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Impact of Vitamin D during Pregnancy towards Postpartum Depression: A Meta-Analysis of Dose-response Association and Intervention

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Impact of Vitamin D during Pregnancy towards Postpartum Depression: A Meta-Analysis of Dose-response Association and Intervention

Short title: Prenatal Vitamin D and Postpartum Depression

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ABSTRACT

Introduction: Serum vitamin D (25(OH)D) concentration has been associated with PPD in previous studies. However, whether there is a dose-response relationship and if its supplementation during pregnancy can improve symptoms after delivery remains unclear.

Methods: Five databases were searched on September 27, 2025. Cohort studies were included for dose-response meta-analysis (DRMA), while randomized controlled trials (RCTs) were included for meta-analysis (MA) of supplementation. The outcome for MA of supplementation was postpartum Edinburgh Postnatal Depression Scale (EPDS) score using the effect measure of mean difference (MD), while the outcome for DRMA was the odds ratio (OR) of PPD after delivery. Certainty was assessed using GRADE for MA of supplementation.

Results: Only two prospective cohort studies were included for DRMA and two RCTs were included for MA of supplementation. There was a significant log linear dose-response relationship between 25(OH)D serum concentration and developing PPD

with β = -0.0256 (95% CI = -0.0454 to -0.0057). Every 10 nmol/L increase was associated with OR = 0.77 (95% CI = 0.63 to 0.94). Meta-analysis found a significant reduction in EPDS scores at 4 weeks after delivery (MD = -2.70; 95% CI = -3.68 to -1.71; low certainty).

Conclusion: Vitamin D serum concentration during pregnancy might be log linearly associated with developing PPD after delivery and its supplementation during pregnancy may improve PPD symptoms at 4 weeks postpartum. However, findings should be interpreted cautiously as evidence is limited to the small number of studies.

Keywords: Maternal health, Postpartum depression, Vitamin D.

INTRODUCTION

Postpartum depression (PPD) is a depressive episode that starts during pregnancy or within the first four weeks of birth.[1] This condition has a high prevalence and represents a significant burden for mothers. A meta-analysis of 565 studies conducted between January 2000 to July 2021 found a pooled global prevalence of 17.22% among pregnant populations with significantly lower prevalence in high income countries (15.54%) compared to upper-middle (19.68%), lower-middle (20.14%), and low income (20.02%) countries.[2] This is particularly concerning as PPD is associated with poorer maternal and infant outcomes, including poorer maternal-infant bonding, reduced early breastfeeding initiation, reduced exclusive breastfeeding, and impaired offspring cognitive function.[3,4,5]

Vitamin D has been increasingly linked to depressive symptoms. Several studies have suggested that this association may be mediated by the widespread expression of vitamin D receptors (VDR) in brain regions implicated in depression, as well as their role in modulating neurotrophic factors. Vitamin D receptors are expressed in the prefrontal cortex, hippocampus, and the substantia nigra. In the substantia nigra, it has been reported that higher VDR expression (indicating vitamin D deficiency) could delay dopamine cell differentiation, thus leading to dopamine mediated behavioural deficits such as depression. On the other hand, neurotrophic agents are crucial for the survival and growth of neurons, which may have implications for maintaining optimal functions in the brain regions involved in depression pathogenesis.[6]

This link is not merely mechanistic and has been observed clinically. Systematic reviews and meta-analyses of observational studies have reported that vitamin D serum levels were lower across diverse depressed populations compared to their

respective non depressed controls.[7,8] Similar findings have been reported in studies comparing antenatal and postnatal women with depression and without depression.[9,10] However, existing observational studies investigating the association of vitamin D levels during pregnancy and PPD had varying baseline vitamin D concentrations. Although an association has been identified, it remains unclear whether a dose-response relationship exists. Furthermore, while vitamin D supplementation during pregnancy has been proposed as a potential intervention, a systematic synthesis of the available evidence is lacking. To address this knowledge gap, we conducted a systematic review and meta-analysis to evaluate the dose-response association of serum vitamin D concentration [25(OH)D] during pregnancy with developing PPD after delivery, as well as to assess the effect of vitamin D supplementation on PPD symptoms after delivery.

METHOD

Design and registration

This systematic review and meta-analysis adhered to the recommendations from PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[11] This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on October 8, 2025, under the registration number CRD420251163808.

Search strategy

A systematic search was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Scopus, Proquest, and Epistemonikos to identify relevant studies. To ensure a comprehensive retrieval of literature, supplementary search methods were employed, including backward citation searching and handsearching of preprint servers and databases such as ScienceDirect and Google Scholar. No restrictions were placed on language or publication date. Keywords used in the search included combinations of ("Vitamin D" OR "25-hydroxyvitamin D" OR "Cholecalciferol") AND ("Postpartum Depression" OR "Postnatal Depression") AND ("Pregnancy" OR "Antenatal"). The full search strategy used for each database is found in the supplementary file (S2). Last database search was conducted on 2 October, 2025.

Eligibility criteria

Studies were selected based on eligibility criteria defined using the Population, Intervention/Exposure, Comparator, Outcomes, and Study Design (PICOS) framework.[11] The population was pregnant women, regardless of trimester. For the dose-response analysis, the exposure was serum 25(OH)D during pregnancy, compared against a reference concentration, with the outcome being the odds ratio (OR) for developing PPD. Studies that did not report OR for at least three categorical levels were excluded. For the interventional analysis, the intervention consisted of vitamin D supplementation initiated during pregnancy, compared to a placebo or usual care, with the primary outcome being postpartum depression scores. Prospective cohort studies were included for the dose-response analysis, whilst only randomised controlled trials (RCTs) were eligible for the interventional analysis. Vitamin D supplementation combined with other nutrients (e.g. broad-spectrum micronutrient supplementation) was excluded. Translations were carried out for studies reported in languages other than English. No limitation on the time of publication was applied.

