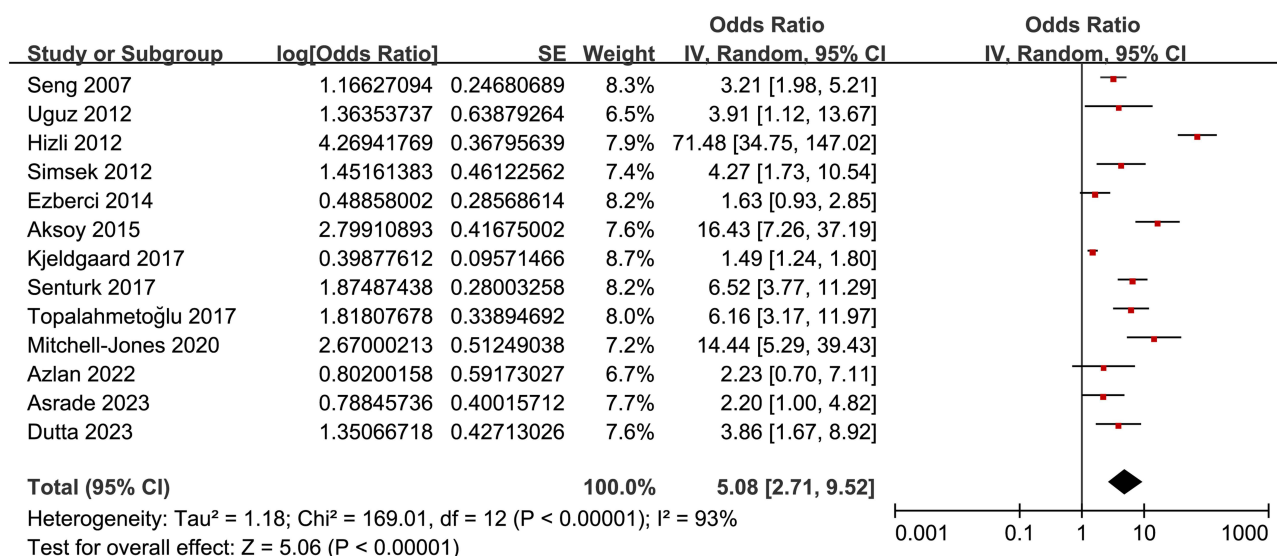


Figure 2 Forest plots for the meta-analysis of the association between depression and the risk of HG.

Such hormonal changes may intensify nausea and vomiting via central pathways, regulating gastrointestinal motility and appetite.^{38–40} In depressive disorders, dysregulation of the HPA axis typically manifests as hyperactivation, characterized by elevated levels of corticotropin-releasing hormone, increased adrenocorticotrophic hormone drive, and higher circulating cortisol levels, reflecting an exaggerated stress response. While atypical presentations with blunted cortisol responses can occur, the predominant pattern is one of HPA-axis overactivity.⁴¹ These alterations may influence stress sensitivity and emotional responses, while should not be interpreted as evidence of a shared biological mechanism with HG. Additionally, altered levels of neurotransmitters, such as serotonin and dopamine, which are implicated in both mood regulation⁴² and emetic responses,⁴³ may mediate overlapping pathways between depression and HG. Depression has also been associated with systemic inflammation, characterized by elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), which may further exacerbate gastrointestinal symptoms.⁴⁴ However, rather than suggesting a shared physiological pathway, the frequent co-occurrence of depressive symptoms in HG is more plausibly explained by the profound physical and functional burden imposed by the condition. The disabling nausea, vomiting, dehydration, and loss of daily functioning associated with HG can significantly impact emotional well-being, leading to heightened distress and depressive symptoms.^{45,46} Therefore, the association observed in most studies likely reflects a psychological response to the severity of HG, rather than a common underlying biological mechanism.

