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Vitamin D Supplementation during Pregnancy and Maternal and Neonatal Outcomes: results from a quantitative umbrella meta-analysis

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Abstract

Background: This umbrella meta-analysis aimed to examine the effect of prenatal vitamin D supplementation on maternal and neonatal outcomes.

Methods: Scopus and PubMed were searched up to September 2024 to include relevant studies. The outcomes included gestational diabetes mellitus (GDM), preeclampsia, cesarean section, preterm delivery (PTD), low birth weight (LBW), small for gestational age (SGA), stillbirth, neonatal mortality, birth weight, birth length, and head circumference at birth. Standardized mean difference (SMD) and relative risk (RR) with their 95% confidence intervals (CI) were used as effect sizes to pool the data using a random effects model.

Results: Thirty-five studies with 188,370 participants were included. Vitamin D supplementation lowered the risk of GDM (RR=0.68, 95%CI: 0.53 to 0.88), preeclampsia (RR=0.62, 95%CI: 0.56 to 0.69), PTD (RR=0.77, 95%CI: 0.65 to 0.90), LBW (RR=0.67, 95%CI: 0.54 to 0.84), SGA (RR=0.73, 95%CI: 0.63 to 0.85), stillbirth (RR=0.77, 95%CI: 0.62 to 0.95), and neonatal mortality (RR=0.58, 95%CI: 0.40 to 0.84), while also enhanced birth weight (SMD=75.68, 95%CI: 48.99 to 102.36), birth length (SMD=0.25, 95%CI: 0.18 to 0.33), and head circumference (SMD=0.15, 95%CI: 0.06 to 0.23). These effects were observed with lower doses of vitamin D ((<50,000 IU/week), shorter intervention periods (<14 weeks), and among older participants ((≥ 27 years). Moreover, vitamin D supplementation was linked to the reduced risk of cesarean deliveries in some subgroups.

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Conclusions: Prenatal vitamin D supplementation may be associated with a lower risk of certain adverse maternal and neonatal outcomes and may improve birth anthropometric measurements.

Keywords: Vitamin D, pregnancy, maternal outcomes, neonatal outcomes, umbrella meta-analysis

Background

Vitamin D deficiency during pregnancy has emerged as a significant public health concern, with prevalence ranging from 9% to 94%, depending on country, race, ethnicity, skin color, clothing customs, and dietary intake (1). A systematic review reported the incidence of 25(OH)D deficiency among pregnant women in South East Asia, Western Pacific, Europe, America, and Eastern Mediterranean to be 87%, 83%, 57%, 64%, and 46%, respectively (2). As pregnancy advances, the need for vitamin D rises, which can lead to a deterioration of any existing vitamin D deficiency (3).

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Recent studies have highlighted the potential role of vitamin D in modulating various physiological processes during pregnancy, including immune function, metabolism, inflammation, and vascular health (4). The placenta, decidua, and other key target cells, including immune and endothelial cells, possess the molecular mechanisms necessary for the local synthesis of calcitriol (5). Previous studies have identified dysregulation of maternal and placental vitamin D metabolism, resulting in the reduction in local activation of vitamin D due to the decreased activity of 1α-hydroxylase. Low serum levels of 25-hydroxyvitamin D are associated with an increased risk of developing adverse maternal and

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neonatal outcomes, such as gestational diabetes mellitus (GDM), preeclampsia, and low birth weight (6), emphasizing the need for effective supplementation strategies to mitigate these risks.

The growing body of evidence suggests that vitamin D supplementation during pregnancy may improve maternal health outcomes and improve fetal development. Several meta-analyses have investigated the effects of vitamin D on various pregnancy-related outcomes, revealing that adequate supplementation can lead to improved maternal vitamin D status, increased birth weight, and reduced incidence of adverse events such as preeclampsia, GDM, preterm delivery (PTD), neonatal mortality, as well as low-birth-weight and small-for-gestational-age (SGA) infants (1, 7). However, despite these promising findings, findings across randomized controlled trials (RCTs) (8, 9) and the meta-analyses of RCTs (10-12) are inconsistent possibly due to differences in study design, sample size, dosages, and duration of supplementation. Given the conflicting evidence and the need for a comprehensive assessment of available data, this umbrella meta-analysis aimed to synthesize findings from multiple meta-analyses to assess the effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes.

Methods

Search strategy

A systematic search of all published articles was conducted in the Scopus and PubMed electronic databases up to September 2024 to include pertinent studies. The search was limited to publications in English

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language. The Medical Subject Heading (MESH) and non– MESH terms were applied for the search strategy as follows: Search: ("Vitamin D" OR Ergocalciferols OR “Vitamin D Deficiency” OR cholecalciferol OR Calcitriol OR "Hydroxyvitamin D" OR “25(OH)D” OR “25-hydroxycholecalciferol” OR “25-hydroxyvitamin D” OR “vitamin D3”) AND (pregnancy outcome* OR birth outcome* OR neonatal outcomes OR premature OR preterm OR birth weight OR birth length OR small-for-gestational-age OR gestational diabetes OR stillbirth OR death OR mortality OR birth head OR cesarean, preeclampsia) AND (Pregnancy OR pregnant OR gestational OR maternal OR mother* OR Gestation OR prenatal) AND (meta-analysis). The references list of all previous reviews on relevant topics was manually searched for additional studies. The studies were entered into endnote 8 then duplicate citations were removed. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed for reporting this meta-analysis (13).

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Inclusion criteria

We define the Population, Intervention, Comparator, and Outcome (PICO) criteria to include eligible studies as follows: 1) the population was pregnant women, 2) the intervention was supplementation with vitamin D, 3) the control group received placebo, 4) the outcomes included gestational diabetes mellitus (GDM), preeclampsia, cesarean section, preterm delivery (PTD), low birth weight (LBW), small for gestational age (SGA), stillbirth, neonatal mortality, birth weight, birth length, and head circumference at birth, and 5) study design was meta-analyses of RCTs.

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Moreover, studies were eligible if they reported effect sizes for the effect of vitamin D on the outcomes or provided sufficient data to calculate these values. The studies were excluded if they did not report risk estimates or sufficient data to compute them, were meta-analyses of observational studies, review studies with no quantitative analysis, protocols, letters, and editorials, or had irrelevant intervention/outcome. The studies were independently screened by 2 reviewers to recognize potential eligible studies. The principal author was consulted to address and resolve any disagreement.

Calculating the overlap

In umbrella reviews, primary studies may appear in multiple meta-analyses, potentially biasing results. We assessed overlap visually using a citation matrix and quantified it with three indices: percentage of overlaps, covered area (CA), and corrected covered area (CCA) (14, 15).

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% Overlaps = number of primary studies included in more than one meta-analysis/r

Covered area (CA): $\frac{N}{rc}$

Corrected covered area (CCA): $\frac{N - r}{rc - r}$

Where N is the total number of primary studies (including duplicates), r is the number of rows (studies), and c is the number of columns (meta-analyses). CCA scores were interpreted as follows: 0–5% = mild overlap, 6–10% = moderate, 11–15% = high, and >15% = very high overlap.

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Data extraction

Two authors independently extracted data using a standard data collection form and a third reviewer resolved any conflicts. Extracted data included publication year, name of authors, country, outcomes, mean age, dose and duration of treatment, sample size, risk of bias (RoB) assessment, number of the included studies, and the effect sizes for the outcomes. For network meta-analyses, we extracted data specifically for the vitamin D group compared to placebo. Only data for vitamin D monotherapy were included; studies reporting vitamin D combined with calcium or other interventions were not extracted.

Quality assessment

A Measurement Tool to Assess Systematic Reviews (AMSTAR-2) was used to evaluate the methodological quality of meta-analyses. The AMSTAR-2 comprises 16 items considering various aspects of meta-analyses. Responses to these items are categorized as "Yes," "Partial Yes," or "No" and finally rate the overall quality as high, moderate, low, or critically low (16).