Screening and selection

Screening started on 3 October, 2025. Records were retrieved in citation format from each database and uploaded to Rayyan.ai, a web-based screening and selection software for systematic reviews.[12] Automatic identification of the duplicates was followed by manual selection to eliminate them. Subsequently, two authors (S.N., W.J.T) independently screened the titles and abstracts of the remaining records to identify potentially relevant articles. The full texts of these articles were then retrieved and assessed for final inclusion based on the predefined eligibility criteria. Any disagreements between the two reviewers at any stage of the screening process were resolved through discussion and consensus, with the involvement of a third author if necessary (G.N.U).

Quality Appraisal

Two reviewers independently assessed the methodological quality and risk of bias for the included studies. The Cochrane Risk-of-Bias 2 (RoB-2) tool was used for the RCTs, while the Risk of Bias In Non-randomised Studies - of Exposures (ROBINS-E) tool was utilised for the prospective cohort studies. Two authors conducted the

appraisal, and any discrepancies in the assessment were resolved through a consensus-based discussion involving a third author.

Data extraction

Mean and SDs of postpartum depressive scores were extracted for pairwise meta-analysis. Meanwhile, the sample size and cases of PPD, along with the OR, were extracted for dose-response meta-analysis. Detailed explanations on data extraction for dose-response meta-analysis (DRMA) are provided in the statistical analysis subsection. One author conducted all data extraction, and a second author confirmed it. If conflicts were found, then a discussion involving a third author was conducted until a consensus was reached.

Statistical analysis

Pairwise meta-analysis of interventions was conducted using the “meta” package in R. The effect measures of mean difference (MD) were used for the continuous outcome of postpartum depressive score. A 95% confidence interval was applied. Both fixed- and random-effects models are conducted, but interpretation would focus towards the random-effects model in case of heterogeneity (I^2 >25% or Cochran’s Q test P <0.1).[13] Subgroup analysis, sensitivity analyses, and meta-regression were planned to investigate heterogeneity, but included studies were not adequate. Publication bias was planned to be assessed with funnel plot inspection and Egger’s test, but the number of studies were not adequate (<10).

Dose-response meta-analysis was conducted using the “dosresmeta” package in R. The number of cases and samples, along with the odds ratio (OR) and 95% CIs for at least three quantitative categories of vitamin D concentration, were required from a study. Odds ratios with adjustment for the most covariates were used from each study. However, if a study does not report an adjusted OR, then the unadjusted OR was used. Similarly, if no OR were reported, then the authors would calculate the OR using the reported data without adjusting for covariates. To obtain the vitamin D concentration in quantitative categories, the reported median circulating vitamin D concentration in each category was used. If medians were not reported, means were used. If neither the median nor the mean vitamin D concentration per category was reported, the midpoint of the upper and lower boundaries in each category was used to estimate median exposure level. If the upper boundary for the highest category was

open-ended, the value of the open-ended interval was assumed to be 1.5 times that of the closest category. If a study used a unit other than nmol/L of vitamin D, we converted the unit to nmol/L.[14] A potential non-linear dose-response relationship between serum 25(OH)D (nmol/L) and PPD was modelled by using restricted cubic splines with 3 knots at fixed percentiles (20%, 60%, and 80%). If there was no significant evidence of non-linear relationship, then a linear meta-regression approach was used to model log OR to 25(OH)D. The reference value of 50 nmol/L was selected as it is the commonly used threshold for deficiency (<50 nmol/L), thereby providing a clinically meaningful comparator.[15]

Certainty of Evidence Assessment

An evidence assessment was conducted to determine the efficacy of vitamin D supplementation during pregnancy in reducing postpartum depressive symptoms, aiming to evaluate whether the meta-analysis would reflect the true effect in the real world. The assessment was conducted using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) minimally contextualised approach for a non-null effect.[13] Assessment was conducted by two authors independently, and then conflicts were resolved through a discussion involving a third author.

RESULTS

Study Selection

The systematic literature search identified 1368 articles, with contributions from the following databases: Scopus = 845, PubMed = 155, Cochrane Library = 58, ProQuest = 200, and Epistemonikos = 110. After removing duplicates, 1024 articles remained for the initial screening. Titles and abstracts were reviewed, resulting in the exclusion of 991 articles and the remaining 33 full-text articles were sought after. However, three articles could not be retrieved. Subsequently, 30 full-text articles were assessed for eligibility. Of these, five studies were excluded for the following reasons: incorrect study design (n = 7), inappropriate time frame (n = 3), wrong outcome (n = 3), wrong population (n = 3), and inadequate data for meta-analysis (n = 4). Ultimately, four studies from four articles met the selection criteria. Two prospective cohort studies were included for DRMA and two RCTs were included for MA of supplementation. The flow chart can be seen in the provided supplementary file (S1).

Characteristics of Studies

The two cohort studies included were prospective. Gur *et al* 2014 measured vitamin D at 24-28 weeks of pregnancy and used a score of ≥12 on the EPDS at 6 months postpartum as the cutoff definition for PPD. The study did not report any adjusted ORs; thus, the authors calculated the OR without adjusting for covariates. They reported adjusted ORs (Table 1).

Table 1. Characteristics of included cohort studies for dose-response meta-analysis.