Subgroup analyses yielded additional insights. The stronger association observed in younger women may reflect the elevated hormonal sensitivity, limited psychosocial support, or lower resilience to pregnancy-related stressors in this population. First-time maternal anxieties and a lower threshold for experiencing or reporting somatic symptoms may also contribute to this vulnerability.^{47,48} The timing of depression assessment could be a principal factor, in which studies evaluating depression at the time of HG diagnosis demonstrated a stronger association than those assessing depression prior to HG onset. This may reflect either a true exacerbation of depressive symptoms due to the physical burden of HG or shared acute-phase pathophysiology. In terms of measurement tools, the stronger association observed in studies using BDI and EPDS may be attributed to their higher sensitivity in detecting subclinical depressive symptoms, particularly somatic and cognitive features that may overlap with HG symptoms.^{49,50} In contrast, instruments (eg, the HADS-D), which were designed to minimize the influence of somatic symptoms to avoid confounding with physical illness, may underestimate the severity of depression in pregnant women experiencing HG.⁵¹

Rather than indicating a shared physiological pathway, the frequent co-occurrence of depressive symptoms in HG is more plausibly explained by the profound physical and functional burden imposed by the condition. HG is an exceptionally debilitating somatic illness characterized by relentless nausea, vomiting, dehydration, electrolyte imbalance, and an inability to maintain daily activities, all of which can impose remarkable psychological strain. A substantial