Statistical analysis

Standardized mean difference (SMD) and relative risk (RR) with their 95% confidence intervals (CI) were used as effect sizes to pool the data. Heterogeneity between studies was assessed through Cochran’s Q test and I2 values, with I2 ≥ 50% indicating a significant heterogeneity (17, 18). Data were pooled using the DerSimonian and Laird random effects models, which consider between-study variation. We conducted subgroup analyses

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according to sample size, age of subjects, vitamin D dose, treatment duration, and quality of studies to investigate the sources of heterogeneity. Meta-regression analysis was also conducted to investigate the effect of maternal age, dose and duration of vitamin D supplementation, RoB, and sample size on the pooled effect sizes. Sensitivity analysis was applied to evaluate the extent of dependency of the overall effect size on a specific study. Funnel plots were visually inspected, and the statistical significance of Egger's test were used to evaluate publication bias (19). All statistical analyses were conducted with Stata, version 14.0 (Stata Corp., College Station, TX). $P < 0.05$ was considered statistically significant.

Results

Characteristics of the included studies

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Out of 577 studies identified through the literature search, 110 duplicates were eliminated. Screening the titles and abstracts led to the removal of an additional 415 studies, leaving 52 for full-text evaluation. Ultimately, 35 studies (1, 3, 7, 10-12, 20-48) met the criteria for inclusion in this umbrella meta-analysis. The process of study selection is reported in Fig.1. The sample size of studies varied from 374 to 44922 participants, with a total sample size of 188,370 subjects. Intervention doses varied from 2,000 to 200,000 IU per week, with a median dose of 50,000 IU per week. The duration of supplementation ranged from 6 to 22 weeks, with a median of 14 weeks. The mean ages of participants varied from 21.7 to 30.2 years, with a median age of 27 years. Data on outcomes were collected as follows: preeclampsia was reported in 21 studies (1, 3, 7, 10-12, 20-26, 29, 30, 32,

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35, 36, 41, 45, 48), GDM in 8 studies (1, 7, 22, 26, 29, 31, 37, 43), PTD in 17 studies (1, 7, 10, 20, 22, 23, 26, 29, 30, 32-36, 38, 41, 47), cesarean section in 9 studies (7, 10, 11, 22, 26, 29, 30, 36, 38), birth weight in 12 studies (1, 7, 10, 11, 22, 26, 28, 29, 34, 40-42), LBW in 8 studies (7, 10, 20, 22, 26, 29, 34, 41), birth length in 10 studies (7, 10, 11, 22, 26, 28, 29, 41, 42, 44), SGA in 8 studies (10, 20, 22, 23, 26-28, 41), stillbirth in 4 studies (7, 10, 26, 29), neonatal mortality in 7 studies (7, 10, 26, 27, 29, 46, 47), and head circumference at birth in 6 studies (7, 10, 26, 29, 41, 42). The trials included in the meta-analyses generally assessed bias using the Cochrane tool (49). There was significant heterogeneity in the quality of the primary trials within the meta-analyses, with the proportion of high-quality trials ranging from 0% to 100% across the meta-analyses. According to AMSTAR-2 criteria, the quality of the studies was classified as high for 11 studies, moderate for 13 studies, and low for another 11 studies (Table S1). The characteristics of the included studies are given in Table 1.

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Maternal outcomes

Gestational diabetes

Pooled analysis revealed that prenatal vitamin D supplementation decreased the risk of GDM by 32% (RR = 0.68, 95% CI: 0.53 to 0.88), with significant heterogeneity across the studies (I^2 = 55.0%, P = 0.02) (Fig.2). In subgroup analyses, this effect was supported by high-quality studies and those with larger sample sizes (≥2000 participants) when lower doses of vitamin D (<50,000 IU/week) were administered (Table 2).

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Preeclampsia

Vitamin D supplementation during pregnancy was associated with a reduced risk of preeclampsia (RR = 0.62, 95% CI: 0.56 to 0.69) (Fig.2), showing no significant heterogeneity and maintaining consistency across all subgroups (Table 2).

Preterm delivery

When all effect sizes were pooled, a significant reducing effect of vitamin D on PTD was observed (RR = 0.77, 95% CI: 0.65 to 0.90) (Fig.2), with no remarkable evidence of heterogeneity (Fig. 2). This effect was found in low-quality studies with smaller sample sizes involving individuals aged ≥ 27 years, specifically when lower doses of vitamin D (<50,000 IU/week) were administered for shorter durations (<14 weeks) (Table 2).

Cesarean section

We identified no effect of maternal vitamin D supplementation on cesarean section delivery in the overall analysis (Fig. 2). There was considerable heterogeneity among the studies (I^2 = 69.3%, P = 0.001). However, in the stratified analysis, vitamin D reduced the odds of cesarean section delivery in moderate-quality studies with smaller sample sizes involving participants aged ≥ 27 years, particularly when given for <14 weeks (Table 2).

Neonatal outcomes

Anthropometric measurements at birth

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Supplementing pregnant women with vitamin D increased infant birth weight by 75.68 g (SMD = 75.68, 95% CI: 48.99 to 102.36), birth length by 0.25 cm (SMD = 0.25, 95% CI: 0.18 to 0.33), and head circumference by 0.15 cm (SMD = 0.15, 95% CI: 0.06 to 0.23) (Fig. 3). The positive effects on birth weight and birth length were supported by various subgroups. The effect on head circumference was observed in high-quality studies involving subjects aged ≥ 27 years, specifically when vitamin D was administered for shorter durations (<14 weeks), irrespective of the doses of intervention (Table 2). Vitamin D supplementation was also significantly associated with a lower risk of LBW infants (RR = 0.67, 95% CI: 0.54 to 0.84), which was supported by subgroup analyses (Fig. 3). Moreover, there was a significant reduction in the risk of SGA infants after vitamin D supplementation (RR = 0.73, 95% CI: 0.63 to 0.58) (Fig. 3), specifically when lower doses of vitamin D (<50,000 IU/week) were administered (Table 2).

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Stillbirth

Prenatal vitamin D supplementation reduced the odds of stillbirth by 23% (RR = 0.77, 95% CI: 0.62 to 0.95) (Fig. 3). This effect was found in high-quality studies with ≥2000 participants (Table 2).

Neonatal mortality

There was a significant reduction in the risk of neonatal mortality after supplemental use of vitamin D during pregnancy (RR = 0.58, 95% CI: 0.40 to 0.84) (Fig. 3), This effect was found in subjects aged ≥ 27 years,

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specifically when lower doses of vitamin D (<50,000 IU/week) were administered for shorter durations (<14 weeks) (Table 2).

Meta-regression analysis

The impact of vitamin D supplementation on cesarean sections was influenced by the sample sizes of the studies (B = 0.001, SE = 0.006, P = 0.03) (Fig. S1) and the duration of supplementation (B = 0.05, SE = 0.1, P = 0.04) (Fig. S2). For preeclampsia, the pooled result was affected by the dosage of supplementation (B = 0.002, SE = 0.09, P = 0.02) (Fig. S3). Regarding birth weight, the effect was influenced by the duration of supplementation (B = -13.90, SE = 3.66, P = 0.005) (Fig. S4). For LBW (B = 0.004, SE = 0.0001, P = 0.04) (Fig. S5) and neonatal mortality (B = 0.0007, SE = 0.0002, P = 0.03) (Fig. S6), the associations were affected by the sample sizes of the studies. Additionally, the pooled effect size for neonatal mortality was influenced by the age of participants (B = -0.17, SE = 0.6, P = 0.04) (Fig. S7).