Author, year	Country	Time of Vitamin D Measurement	PPD Definition	Time of PPD Assessment	Adjusted Covariates
Gur, 2014[17]	Turkey	24-28 weeks of pregnancy	EPDS ≥12	6 months postpartum	None
Robinson, 2014[18]	Australia	18 weeks of pregnancy	6+ symptoms on the EPDS	3 days postpartum	Pre-pregnancy body mass index, maternal age, maternal education, total family income, maternal smoking, maternal alcohol intake, hypertensive diseases of pregnancy, proportion of optimal birth weight, child gender, SCN admission and season of birth; Perth, Western Australia 1989–1992

Both RCTs included were single-centre studies in Iran. Both also used the same vitamin D supplementation dose, which is 2,000 IU from 26-28 weeks pregnancy until delivery. Both RCTs had a key exclusion criterion of EPDS baseline >13. Thus, only including those without a high risk of PPD during pregnancy (Table 2).

Table 2. Characteristics of included randomised controlled trials for meta-analysis.

Author, year	Single/ Multi Centre	Country	Sample Size (I/C)	Key Exclusion Criteria	Age (I/C)*	Baseline EPDS (I/C)*	Vitamin D Dose	Control Group	PPD Scale (time frame)
Vaziri, 2016[19]	Single center	Iran	75/78	EPDS baseline scores of >13	26.40 ± 4.88 / 26.22 ± 4.33	8.44 ± 3.89 / 8.64 ± 3.81	2,000 IU from 26-28 weeks until delivery	Placebo	EPDS (4 week postpartum)

Dabbaghmanesh, 2019[20]	Single center	Iran	46/52	EPDS baseline scores of >13	26.04 ± 5.07 / 26.61 ± 4.01	8.52 ± 3.61 / 8.00 ± 3.69	2,000 IU from 26-28 weeks until delivery	Placebo	EPDS (4 week postpartum)

*Data are presented as mean ± standard deviation
Abbreviations: I, intervention group; C, control group; EPDS, Edinburgh Postpartum Depression Scale

Risk of Bias

For both cohort studies, risk of bias assessment was performed using the ROBINS-E instrument. The study by Gur *et al.* (2014) was rated as having an overall level of 'Some Concerns'. Although this study had good exposure and outcome measurements, concerns arose from the participant selection and confounding domains due to the use of very strict exclusion criteria that could potentially cause bias. Meanwhile, the study by Robinson et al. 2014 was assessed as having a 'High Risk of Bias'. This high-risk assessment was mainly due to the failure to control for a very important confounding variable, namely the mother's mental health history during pregnancy. Additionally, there were several concerns in the domains of outcome measurement and missing data.

Both included RCTs were judged as high risk of bias. Vaziri *et al*. 2016 did not report allocation concealment in their article. Furthermore, there was a baseline imbalance in the proportion of planned pregnancy (higher in the vitamin D group) and using other supplements (higher in the control group), this resulted in a high risk of bias in domain one. The second domain was rated as having some concerns due to the non-blinding of participants, but no information regarding deviations from the intended intervention was reported. Since the participant was not blinded to the intervention, the outcome is likely biased, given that EPDS is a self-reported scale. Overall, these limitations result in an overall high risk of bias. In Dabbaghmanesh *et al*. 2019, allocation concealment was not reported; however, no baseline imbalance was found, resulting in some concerns of bias in the randomization process. A substantial portion of outcome data was missing in the study, but the reasons for its absence were not reported, resulting in a high risk of bias in domain three. Overall, the study was judged to have a high risk of bias (Figure 1).