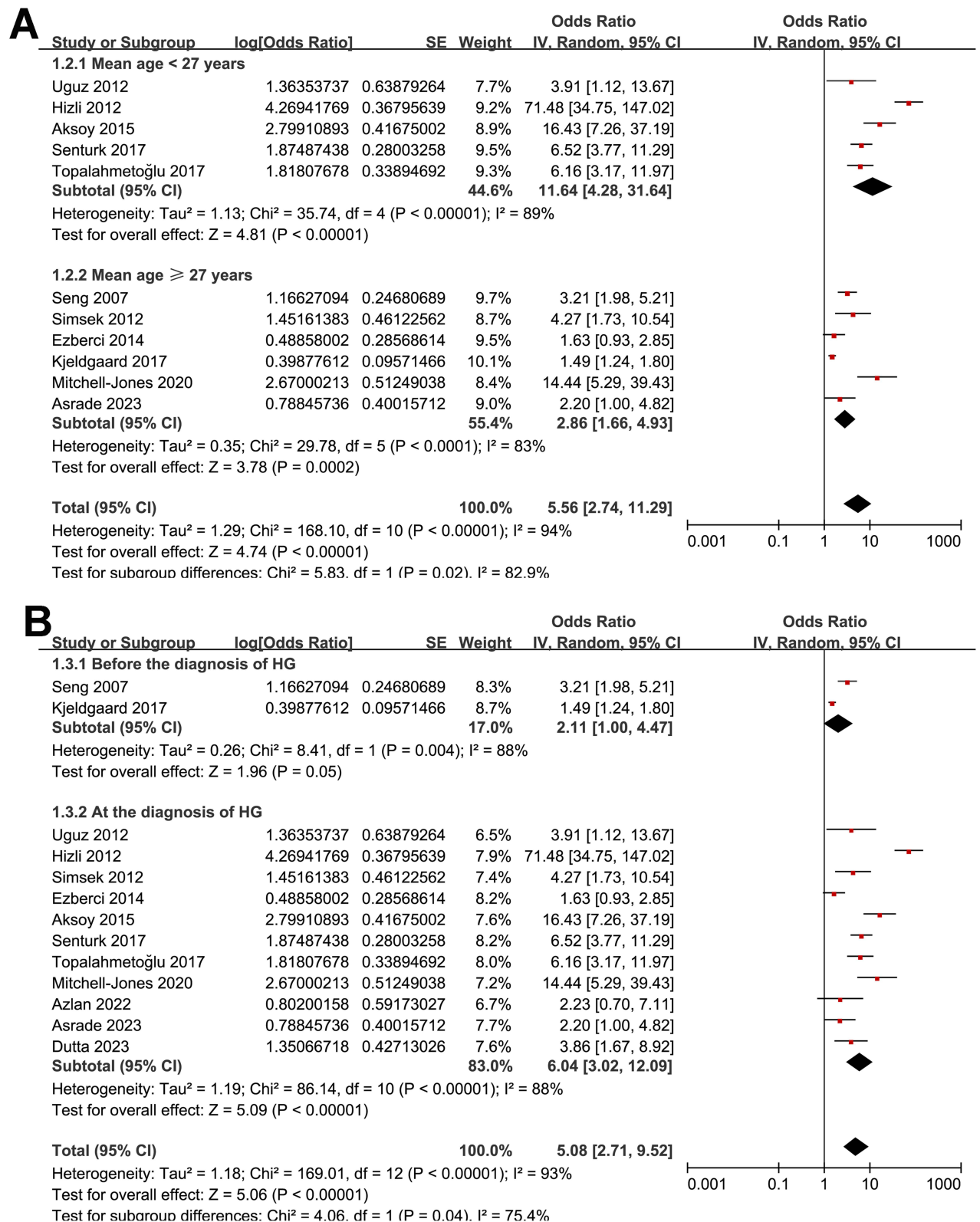


Figure 3 Forest plots for the subgroup analyses of the association between depression and the risk of HG; (A) subgroup analysis according to mean ages of the pregnant women; and (B) subgroup analysis according to timing of depression evaluation.