Overlap calculation and Sensitivity analysis

Based on the citation matrix (Supplementary file 1), the CCA score was 10%, indicating a mild overlap, with most primary studies unique to individual meta-analyses and minimal risk of bias from duplicated data. Sensitivity analyses, including the exclusion of meta-analyses with the highest pairwise overlap (≥10% CCA), did not change the overall results, supporting the robustness and reliability of the findings. For all outcomes, the pooled effect sizes were not influenced by the results of individual

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studies during the sensitivity analysis, showing the reliability of the findings.

Publication bias

There was significant publication bias for PTD, birth length, and LBW, while no evidence of publication bias was detected for other outcomes (Fig. 4).

Discussion

We performed this umbrella meta-analysis to evaluate the effect of vitamin D supplementation in pregnant women on maternal and neonatal outcomes. The results revealed that prenatal vitamin D supplementation reduces the risk of adverse maternal and neonatal outcomes, including GDM, preeclampsia, cesarean section, PTD, LBW, SGA, stillbirth, and neonatal mortality, while also improving anthropometric measurements at birth. Generally, these effects were observed with lower doses of vitamin D (<50,000 IU/week), shorter durations of interventions (<14 weeks), and in older subjects (≥ 27 years).

Vitamin D supplementation during pregnancy has garnered significant attention due to its potential impact on maternal and neonatal health outcomes. Nevertheless, debate continues over the clinical evidence concerning the impact of vitamin D supplementation on pregnancy complications. The age-specific, dose-specific, and intervention duration-specific effects observed in the present study can be explained by several interrelated factors. Due to age-related changes such as the reduced ability of the skin to synthesize vitamin D from sunlight and decreased

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renal function to activate vitamin D, older adults often have vitamin D deficiency (50, 51). Thus, older women may begin pregnancy with lower baseline levels of vitamin D, making them more responsive to supplementation (52). Even modest increases in vitamin D levels can lead to substantial improvements in health outcomes, particularly for those already at risk for deficiencies. Older pregnant women often face increased risks for adverse outcomes, making them more likely to benefit from supplementation (53). In agreement with our study, some studies have showed that lower doses of vitamin D can be effective in improving health outcomes during pregnancy without the need for higher doses and long durations of supplementation (25, 27). These findings highlight the potential for tailored supplementation strategies to optimize maternal and neonatal health outcomes during pregnancy.

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Vitamin D supplementation during pregnancy exerts beneficial effects on maternal and neonatal outcomes through various mechanisms, including improving calcium metabolism, modulating immune responses, reducing inflammation and oxidative stress, regulating gene expression, influencing angiogenesis, and maintaining hormonal balance (54-56). Vitamin D is crucial for calcium absorption and metabolism, which is essential for fetal bone development (57). During pregnancy, there is an increased demand for calcium to support the growing fetus. Vitamin D facilitates the absorption of calcium from the intestines and mobilizes calcium from the maternal skeleton when necessary, ensuring that both maternal and fetal needs are met. This process helps improve the anthropometric indices of neonates (58). On the other side, the role of vitamin D could reduce blood

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pressure levels by maintaining calcium homeostasis and may directly inhibit the growth of vascular smooth muscle cells, thereby decreasing the risk of preeclampsia (59). Additionally, vitamin D serves as a potent endocrine regulator of renin production and may influence the renin-angiotensin system, which is essential for managing blood pressure (45). Vitamin D might also affect the production of adipokines that are linked to endothelial and vascular health, further lowering the likelihood of preeclampsia (45). Vitamin D plays a significant role in modulating the immune system, which is particularly important during pregnancy. It enhances maternal tolerance to paternal and fetal alloantigens, reducing the risk of immune-related complications such as preeclampsia and GDM (60, 61). The overall effect of vitamin D on adaptive immune responses results in a shift towards a more tolerogenic state (62), which is essential for maternal immune adaptation and the preservation of a healthy pregnancy. Accumulating evidence has shown that administering vitamin D increases regulatory T cell responses while generally decreasing pro-inflammatory responses (63). This adjustment promotes maternal tolerance and may lower the risk of pregnancy complications. Vitamin D supplementation has been shown to reduce oxidative stress during pregnancy (64). Elevated oxidative stress is linked to various adverse outcomes, including preeclampsia, PTD, GDM, and fetal growth restriction (65). By lowering oxidative stress markers, vitamin D may help mitigate these risks, contributing to better maternal and neonatal health outcomes. Vitamin D receptors (VDR) are expressed in various tissues, including the placenta and decidua (66). Vitamin D influences the expression of genes

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involved in implantation, placentation, and vascular development (67). Placental and vascular dysfunctions play crucial roles in the pathogenesis of preeclampsia, stillbirth, and PTD (68). This regulation can affect placental function and fetal growth, ultimately impacting birth outcomes such as anthropometric measurements at birth and stillbirth. In this line, studies have indicated that newborns born to mothers with severe vitamin D deficiency exhibited shorter birth lengths, smaller head circumferences, and lower birth weights (22). Vitamin D is involved in angiogenesis, which is critical for adequate placental blood flow and nutrient delivery to the fetus (69). Dysregulation of this process can lead to complications such as preeclampsia and restricted fetal growth (70). Moreover, vitamin D may also interact with other hormones involved in pregnancy, such as progesterone (71). It has been suggested that vitamin D binding protein (VDBP) can transport progesterone during late gestation, which may further influence pregnancy outcomes (72). These mechanisms collectively contribute to a healthier intrauterine environment, promoting optimal fetal development and reducing the risk of adverse outcomes.

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The findings of this umbrella meta-analysis underscore the significant clinical implications of vitamin D supplementation during pregnancy. By demonstrating that prenatal vitamin D intake can markedly reduce the risks of adverse outcomes, healthcare providers may consider vitamin D supplementation an essential component of prenatal care, especially in countries with a high prevalence of for vitamin D deficiency. The observed benefits, particularly with lower doses and shorter intervention durations in older pregnant women, suggest that targeted supplementation could

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enhance maternal and neonatal health outcomes. However, these findings should be framed as exploratory or hypothesis-generating rather than conclusive. This evidence supports the need for public health initiatives to promote adequate vitamin D levels among pregnant women, potentially leading to improved health trajectories for both mothers and their infants. There is a need to translate current findings into public health policies aimed at preventing maternal and neonatal complications associated with vitamin D deficiency. Integrating evidence-based supplementation strategies into national guidelines, awareness programs, and prenatal care protocols could help reduce the prevalence of deficiency and improve maternal and neonatal outcomes.

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Existing guidelines and expert consensus highlights important considerations for prenatal vitamin D supplementation. Several professional bodies emphasize maintaining adequate vitamin D status during pregnancy, though formal recommendations vary. For example, the American College of Obstetricians and Gynecologists suggests considering higher supplementation (e.g., 1,000–2,000 IU/day) for women at risk of deficiency to achieve sufficiency, with doses up to 4,000 IU/day generally regarded as safe in pregnancy, while routine screening and universal supplementation beyond standard prenatal vitamins remain areas of debate (73). Some expert groups recommend daily intakes of 2,000–4,000 IU to achieve target serum 25-hydroxyvitamin D levels (≥30–40 ng/mL), particularly in high-risk populations, although a clear consensus on optimal dosing and timing has not been established (74). In contrast, global organizations such as WHO currently do not recommend

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routine vitamin D supplementation for all pregnant women solely to improve perinatal outcomes, reflecting limited direct evidence of benefit in general populations (75). Collectively, these guidelines underscore key research priorities including defining evidence-based dosing strategies, determining the most effective timing for initiation, tailoring supplementation based on baseline status, and further evaluating the safety of higher doses, particularly in diverse populations.