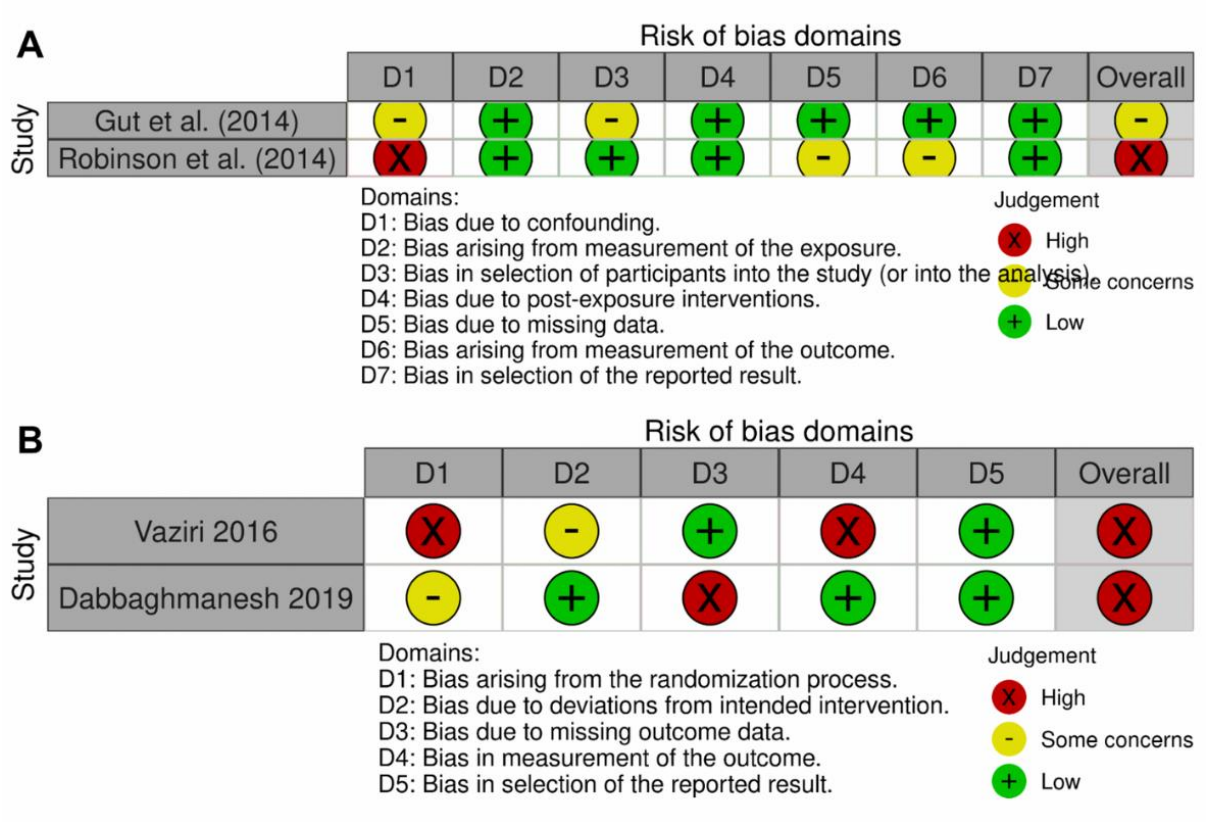

Figure 1. Risk of bias of included (A) cohort studies and (B) randomised controlled trials. Cohort studies were assessed using the ROBINS-E tool, and randomized controlled trials were evaluated using the RoB 2 tool. ROBINS-E domains include bias due to confounding, participant selection, exposure classification, deviations from intended exposures, missing data, outcome measurement, and selection of the reported result. RoB 2 domains include bias arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. The overall risk-of-bias judgment was determined based on domain-level assessments, with the highest level of risk in any domain contributing to the overall rating.

Dose-Response Association of Vitamin D Levels during Pregnancy towards developing PPD

Two cohort studies (Gur *et al*. 2014; Robinson *et al*. 2014) reported sufficient data for DRMA. Robinson *et al*. 2014 reported adjusted OR, while Gur *et al*. 2014 did not; therefore, OR was calculated from the available data without adjustment for covariates. The restricted cubic splines analysis did not show evidence of a significant non-linear relationship (p = 0.97). In contrast, the log-linear model showed a significant dose-response relationship, with each 1 nmol/L increase associated with β = -0.0256 (95% CI = -0.0454 to -0.0057; P = 0.0012). However, it should be noted that the spline

analysis should be considered exploratory due to the lack of studies. Model estimates predicted that for every 10 nmol/L increase in serum concentration, there were lower 0.77 lower odds of PPD (95% CI = 0.63 to 0.94). Serum 25(OH)D concentrations below 50 nmol/L were significantly associated with higher odds of PPD, whereas concentrations above were associated with lower odds. There was high heterogeneity indicated by I^2 = 75.3% and the Cochran's Q test (P = 0.004). The dose-response relationship is plotted in Figure 2. However, sensitivity analysis excluding unadjusted OR found a trend for no significant evidence for restricted cubic spline (P = 0.47) and linear regression models (P = 0.22).