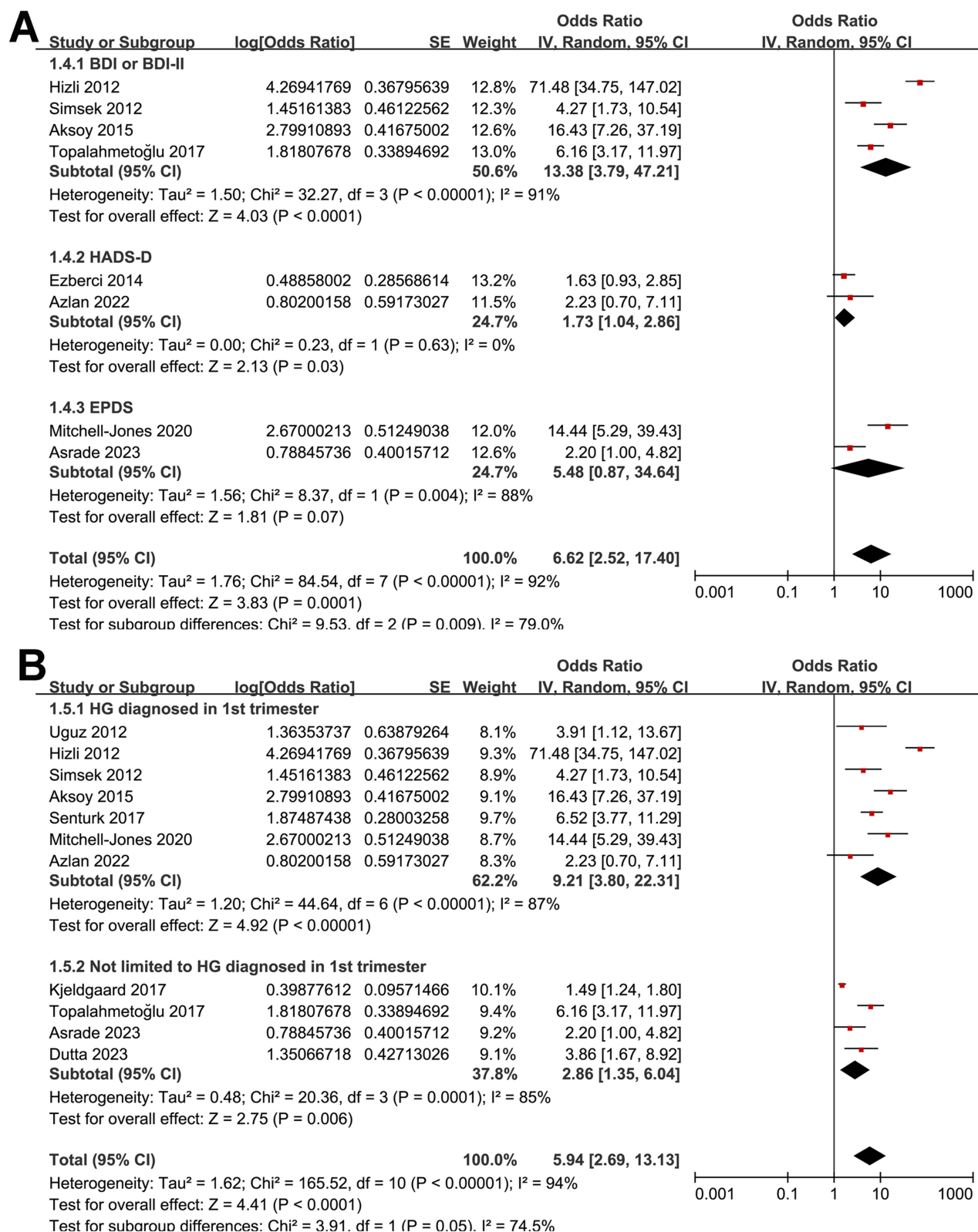


Figure 4 Forest plots for the subgroup analyses of the association between depression and the risk of HG; (A) subgroup analysis according to tools used for depression evaluation; and (B) subgroup analysis according to timing of HG diagnosis.