This is the first quantitative umbrella meta-analysis investigating the impact of prenatal vitamin D supplementation on maternal and neonatal outcomes. The strengths of the present study lie in its examination of various maternal and neonatal outcomes, comprehensive subgroup analyses, and meta-regression analyses aimed at identifying sources of heterogeneity, as well as a substantial number of studies with a relatively large pooled sample size. This study has several limitations. Significant heterogeneity was observed for some outcomes, which may restrict the generalizability of the findings. Meta-regression and subgroup analyses indicated that the heterogeneity among the studies can be attributed to differences in sample size, dosage and duration of supplementation, participant age, and study quality. Additionally, other confounding factors not evaluated in the available studies, such as diet, skin characteristics, seasonality, sun exposure, ethnicity, and weight gain during pregnancy could also contribute to the observed heterogeneity. Variations in supplementation dose and duration across studies may have influenced the observed outcomes, despite partial standardization. Well-designed, multicenter randomized controlled trials with standardized dosing

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regimens and outcome assessments are needed to strengthen the evidence base and support more precise clinical recommendations. Moreover, insufficient reporting across the included studies limited our ability to conduct detailed subgroup or stratified analyses based on geographic location, season, or supplementation regimen, factors that may have contributed to the observed heterogeneity and should be investigated in future research. Second, the included studies did not report sufficient data on the baseline serum levels of vitamin D. As a result, it was not possible to determine whether the observed effects were more pronounced among women with pre-existing vitamin D deficiency or whether supplementation was administered irrespective of baseline status. Future research should prioritize reporting baseline serum vitamin D levels to allow for more precise subgroup analyses and clearer interpretation of supplementation effects. Third, significant publication bias was observed for several outcomes, as the search was limited to English-language publications, suggesting that some studies may have been excluded. Fourth, determining the optimal and safe vitamin D supplementation dose for different maternal age groups is an important issue. The existing evidence is limited by variability in dosing regimens and a lack of stratified analyses by age, ethnicity, and baseline nutritional status, which precludes definitive dose-specific recommendations. Future well-designed, large-scale RCTs across diverse populations are needed to establish age- and population-specific dosing strategies that maximize efficacy while ensuring safety. Fifth, the most appropriate timing for initiating vitamin D supplementation during pregnancy remains unclear. The included studies

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varied considerably in the gestational age at which supplementation was initiated, and few directly compared outcomes based on timing of initiation. This heterogeneity limits conclusions regarding whether earlier supplementation confers greater benefits than initiation later in pregnancy. Future randomized controlled trials specifically designed to compare different initiation time points are needed to clarify the optimal timing of vitamin D supplementation during pregnancy. Lastly, although our findings suggest a relationship between vitamin D supplementation and the assessed outcomes, they should be interpreted as associative rather than causal. Variability in study designs, supplementation protocols, dosages, and follow-up durations, limits the ability to infer a direct causal effect of vitamin D. Future research should examine the effects of vitamin D supplementation in combination with other vitamins or minerals to better reflect real-world nutritional interventions. Additionally, key modifying factors such as maternal BMI, skin pigmentation, sun exposure, dietary intake, and seasonality should be systematically assessed due to their potential influence on vitamin D status and outcomes. Targeted supplementation strategies for older pregnant women and those at higher risk of deficiency warrant particular attention. Finally, future studies should consistently include baseline serum vitamin D assessments to allow for stratified analyses and more precise interpretation of supplementation effects.

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Conclusions

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In conclusion, prenatal vitamin D supplementation may be associated with a lower risk of certain adverse maternal and neonatal outcomes and may improve birth anthropometric measurements. Although these findings suggest that vitamin D could be considered an important component of prenatal care, our findings indicate associations between prenatal vitamin D supplementation and certain maternal and neonatal outcomes, suggesting potential benefits rather than definitive prevention of all adverse events. Interpretation should be cautious due to key limitations, including considerable heterogeneity among studies, potential publication bias for some endpoints, and limited reporting of baseline vitamin D status. These factors reduce the certainty of the evidence and highlight the need for well-designed, large-scale randomized trials to confirm the observed associations and guide optimal supplementation strategies. There is also a need for data on the optimal and safe dosages, supplementation protocols, the appropriate timing for starting vitamin D supplementation, and the effects of vitamin D when taken alongside other minerals and vitamins to guide policy decisions effectively.

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Declarations

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Liping Lin: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Qijuan Zhu: Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Yunshan Xiao: Writing – review & editing, Supervision, Investigation, Funding acquisition, Methodology. Xueqin Zhang: Writing – review & editing, Writing – original draft, Funding acquisition, Investigation, Supervision, Conceptualization, Methodology.

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Figure captions

Figure 1. Flow diagram for the process of study selection

Figure 2. Meta-analysis for the effect of vitamin D supplementation during pregnancy on preeclampsia (A), caesarean section (B), preterm delivery (C), and gestational diabetes (D).

Figure 3. Meta-analysis for the effect of vitamin D supplementation during pregnancy on birth weight (A), birth length (B), head circumference (C), low birth weight (D), neonatal mortality (E), small for gestational age (F), and stillbirth (G).

Figure 4. Publication bias for preeclampsia (A), preterm delivery (B), birth weight (C), and birth length (D)

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Table captions

Table 1. Characteristics of studies included in the umbrella meta-analysis

NR: not reported, GDM: gestational diabetes, PTD: preterm delivery, LBW: low birth weight, SGA: small for gestational age

Table 2. Overall and subgroup analyses for the effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes

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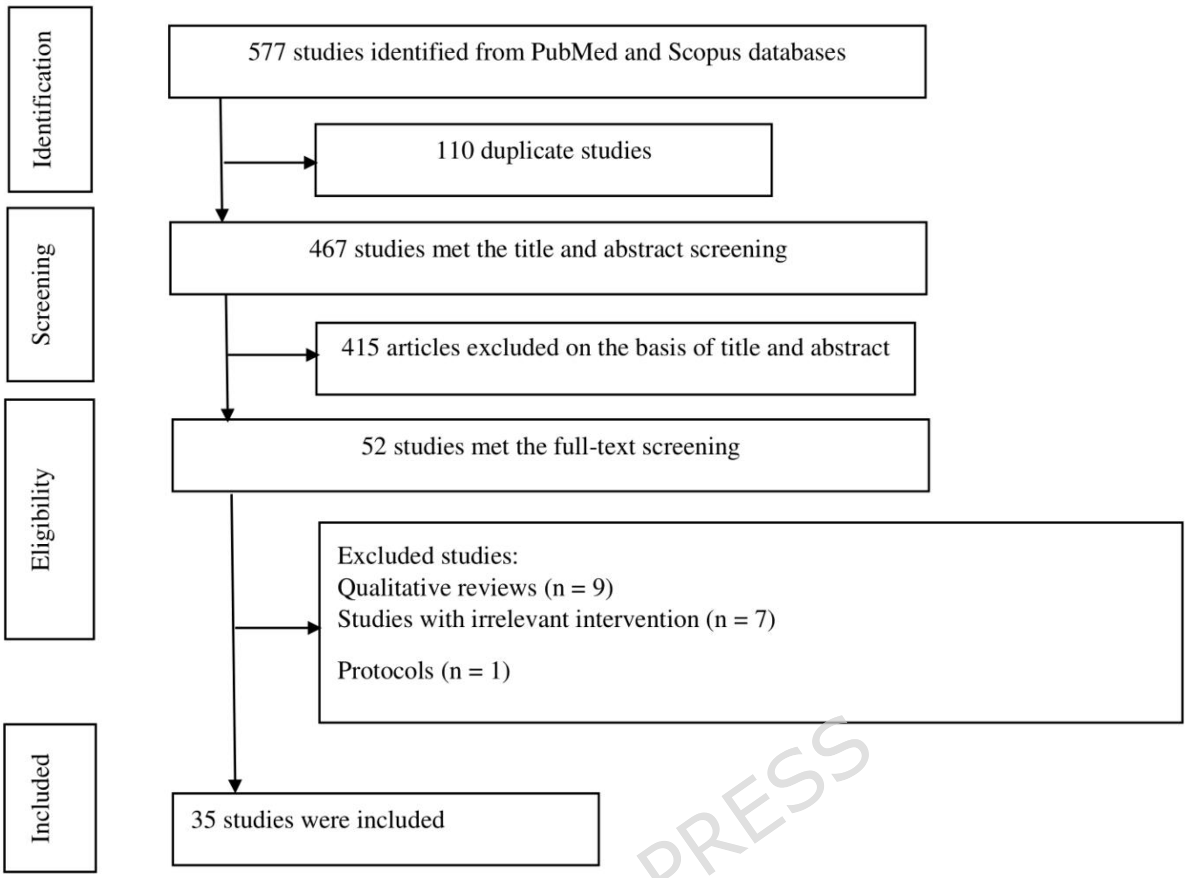