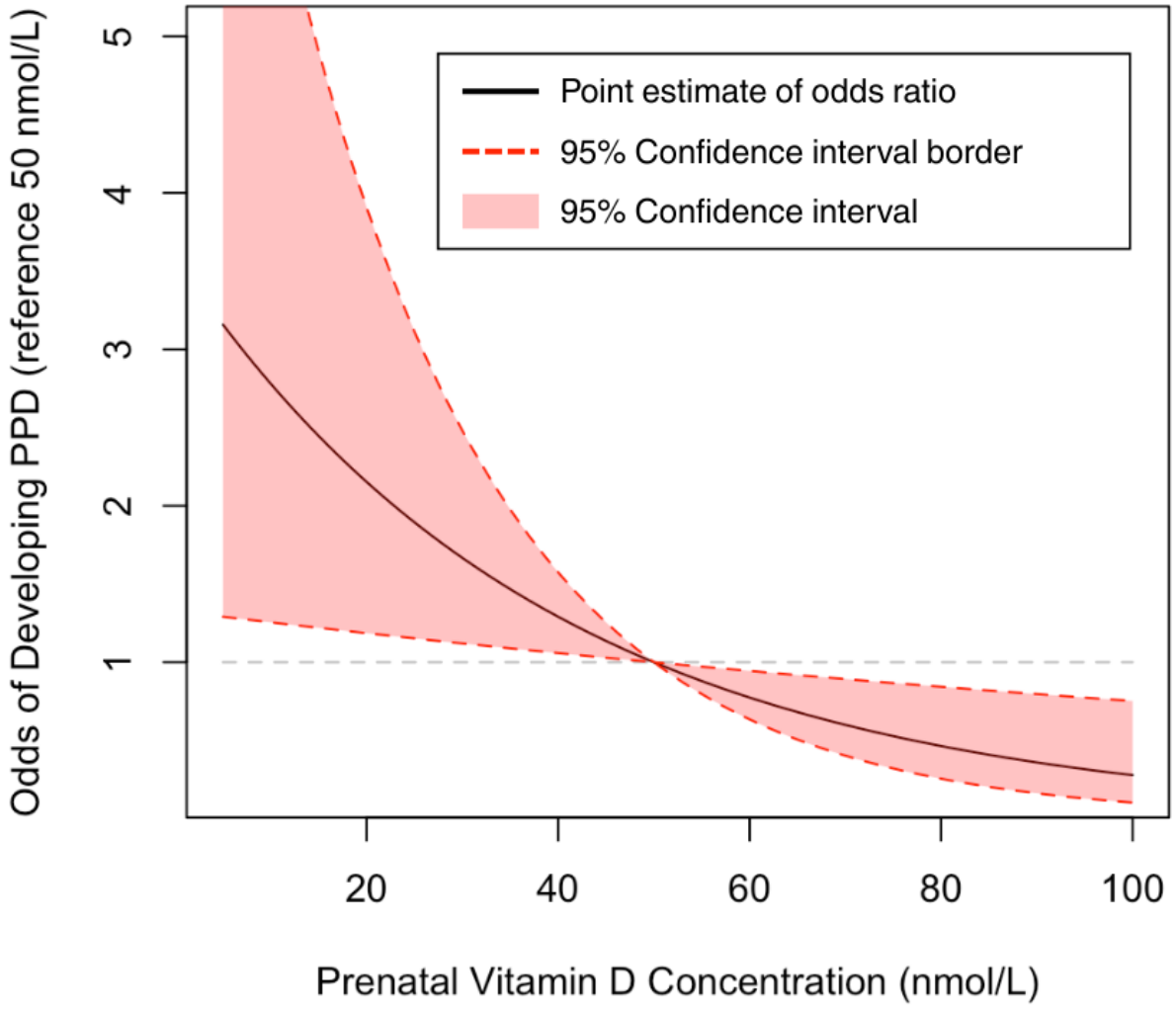

Figure 2. Dose-response relationship of vitamin D serum concentration during pregnancy and odds of developing PPD.

Efficacy of Vitamin D Supplementation during Pregnancy towards PPD Symptoms

Two RCTs (Dabbaghmanesh *et al*. 2019; Vaziri *et al*. 2016) were eligible for meta-analysis of the efficacy of vitamin D supplementation during pregnancy towards PPD symptoms. Dabbaghmanesh *et al*. 2019 assessed EPDS at 4 weeks postpartum, while Vaziri *et al*. 2016 assessed EPDS at 4 weeks and 8 weeks postpartum. Meta-analysis was conducted at 4 weeks postpartum, as this was the only common time frame reported by both studies. Meta-analysis showed that vitamin D supplementation during pregnancy led to a statistically significant reduction of PPD symptoms (MD = -2.70; 95% CI = -3.68 to -1.71), with minimal heterogeneity indicated by I^2 = 0% and Cochran's Q test (P = 0.86; Figure 3).

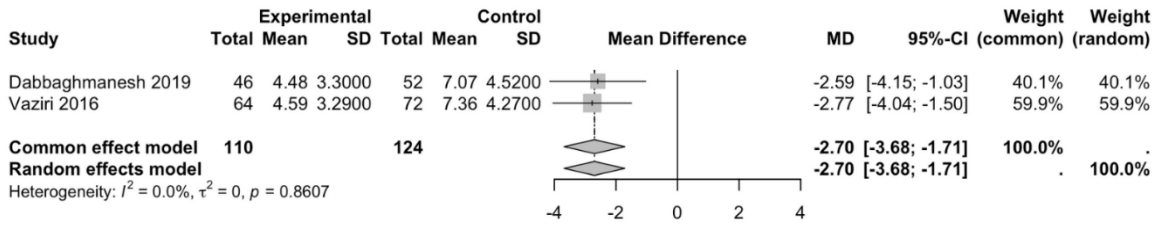

Figure 3. Forest plot for meta-analysis of the efficacy of vitamin D supplementation during pregnancy towards postpartum depressive symptoms.

Certainty of Evidence Assessment

Certainty of evidence assessed by the authors was deemed as low, a rate down of two levels due to serious concerns about risk of bias and indirectness. Both RCTs included were judged to be high risk of bias, with some bias favouring the vitamin D supplementation group. These included a higher rate of wanted pregnancy in the vitamin D group alongside non-blinding of participants in Vaziri *et al.* 2016, and lack of reporting of the reasons behind missing outcome data in Dabbaghmanesh *et al.* 2019. Serious concern of indirectness was identified, as both RCTs included only low risk pregnant women (EPDS < 13) in Iran, thereby limiting the generalizability to other ethnic groups and high risk pregnant populations. There was no serious concern about inconsistency, as heterogeneity was minimal (I^2 = 0%). Lastly, publication bias could not be assessed due to a lack of studies. Overall, using GRADE recommended

language, vitamin D supplementation during pregnancy may improve PPD symptoms at 4 weeks after delivery.[21] The summary of findings is presented in Table 3.

Table 3. Summary of finding for the efficacy of vitamin D supplementation during pregnancy towards postpartum depressive symptoms.

No of studies	No of patients: Vitamin D	No of patients: Placebo	Absolute effect (95% CI)	Certainty	Plain language summary
Postpartum depressive symptoms measured by EPDS at 4 weeks postpartum					
2 randomised trials	110	124	2.70 points lower (3.68 lower to 1.71 lower)	⨁⨁◯◯ **Low**	Vitamin D supplementation during pregnancy may improve postpartum depressive symptoms at 4 weeks after delivery

DISCUSSION

Previous meta-analyses exploring the relationship between maternal vitamin D and postpartum depression (PPD) have generally reported an inverse association, but with inconsistent magnitude and certainty due to methodological and clinical heterogeneity. Gould *et al.* (2022)[22] and Centeno *et al.* (2024)[23] both identified that lower maternal serum 25(OH)D concentrations were associated with greater odds of depressive symptoms during or after pregnancy. However, their pooled effect sizes varied widely (pooled ORs ranging from 0.62 to 0.81 across categories of deficiency). These studies, however, did not evaluate a formal dose-response relationship, and their subgroup analyses were limited by between-study variation in vitamin D thresholds, timing of assessment, and depression scales used.