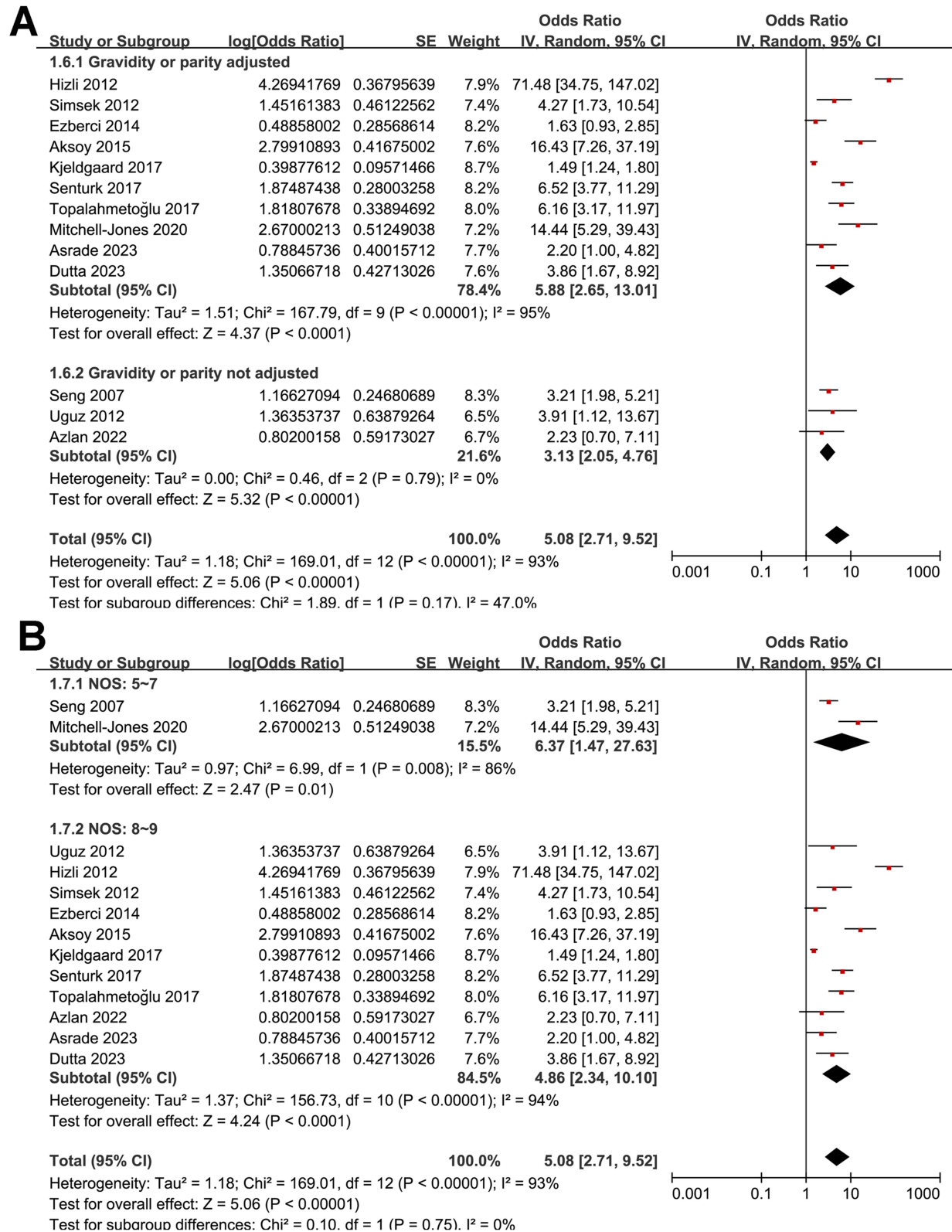


Figure 5 Forest plots for the subgroup analyses of the association between depression and HG; (A) subgroup analysis according to whether gravidity or parity was adjusted in the analysis; and (B) subgroup analysis according to the study quality scores.

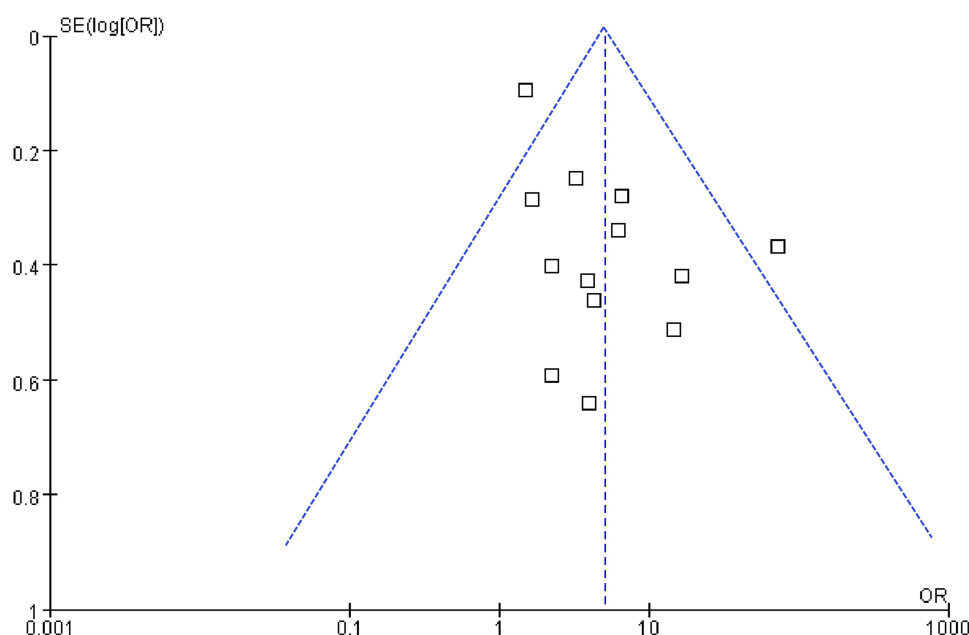


Figure 6 Funnel plots for estimating the potential publication biases underlying the meta-analyses of the association between depression and the risk of HG.