Figure 1. Flow diagram for the process of study selection

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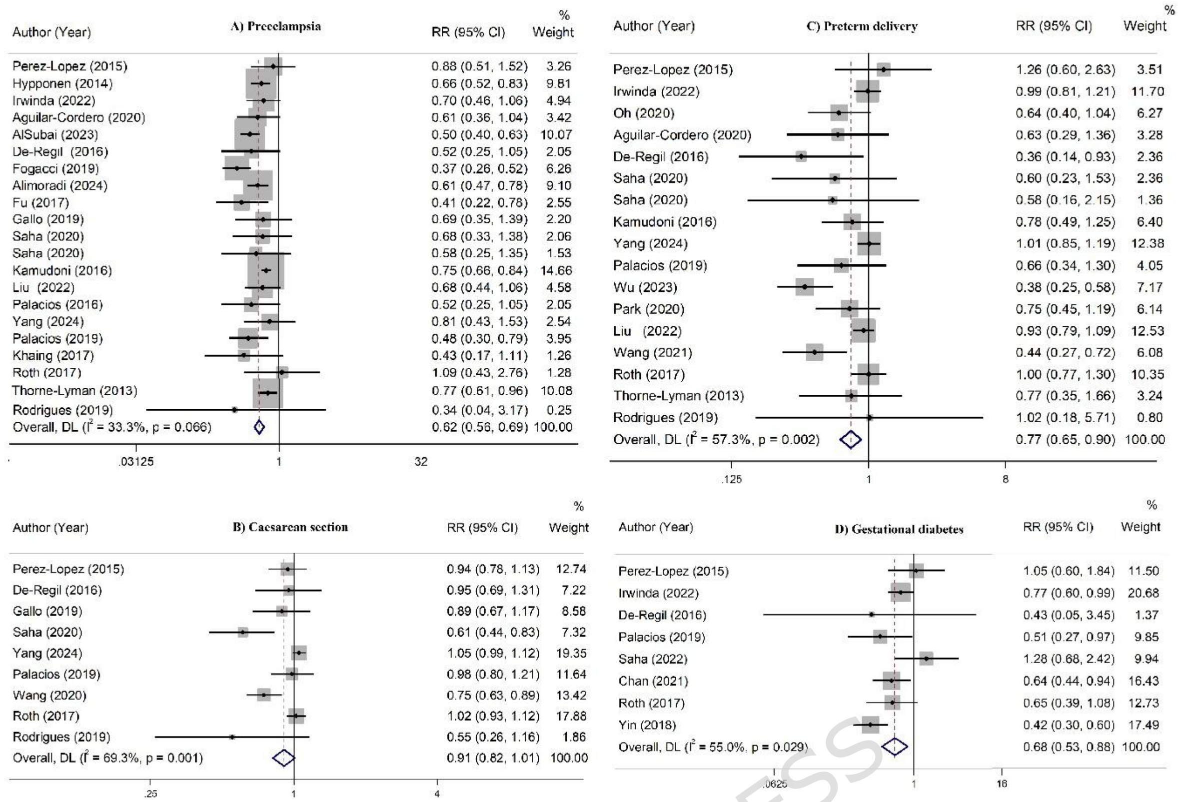

Figure 2. Meta-analysis for the effect of vitamin D supplementation during pregnancy on preeclampsia (A), caesarean section (B), preterm delivery (C), and gestational diabetes (D).

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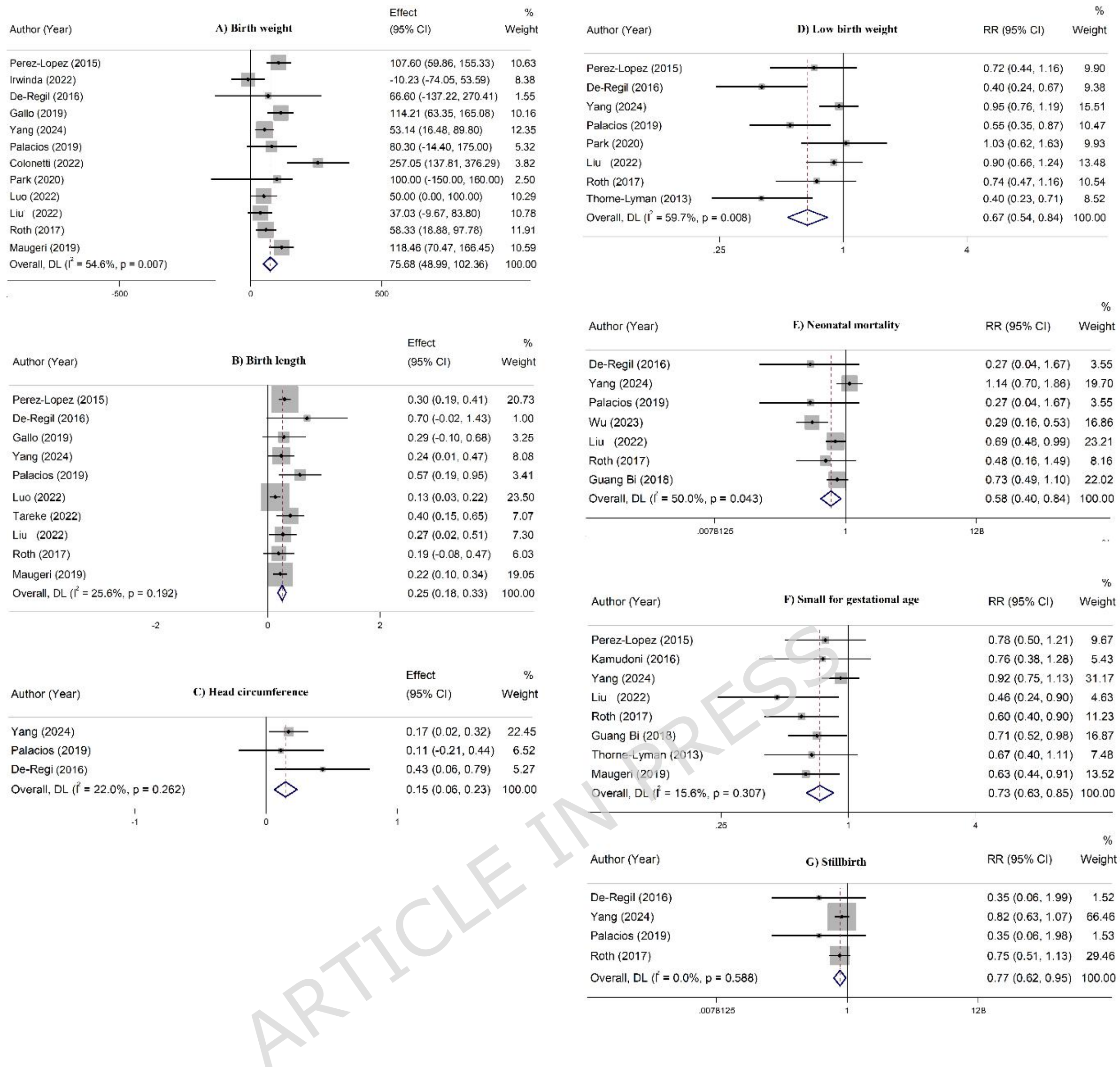

Figure 3. Meta-analysis for the effect of vitamin D supplementation during pregnancy on birth weight (A), birth length (B), head circumference (C), low birth weight (D), neonatal mortality (E), small for gestational age (F), and stillbirth (G).