Our findings extend these prior observations by providing the first quantitative dose–response synthesis demonstrating a continuous reduction in PPD risk with increasing vitamin D levels during pregnancy. We found a log linear relationship, with every 10 nmol/L increase in prenatal vitamin D associated with 23% lower odds of PPD (OR =

0.77; 95% CI = 0.63–0.94), albeit with between-study heterogeneity (I^2 = 75.3%) and confounding bias. Our result suggests that serum concentrations below 50 nmol/L increase the risk of PPD, a finding consistent with the deficiency cut-offs proposed by Szpunar (2023).[24] However, it is important to mention that upon exclusion of unadjusted OR, evidence for a dose-relationship became statistically insignificant. More studies to increase sample size are needed as only two prospective cohort studies are currently available.

Besides its primary function in bone metabolism, vitamin D has numerous effects in other systems, including the immune, cardiovascular, and neuroendocrine systems. In a consensus statement, Mattioli et al. (2025) detail that vitamin D has an anti-inflammatory effect, and it modulates endothelial and neurohormonal systems due to the widespread distribution of vitamin D receptor (VDR) in the body.[25] Supporting this systemic effect, Pagnoni et al. (2025) show that vitamin D deficiency has cardiovascular consequences and worsens echocardiographic findings, reinforcing vitamin D's role in the regulation of vascular and inflammatory systems.[26] These mechanisms may be especially relevant to postpartum depression (PPD) because there is growing evidence that neuroinflammation, the disruption of the hypothalamic–pituitary–adrenal (HPA) axis, and altered monoaminergic signaling, particularly with regard to dopamine, are involved in the pathology of PPD. Vitamin D has demonstrated the ability to suppress the production of pro-inflammatory cytokines, modify neurotrophic factors, and improve dopaminergic transmission, thus supporting its presumed role in the protection against depression. Subsequently, the consensus recommends that vitamin D supplementation should be adjusted depending on the individual's baseline level and risk factors, which aligns with our findings of a dose–response relationship. This suggests that vitamin D may provide more mental health benefits in pregnant women with deficiency. This may also account for the differences in outcomes of various studies, and supports the importance of personalized supplementation strategies in pregnant women.

Interestingly, the point estimate and confidence interval of our meta-analysis of supplementation do not cross the minimal important difference estimated in a previous study, but we argue that the difference found in our meta-analysis may still be clinically significant. Our meta-analysis found a statistically significant reduction of 2.70 points on the EPDS scale at four weeks after delivery (low certainty). The study by Mao *et al.* 2021[29] estimated that the minimal important difference for a clinically relevant

improvement for EPDS is a 4-point reduction. They reached this estimate by taking the average score of the distribution-based method (0.5 SD and standard error of the measurement) and the anchor-based method (9-item Patient Health Questionnaire [PHQ-9], 7-item Generalized Anxiety Disorder [GAD-7], and participants' self-appraisal served as anchors). However, this estimate may not accurately reflect the minimal important difference for our meta-analysis as it is a between-group comparison, while their study measured within-group changes. Additionally, a 4-point reduction may also not reflect the threshold for an important prophylactic effect. In Vaziri *et al.* 2016, it is reported that the proportion of mothers with EPDS < 9 was significantly higher in the vitamin D group than in the control group (90% vs 59.7%; P = <0.001). Additionally, the proportion of women having EPDS >13 was 8.3% in the control group compared to 0% in the vitamin D group. Thus, the estimate we found in this meta-analysis still has the potential to be clinically important. Further studies investigating the threshold for an important difference are needed to properly evaluate the clinical significance of these findings.

Robust neurobiological and endocrine mechanisms support the observed association between maternal vitamin D status and postpartum depression risk. The active metabolite, $1,25(OH)_2D$, interacts with VDRs which are abundantly expressed in mood-regulating brain regions such as the prefrontal cortex, hippocampus, and amygdala.[30] Through genomic modulation, vitamin D enhances tryptophan hydroxylase-2 (TPH2) expression, the rate-limiting enzyme in central serotonin synthesis, thereby promoting serotonergic neurotransmission and improving emotional regulation. Deficiency in vitamin D has been associated with reduced serotonin production and increased depressive vulnerability, which may explain the dose-dependent relationship identified in this study.[31]

Beyond its neurotransmitter effects, vitamin D serves as an immunomodulatory and anti-inflammatory agent. It suppresses pro-inflammatory cytokines such as IL-6 and TNF-α while augmenting anti-inflammatory cytokine activity, potentially mitigating neuroinflammation, a key contributor to the pathophysiology of depression.[32] During pregnancy and the postpartum period, the maternal immune system undergoes dynamic modulation, and dysregulation of this balance has been implicated in perinatal mood disorders. By maintaining immune homeostasis, vitamin D may protect against such inflammatory shifts.