body of literature demonstrates that HG is associated with significant increases in anxiety, depressive symptoms, emotional distress, and impaired quality of life. For instance, the comprehensive systematic review by Mitchell-Jones et al¹⁴ found significantly elevated rates of psychological morbidity in patients with HG compared with healthy pregnant controls. Similar findings have been consistently reported in multiple case-control and cohort studies,^{20,23,25,28,29} demonstrating that HG profoundly affects emotional well-being through mechanisms, such as prolonged functional impairment, inability to work or care for oneself, repeated hospitalizations, and anxiety regarding pregnancy progression. Taken together, these data strongly demonstrate that the depressive symptoms observed in patients with HG largely reflect a psychological response to the overwhelming somatic severity and chronicity of the condition, rather than evidence of a shared biological mechanism or a causal contribution of depression to the onset of HG.

Strengths and Limitations

This meta-analysis has several strengths. Firstly, this meta-analysis was grounded in an up-to-date, comprehensive literature search across three major databases and incorporated a large aggregate sample size. Secondly, the majority of the included studies employed validated diagnostic instruments for both depression and HG, with adjustments for key confounders, such as maternal age, gestational age, parity, and BMI. Thirdly, extensive sensitivity and subgroup analyses were conducted to explore heterogeneity and assess the robustness of the findings. These methodological strengths enhance confidence in the observed associations and yield clinically relevant insights. However, several limitations warrant consideration. All the included studies employed a case-control design, limiting the ability to infer temporal or causal relationships between depression and HG. The analysis relied on study-level rather than individual participant data, restricting the ability to uniformly control for confounders or perform more detailed stratifications, such as trimester-specific depression severity, parity, or ethnicity. Moreover, important factors, such as prior psychiatric history, antidepressant use, psychosocial stress, partner support, and socioeconomic status⁵² were not consistently reported and could not be examined in subgroup analyses. Consequently, the influences of these variables remained unresolved. Lastly, in several studies, it was infeasible to determine whether depression assessments were conducted prior to the onset of vomiting, complicating the interpretation of the temporal relationship between the two conditions.

Comparison with Existing Literature

From a clinical perspective, these findings underscore the importance of integrating mental health screening into early antenatal care. Pregnant women presenting with depressive symptoms may warrant closer monitoring for signs of HG, and vice versa, in which women with severe HG may benefit from psychological support and evaluation. Early identification and intervention could mitigate the severity of both conditions and improve maternal and fetal outcomes. Although the findings do not establish causality, they highlight a potentially modifiable risk factor, requiring greater emphasis in prenatal care. Future research should prioritize prospective cohort studies featuring repeated assessments of depressive symptoms throughout pregnancy to clarify temporal relationships. Exploring biological markers of stress and inflammation may further elucidate underlying mechanisms and help identify women who are at elevated risk. Additionally, studies assessing the effects of early psychological interventions on HG outcomes can provide valuable insights for developing integrated treatment strategies. Consequently, multidisciplinary research involving obstetricians, psychiatrists, and public health professionals is warranted to address the complex interaction between mental health and pregnancy-related complications.

Conclusions

In conclusion, depressive symptoms are frequently identified in patients with HG, reflecting the significant psychological toll of this severe and debilitating condition. Since nearly all included studies assessed depression at the time of HG diagnosis, the temporal relationship remains elusive; however, available evidence demonstrates that HG is more likely to contribute to the development of depressive symptoms than the other way around. These findings highlight the need to integrate mental health assessment with support into the comprehensive care of patients with HG. Further prospective research is necessary to clarify the progression of these symptoms and to identify effective strategies for supporting the psychological well-being of this population.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors confirm that they have no conflicts of interest to declare.

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