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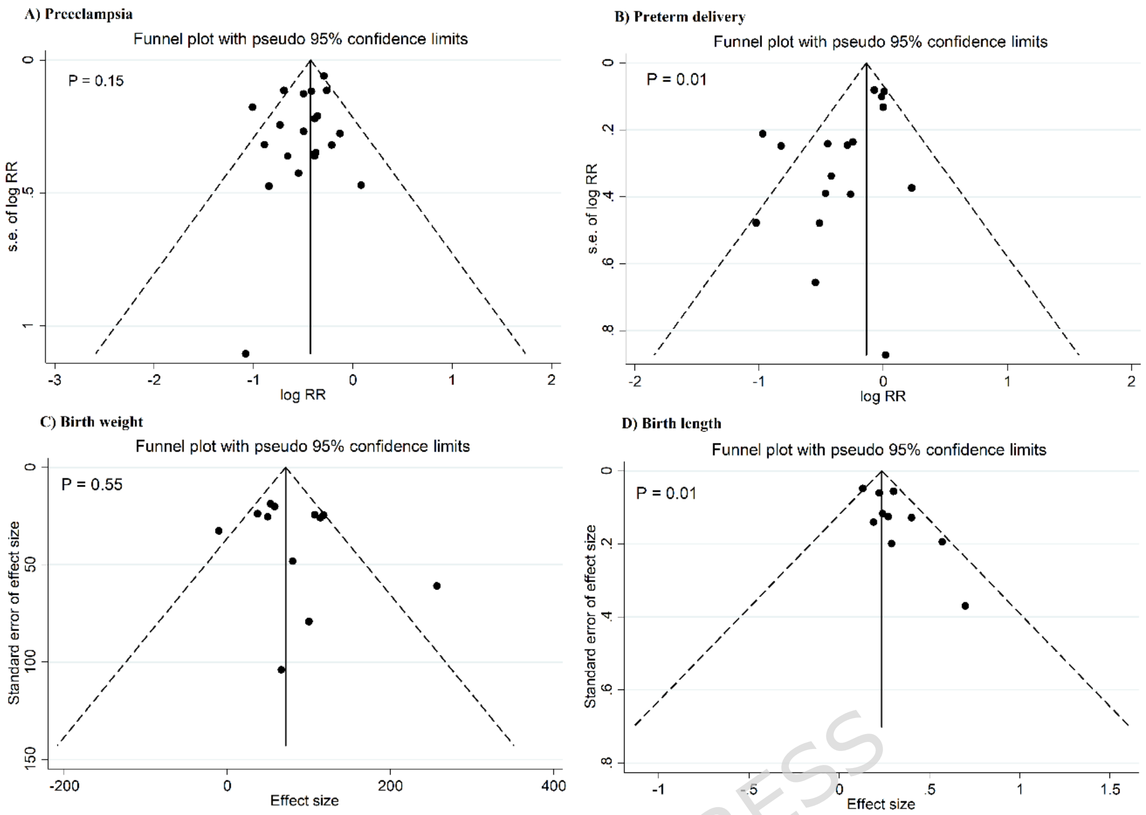

Figure 4. Publication bias for preeclampsia (A), preterm delivery (B), birth weight (C), and birth length (D)

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Table 1. Characteristics of studies included in the umbrella meta-analysis

Study	Country	Year	No of studies	Sample size	Dose (IU/week)	Duration (week)	Mean age (Year)	Bias assessment, proportion of high quality studies	Outcomes	Quality
Perez-Lopez	Spain	2015	13	2299	115000	14	26.98	Cochrane tool,10/13	Preeclampsia, GDM, PTD, birth weight, LBW, birth length, SGA, caesarean section	Moderate
Hypponen	Australia	2014	2	376	NR	NR	NR	NR	Preeclampsia	Moderate
Irwinda	Indonesia	2022	27	7321	44000	22	NR	Cochrane tool,17/27	Preeclampsia, GDM, PTD, birth weight	Moderate
Oh	Canada	2020	11	1262	NR	NR	NR	Cochrane tool, 8/11	PTD	Low
Aguilar-Cordero	Spain	2020	7	1518	NR	20	NR	Cochrane tool, 2/7	Preeclampsia, PTD	High
AlSubai	Ireland	2023	10	3451	16000	NR	NR	Cochrane tool, 0/10	Preeclampsia	Moderate
De-Regil	Canada	2016	15	2959	20700	15	27	Cochrane tool,4/15	Preeclampsia, GDM, PTD, birth weight, LBW, birth length, stillbirth, caesarean section, neonatal mortality, birth head circumference	High
Fogacci	Italy	2019	27	5123	24000	NR	27.07	Cochrane tool,19/27	Preeclampsia	Moderate
Alimoradi	Iran	2024	19	NR	NR	NR	NR	Cochrane tool, NR	Preeclampsia	Low
Fu	China	2017	8	25593	81000	NR	NR	NR	Preeclampsia	Low
Gallo	USA	2019	17	2844	41000	11	29.1	Cochrane tool, 16/17	Preeclampsia, birth weight, birth length, caesarean section	Moderate
Saha	India	2020	6	476	130000	6	30.22	Cochrane tool,6/6	Preeclampsia, PTD,	High
Saha	India	2020	5	380	19000	6	29.82	Cochrane tool,5/5	Preeclampsia, PTD, caesarean section	High
Kamudoni	UK	2016	5	24190	NR	NR	NR	Cochrane tool, NR	Preeclampsia, PTD, SGA	Low
Liu	China	2022	NR	NR	NR	NR	NR	Cochrane tool, NR	Preeclampsia	High
Palacios	Puerto Rico	2016	6	2965	60000	12	NR	Cochrane tool, NR	Preeclampsia	Low
Yang	United States	2024	66	17276	14000	NR	NR	Cochrane tool, 25/66	Preeclampsia, PTD, birth weight, LBW, birth length, SGA, stillbirth, birth head circumference, caesarean section, neonatal mortality	High
Palacios	USA	2019	30	6941	37000	11	24.5	Cochrane tool,11/30	Preeclampsia, GDM, PTD, birth weight, LBW, birth length, stillbirth, birth head circumference, caesarean section, neonatal mortality	High
Khaing	Thailand	2017	7	1526	NR	NR	23.21	Cochrane tool, NR	Preeclampsia	High
Wu	China	2023	20	1682	45000	8	27.53	Cochrane tool, 18/20	PTD, neonatal mortality	Moderate
Wang	China	2020	19	1493	54000	8	27.29	Cochrane tool,10/19	Caesarean section	Moderate
Colonetti	Brazil	2022	10	3395	33000	10	25.82	Cochrane tool,11/17	Birth weight	Moderate
Park	Canada	2020	NR	NR	NR	NR	NR	Cochrane tool, NR	PTD, birth weight, LBW	Low
Luo	China	2022	23	4558	20000	15	21.7	Cochrane tool,15/23	Birth weight, birth length, birth head circumference	Moderate
Saha	China	2022	13	1104	70000	7	29.72	Cochrane tool,13/13	GDM	Moderate
Tareke	Ethiopia	2022	25	44922	64000	23	NR	Cochrane tool, 12/25	birth length	Moderate
Chan	China	2021	5	NR	NR	NR	NR	NR	GDM	Low
Liu	China	2022	13	6238	28000	NR	NR	NR	PTD, birth weight, LBW, birth length, SGA, birth head circumference, neonatal mortality	Low
Wang	China	2021	17	1432	NR	NR	NR	NR	PTD	Low
Roth	Canada	2017	43	8406	NR	NR	NR	Cochrane tool, 21/43	Preeclampsia, GDM, PTD, birth weight, LBW, birth length, SGA, stillbirth, birth head circumference, caesarean section, neonatal mortality	High
Guang Bi	Canada	2018	24	5405	77000	17	21.85	Cochrane tool, 10/24	SGA, neonatal mortality	Moderate
Thorne-Lyman	USA	2013	5	933	200000	12	26.83	NR	Preeclampsia, PTD, LBW, SGA	Low
Maugeri	Italy	2019	13	1928	151000	14	NR	Cochrane tool,12/13	Birth weight, birth length, SGA	High
Rodrigues	Brazil	2019	6	374	4800	8	30.2	Cochrane tool, 5/6	Preeclampsia, PTD, caesarean section	High
Yin	China	2018	6	NR	NR	NR	NR	NR	GDM	Low