Additionally, vitamin D influences hypothalamic–pituitary–adrenal (HPA) axis stability, reducing cortisol hyperreactivity to stress. It also enhances neuroplasticity via the upregulation of brain-derived neurotrophic factor (BDNF) and supports neuronal survival through antioxidant mechanisms.[33] These converging pathways—neurotransmitter synthesis, immune regulation, stress adaptation, and neurotrophic support—form a biologically coherent rationale for the beneficial effects observed in our dose–response and interventional analyses. The modest yet significant clinical effect detected, even in trials with high risk of bias, suggests that vitamin D may exert a causal, biologically grounded influence on mood regulation during the perinatal period, contingent on adequate serum repletion.[34]

Our findings could have clinical implications. The relationship between vitamin D and developing PPD indicates that screening and correcting vitamin D deficiency in pregnant women could be considered as a preventive strategy for PPD, especially in populations at high risk for deficiency. However, vitamin D supplementation should not be a stand-alone treatment for established PPD; instead, it should be integrated with other standard psychological and pharmacological interventions that have been proven to provide clinically significant improvements. From a public health perspective, ensuring adequate maternal vitamin D, whether through supplementation, nutrition, or sufficient sun exposure, could be beneficial in improving mental well-being postpartum at a larger scale.

However, there are several limitations to our meta-analysis. Serious limitations exist regarding indirectness or the applicability of supplementation to the general population of pregnant women, as both RCTs were conducted in Iran excluding pregnant women at high risk for PPD (EPDS > 13). Extrapolation of this finding to other ethnic groups or high risk pregnant women should be with serious caution. Additionally, identical doses of 2,000 IU daily, starting from 26-28 weeks of gestation until delivery, limits insight into dose-response interaction.

Furthermore, it should be explicitly mentioned that pooled estimates in our meta-analyses are fragile due to the limited number of studies. They are highly susceptible to individual study effects and random error. Given the small number of included studies, future research has the potential to substantially alter the pooled estimates. These findings should be considered preliminary pending larger and more rigorous studies.

Gur et al. 2014 did not report adjusted OR, leading to confounding bias. Secondly, the cutoff for PPD in the two studies differs: Gur et al. 2014 used EPDS ≥12, while Robinson et al. 2014 used six or more symptoms in the EPDS scale (not using the total score). To resolve these limitations, we propose that further prospective cohort studies reporting adjusted OR values and more standardised cut-off values for PPD are still needed to obtain more accurate estimates.

CONCLUSION

In conclusion, this study found a potential log-linear relationship between prenatal serum 25(OH)D and developing PPD after delivery, alongside it prenatal supplementation may improve PPD symptoms 4 weeks after delivery, but the current number of studies are limited. Prospective cohort studies adjusting for confounding factors are still needed. Current randomized evidence is strictly limited to pregnant women with EPDS ≤ 13 in Iran, therefore larger and more diverse RCTs are needed to confirm the efficacy of supplementation before considering wide use. The available trials used 2,000 IU daily; however, optimal dosing remains uncertain.

AVAILABILITY OF DATA, CODE AND OTHER MATERIALS

The template data collection forms, data extracted from included studies, data used for all analyses, analytic code, and any other materials used in this review may be given to persons upon request to the corresponding author, and they are deemed valid by the authors.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

SPN: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization,

Writing – original draft preparation, Writing – review and editing, Final approval of manuscript.

GNU: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft preparation, Writing – review and editing, Final approval of manuscript.

JFW: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft preparation, Writing – review and editing, Final approval of manuscript.

WJT: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft preparation, Writing – review and editing, Final approval of manuscript.

DFFA: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft preparation, Writing – review and editing, Final approval of manuscript.

Handling Editor: Dr. Marco Antonio Caldieraro

REFERENCES

1. Edition F. Diagnostic and statistical manual of mental disorders. Am Psychiatric Assoc. 2013;21(21):591-643.
2. Wang Z, Liu J, Shuai H, Cai Z, Fu X, Liu Y, et al. Mapping global prevalence of depression among postpartum women. Translational psychiatry. 2021;11(1):543.
3. Sanni SO, Adeoye IA, Bella-Awusah TT, Bello OO. Influence of postpartum depression on maternal-infant bonding and breastfeeding practices among mothers in Abeokuta, Ogun state. Discover Mental Health. 2024;4(1):46.
4. Papadopoulou SK, Pavlidou E, Dakanalis A, Antasouras G, Vorvolakos T, Mentzelou M, et al. Postpartum depression is associated with maternal sociodemographic and anthropometric characteristics, perinatal outcomes, breastfeeding practices, and mediterranean diet adherence. Nutrients. 2023;15(17):3853.
5. Sanger C, Iles JE, Andrew CS, Ramchandani PG. Associations between postnatal maternal depression and psychological outcomes in adolescent

offspring: a systematic review. Archives of women's mental health. 2015;18(2):147-62.

6. Geng C, Shaikh AS, Han W, Chen D, Guo Y, Jiang P. Vitamin D and depression: mechanisms, determination and application. Asia Pacific journal of clinical nutrition. 2019;28(4):689-94.
7. Ju S-Y, Lee Y-J, Jeong S-N. Serum 25-hydroxyvitamin D levels and the risk of depression: a systematic review and meta-analysis. The Journal of nutrition, health and aging. 2013;17(5):447-55.
8. Li H, Sun D, Wang A, Pan H, Feng W, Ng CH, et al. Serum 25-hydroxyvitamin D levels and depression in older adults: a dose–response meta-analysis of prospective cohort studies. The American Journal of Geriatric Psychiatry. 2019;27(11):1192-202.
9. Centeno LOL, Fernandez MdS, Muniz FWMG, Longoni A, de Assis AM. Is Serum Vitamin D Associated with Depression or Anxiety in Ante-and Postnatal Adult Women? A Systematic Review with Meta-Analysis. Nutrients. 2024;16(21):3648.
10. Ribamar A, Almeida B, Soares A, Peniche B, Jesus P, Cruz S, Ramalho A. Relationship between vitamin D deficiency and both gestational and postpartum depression. Nutr Hosp. 2020;37(6):1238-45.
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ [Internet]. 2021 Mar 29;372:n71
12. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A: Rayyan—a web and mobile app for systematic reviews. Systematic reviews 2016, 5:1-10.
13. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health. 2019;22:153-160.
14. Shim SR, Lee J. Dose-response meta-analysis: application and practice using the R software. Epidemiol Health. 2019;41:e2019006
15. Medicine IO. Dietary reference intakes for calcium and vitamin D. National Academies Press eBooks. 2011.
16. Ignacio Neumann SB, Joerg Meerpohl, Marina Davoli, Pablo Alonso Coello, Elie Akl, Philipp Dahm, Nicole Skoetz, Jun Xia, Jan Brozek, Holger J. Schünemann. Overview of the GRADE approach [updated Aug 14, 2025; cited