NR: not reported, GDM: gestational diabetes, PTD: preterm delivery, LBW: low birth weight, SGA: small for gestational age

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Table 2. Overall and subgroup analyses for the effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes

			Test of effect	**Test of heterogeneity**	
Outcomes	**Subgroups**	**Studies**	**RR, SMD (95%CI)**	**I^2 (%)**	***P***
Gestational diabetes	Overall	8	0.68 (0.53 to 0.88)	55.0	0.029
Duration of intervention	≥ 14 weeks	3	0.80 (0.64 to 1.01)	0.0	0.516
	< 14 weeks	2	0.81 (0.33 to 1.99)	75.0	0.045
	NR	3	0.54 (0.40 to 0.73)	39.2	0.193
Dose of vitamin D	≥ 50000 IU/week	2	1.15 (0.75 to 1.74)	0.0	0.647
	< 50000 IU/week	3	0.72 (0.57 to 0.91)	0.0	0.445
	NR	3	0.54 (0.40 to 0.73)	39.2	0.193
Sample size	≥2000 participants	5	0.75 (0.61 to 0.91)	0.0	0.495
	<2000 participants	1	1.28 (0.68 to 2.41)	-	_-
	NR	2	0.51 (0.34 to 0.78)	61.2	0.108
Age of participants	≥ 27 years	2	1.17 (0.64 to 2.15)	0.0	0.333
	< 27 years	2	0.74 (0.37 to 1.51)	63.9	0.096
	NR	4	0.61 (0.46 to 0.81)	61.3	0.052
Quality	Low	2	0.51 (0.34 to 0.78)	61.2	0.108
	Moderate	3	0.90 (0.67 to 1.21)	27.0	0.254
	High	3	0.59 (0.40 to 0.87)	0.0	0.810
Preeclampsia	Overall	21	0.62 (0.56 to 0.69)	0.15	0.832
Duration of intervention	≥ 14 weeks	4	0.69 (0.53 to 0.89)	0.0	0.666
	< 14 weeks	7	0.68 (0.57 to 0.81)	0.0	0.756
	NR	10	0.59 (0.50 to 0.71)	64.4	0.003
Dose of vitamin D	≥ 50000 IU/week	5	0.69 (0.55 to 0.87)	15.0	0.319
	< 50000 IU/week	9	0.52 (0.45 to 0.61)	3.1	0.411
	NR	7	0.70 (0.64 to 0.77)	0.0	0.588
Sample size	≥2000 participants	12	0.59 (0.49 to 0.72)	60.5	0.003

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	<2000 participants	7	0.69 (0.60 to 0.79)	0.0	0.903
	NR	2	0.63 (0.50 to 0.78)	0.0	0.675
Age of participants	≥ 27 years	7	0.49 (0.38 to 0.62)	0.0	0.482
	< 27 years	3	0.67 (0.50 to 0.90)	36.1	0.196
	NR	11	0.64 (0.57 to 0.73)	30.5	0.156
Quality	Low	5	0.69 (0.59 to 0.80)	34.9	0.188
	Moderate	6	0.59 (0.47 to 0.73)	53.2	0.046
	High	10	0.62 (0.50 to 0.76)	0.0	0.873
Preterm delivery	Overall	17	0.77 (0.65 to 0.90)	57.3	0.02
Duration of intervention	≥ 14 weeks	4	0.82 (0.54 to 1.26)	48.6	0.120
	< 14 weeks	6	0.51 (0.38 to 0.69)	0.0	0.509
	NR	7	0.84 (0.71 to 1.00)	55.8	0.035
Dose of vitamin D	≥ 50000 IU/week	3	0.88 (0.55 to 1.41)	0.0	0.439
	< 50000 IU/week	9	0.78 (0.62 to 0.96)	67.2	0.002
	NR	5	0.70 (0.51 to 0.97)	58.5	0.047
Sample size	≥2000 participants	8	0.96 (0.87 to 1.05)	3.4	0.404
	<2000 participants	8	0.52 (0.41 to 0.65)	0.0	0.634
	NR	1	0.75 (0.46 to 1.22)	-	_-
Age of participants	≥ 27 years	5	0.43 (0.30 to 0.60)	0.0	0.717
	< 27 years	3	0.85 (0.56 to 1.29)	0.0	0.428
	NR	9	0.87 (0.76 to 1.00)	46.9	0.058
Quality	Low	6	0.73 (0.57 to 0.93)	48.7	0.083
	Moderate	3	0.76 (0.38 to 1.54)	88.5	0.000
	High	8	0.89 (0.74 to 1.07)	16.3	0.302
Stillbirth	Overall	4	0.77 (0.62 to 0.95)	0.0	0.58
Duration of intervention	≥ 14 weeks	1	0.35 (0.06 to 2.02)	-	-
	< 14 weeks	1	0.26 (0.07 to 1.01)	-	-
	NR	2	0.80 (0.64 to 0.99)	0.0	0.714
Dose of vitamin D	< 50000 IU/week	3	0.78 (0.60 to 1.01)	0.0	0.434

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	NR	1	0.75 (0.50 to 1.12)	-	-
Sample size	≥2000 participants	4	0.78 (0.63 to 0.97)	0.0	0.618
Age of participants	≥ 27 years	1	0.26 (0.07 to 1.01)	-	-
	< 27 years	1	0.35 (0.06 to 2.01)	-	_
	NR	2	0.80 (0.64 to 0.99)	0.0	0.714
Quality	High	4	0.78 (0.63 to 0.97)	0.0	0.618
Cesarean section	Overall	9	0.91 (0.82 to 1.01)	69.3	0.001
Duration of intervention	≥ 14 weeks	2	0.94 (0.80 to 1.11)	0.0	0.955
	< 14 weeks	5	0.79 (0.66 to 0.95)	53.2	0.073
	NR	2	1.04 (0.99 to 1.10)	0.0	0.611
Dose of vitamin D	≥ 50000 IU/week	2	0.84 (0.67 to 1.04)	67.2	0.081
	< 50000 IU/week	6	0.89 (0.75 to 1.06)	66.1	0.011
	NR	1	1.02 (0.93 to 1.12)	-	_-
Sample size	≥2000 participants	6	1.02 (0.98 to 1.07)	0.0	0.728
	<2000 participants	3	0.71 (0.61 to 0.82)	0.0	0.425
Age of participants	≥ 27 years	5	0.77 (0.66 to 0.90)	28.9	0.229
	< 27 years	2	0.96 (0.83 to 1.10)	0.0	0.769
	NR	2	1.04 (0.99 to 1.10)	0.0	0.611
Quality	Moderate	3	0.85 (0.73 to 0.99)	38.1	0.199
	High	6	0.95 (0.85 to 1.07)	64.0	0.016
Small for gestational age	Overall	8	0.73 (0.63 to 0.85)	15.6	0.307
Duration of intervention	≥ 14 weeks	3	0.70 (0.56 to 0.86)	0.0	0.756
	< 14 weeks	1	0.67 (0.40 to 1.12)	-	_
	NR	4	0.71 (0.52 to 0.98)	53.4	0.092
Dose of vitamin D	≥ 50000 IU/week	4	0.70 (0.36 to 1.36)	0.0	0.901
	< 50000 IU/week	2	0.69 (0.57 to 0.84)	74.1	0.050
	NR	2	0.65 (0.46 to 0.90)	0.0	0.526
Sample size	≥2000 participants	6	0.75 (0.62 to 0.90)	27.5	0.228
	<2000 participants	2	0.64 (0.48 to 0.86)	0.0	0.847

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Age of participants	< 27 years	3	0.72 (0.57 to 0.91)	0.0	0.900
	NR	5	0.70 (0.55 to 0.90)	49.1	0.097
Quality	Low	3	0.63 (0.45 to 0.88)	0.0	0.524
	Moderate	2	0.73 (0.57 to 0.95)	0.0	0.735
	High	3	0.73 (0.54 to 0.99)	62.8	0.068
Low birth weight	Overall	8	0.67 (0.54 to 0.84)	59.7	0.008
Duration of intervention	≥ 14 weeks	2	0.54 (0.30 to 0.96)	62.4	0.103
	< 14 weeks	2	0.48 (0.36 to 0.65)	0.0	0.863
	NR	4	0.92 (0.78 to 1.07)	0.0	0.754
Dose of vitamin D	≥ 50000 IU/week	2	0.54 (0.37 to 0.78)	21.2	0.281
	< 50000 IU/week	5	0.72 (0.53 to 0.96)	67.3	0.009
	NR	1	0.74 (0.47 to 1.16)	-	-
Sample size	≥2000 participants	6	0.72 (0.56 to 0.92)	60.5	0.027
	<2000 participants	1	0.44 (0.30 to 0.65)	0.0	0.898
	NR	1	1.03 (0.64 to 1.67)	-	-
Age of participants	≥ 27 years	1	0.44 (0.30 to 0.63)	0.0	0.888
	< 27 years	3	0.55 (0.40 to 0.76)	16.9	0.300
	NR	4	0.92 (0.78 to 1.07)	0.0	0.754
Quality	Low	3	0.74 (0.45 to 1.22)	73.0	0.025
	Moderate	1	0.60 (0.42 to 0.85)	0.0	0.537
	High	4	0.65 (0.44 to 0.97)	74.5	0.008
Neonatal mortality	Overall	7	0.58 (0.40 to 0.84)	50.0	0.043
Duration of intervention	≥ 14 weeks	2	0.69 (0.43 to 1.10)	4.1	0.307
	< 14 weeks	2	0.28 (0.16 to 0.48)	0.0	0.973
	NR	3	0.80 (0.53 to 1.22)	42.3	0.177
Dose of vitamin D	≥ 50000 IU/week	1	0.71 (0.48 to 1.06)	0.0	0.346
	< 50000 IU/week	5	0.53 (0.30 to 0.94)	65.8	0.012
	NR	1	0.48 (0.16 to 1.46)	-	_
Sample size	≥2000 participants	6	0.75 (0.57 to 0.98)	16.1	0.310

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	<2000 participants	1	0.28 (0.16 to 0.50)	-	-
Age of participants	≥ 27 years	2	0.28 (0.16 to 0.48)	0.0	0.973
	< 27 years	2	0.69 (0.43 to 1.10)	4.1	0.307
	NR	3	0.80 (0.53 to 1.22)	42.3	0.177
Quality	Low	1	0.69 (0.48 to 0.99)	-	_
	Moderate	2	0.42 (0.20 to 0.91)	59.5	0.060
	High	4	0.62 (0.29 to 1.34)	43.3	0.152
Birth weight	Overall	12	75.68 (48.99 to 102.36)	54.6	0.007
Duration of intervention	≥ 14 weeks	5	69.45 (19.92 to 118.99)	68.6	0.013
	< 14 weeks	3	126.39 (59.72 to 193.06)	37.8	0.169
	NR	4	52.03 (29.01 to 75.06)	0.0	0.834
Dose of vitamin D	≥ 50000 IU/week	2	111.95 (78.35 to 145.54)	0.0	0.836
	< 50000 IU/week	9	68.72 (32.79 to 104.64)	57.5	0.012
	NR	1	58.33 (18.88 to 97.78)	-	-
Sample size	≥2000 participants	10	70.81 (40.65 to 100.97)	62.9	0.004
	<2000 participants	1	114.09 (67.45 to 160.73)	0.0	0.750
	NR	1	100.00 (-55.00 to 255.00)	-	_
Age of participants	≥ 27 years	2	107.22 (59.33 to 155.11)	0.0	0.880
	< 27 years	4	109.14 (43.54 to 174.73)	71.5	0.014
	NR	6	56.19 (23.86 to 88.52)	56.9	0.041
Quality	Low	2	42.28 (-2.47 to 87.02)	0.0	0.446

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	Moderate	5	87.50 (32.11 to 142.88)	71.0	0.002
	High	5	72.84 (45.45 to 100.23)	21.6	0.277
Birth length	Overall	10	0.25 (0.18 to 0.33)	25.6	0.192
Duration of intervention	≥ 14 weeks	5	0.25 (0.14 to 0.35)	56.3	0.057
	< 14 weeks	2	0.47 (0.21 to 0.73)	0.0	0.552
	NR	3	0.24 (0.09 to 0.38)	0.0	0.913
Dose of vitamin D	≥ 50000 IU/week	3	0.28 (0.20 to 0.36)	0.0	0.401
	< 50000 IU/week	6	0.26 (0.13 to 0.40)	35.8	0.155
	NR	1	0.19 (-0.08 to 0.46)	-	_
Sample size	≥2000 participants	9	0.27 (0.17 to 0.36)	36.2	0.129
	<2000 participants	1	0.31 (-0.04 to 0.65)	11.2	0.324
Age of participants	≥ 27 years	2	0.45 (0.12 to 0.77)	0.0	0.532
	< 27 years	3	0.27 (0.09 to 0.45)	77.1	0.013
	NR	5	0.25 (0.16 to 0.33)	0.0	0.766
Quality	Low	1	0.27 (0.02 to 0.52)	-	-
	Moderate	4	0.27 (0.13 to 0.40)	49.3	0.079
	High	5	0.26 (0.15 to 0.38)	13.7	0.327
Birth head circumference	Overall	6	0.15 (0.06 to 0.23)	22.0	0.262
Duration of intervention	≥ 14 weeks	1	0.02 (-0.12 to 0.16)	-	-
	< 14 weeks	2	0.31 (0.09 to 0.52)	12.4	0.319
	NR	3	0.15 (0.06 to 0.25)	0.0	0.943
Dose of vitamin D	≥ 50000 IU/week	1	0.43 (0.07 to 0.79)	0.0	_
	< 50000 IU/week	4	0.13 (0.03 to 0.23)	22.1	0.274
	NR	1	0.13 (-0.05 to 0.31)	0.0	-
Sample size	≥2000 participants	5	0.11 (0.04 to 0.19)	0.0	0.671
	<2000 participants	1	0.43 (0.17 to 0.69)	-	-
Age of participants	≥ 27 years	1	0.43 (0.17 to 0.69)	-	-
	< 27 years	2	0.03 (-0.10 to 0.17)	0.0	0.620

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	NR	3	0.15 (0.06 to 0.25)	0.0	0.943
Quality	Low	1	0.15 (-0.02 to 0.32)	-	-
	Moderate	1	0.26 (-0.06 to 0.57)	-	-
	High	3	0.15 (0.04 to 0.26)	0.0	0.916

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