2025 Oct 10]. Available from: https://book.gradepro.org/guideline/overview-of-the-grade-approach#certainty-of-evidence.

17. Gur EB, Gokduman A, Turan GA, Tatar S, Hepyilmaz I, Zengin EB, et al. Mid-pregnancy vitamin D levels and postpartum depression. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014;179:110-6.
18. Robinson M, Whitehouse AJ, Newnham JP, Gorman S, Jacoby P, Holt BJ, et al. Low maternal serum vitamin D during pregnancy and the risk for postpartum depression symptoms. Archives of women's mental health. 2014;17(3):213-9.
19. Vaziri F, Nasiri S, Tavana Z, Dabbaghmanesh MH, Sharif F, Jafari P. A randomized controlled trial of vitamin D supplementation on perinatal depression: in Iranian pregnant mothers. BMC Pregnancy and Childbirth. 2016;16(1):239.
20. Dabbaghmanesh MH, Vaziri F, Najib F, Nasiri S, Pourahmad S. The effect of vitamin D consumption during pregnancy on maternal thyroid function and depression: a randomized, Placebo-Controlled, clinical trial. Jundishapur Journal of Natural Pharmaceutical Products. 2019;14(2):e65328.
21. Guyatt G, Yao L, Murad MH, Hultcrantz M, Agoritsas T, De Beer H, et al. Core GRADE 6: presenting the evidence in summary of findings tables. bmj. 2025;389.
22. Gould JF, Gibson RA, Green TJ, Makrides M. A systematic review of vitamin D during pregnancy and postnatally and symptoms of depression in the antenatal and postpartum period from randomized controlled trials and observational studies. Nutrients. 2022;14(11):2300.
23. Centeno LOL, Fernandez MdS, Muniz FWMG, Longoni A, de Assis AM. Is Serum Vitamin D Associated with Depression or Anxiety in Ante-and Postnatal Adult Women? A Systematic Review with Meta-Analysis. Nutrients. 2024;16(21):3648.
24. Szpunar MJ. Association of antepartum vitamin D deficiency with postpartum depression: A clinical perspective. Public Health Nutrition. 2020;23(7):1173-8.
25. Mattioli AV, Coppi F, Severino P, Penna C, Pagliaro P, Cas AD, et al. A personalized approach to vitamin D supplementation in cardiovascular health beyond the bone: an expert consensus by the Italian National Institute for Cardiovascular Research. Nutrients. 2024;17:115.

26. Pagnoni G, Giuggioli D, de Pinto M, Maini A, Battigaglia E, Macripò P, et al. Vitamin D insufficiency and cardiovascular involvement in systemic sclerosis: Association with echocardiographic parameters and risk factors. Int J Cardiol Cardiovasc Risk Prev. 2025;27:200502
27. Wang J, Liu N, Sun W, Chen D, Zhao J, Zhang W. Association between vitamin D deficiency and antepartum and postpartum depression: a systematic review and meta-analysis of longitudinal studies. Archives of gynecology and obstetrics. 2018;298(6):1045-59.
28. Tsai Z, Shah N, Tahir U, Mortaji N, Owais S, Perreault M, Van Lieshout RJ. Dietary interventions for perinatal depression and anxiety: a systematic review and meta-analysis of randomized controlled trials. The American journal of clinical nutrition. 2023;117(6):1130-42.
29. Mao F, Sun Y, Wang J, Huang Y, Lu Y, Cao F. Sensitivity to change and minimal clinically important difference of Edinburgh postnatal depression scale. Asian Journal of Psychiatry. 2021;66:102873.
30. Eyles DW. Vitamin D: brain and behavior. Journal of Bone and Mineral Research Plus. 2021;5(1):e10419.
31. Akpınar Ş, Karadağ MG. Is vitamin D important in anxiety or depression? What is the truth? Current nutrition reports. 2022;11(4):675-81.
32. Fenercioglu AK. The anti-inflammatory roles of vitamin D for improving human health. Current Issues in Molecular Biology. 2024;46(12):13514-25.
33. Skoczek-Rubińska A, Cisek-Woźniak A, Molska M, Heyser M, Trocholepsza M, Pietrzak S, Mruczyk K. Impact of Vitamin D Status and Supplementation on Brain-Derived Neurotrophic Factor and Mood–Cognitive Outcomes: A Structured Narrative Review. Nutrients. 2025;17(16):2655.
34. Yuan Y, Qu L, Sun Q, He P, Zhou X. The Association between Vitamin D Deficiency and Perinatal Depression: A Systematic Review and Meta-Analysis. Alpha Psychiatry. 2024;25(6):669.