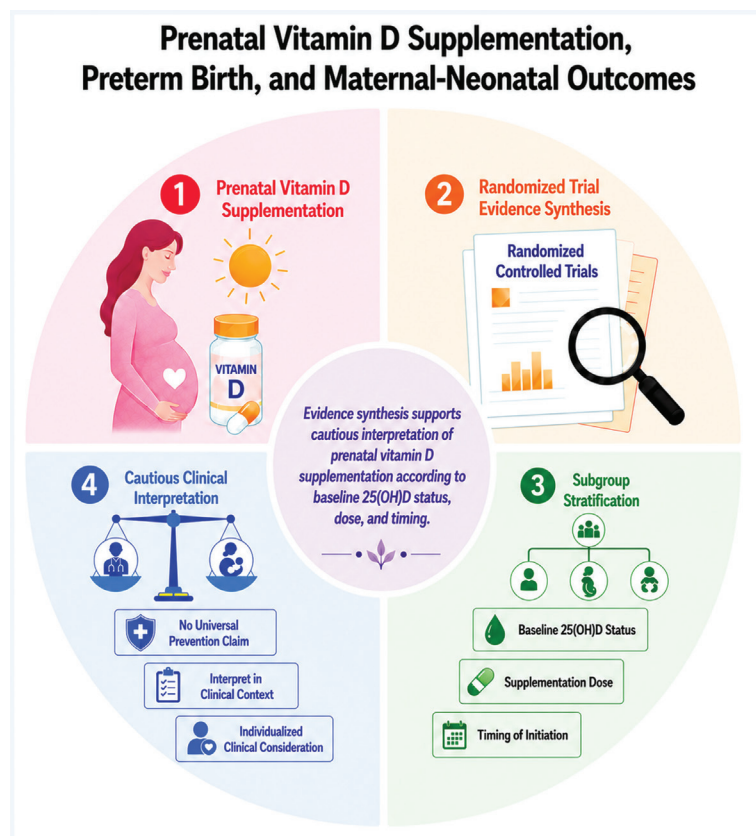


Effects of Vitamin D Supplementation During Pregnancy on Preterm Birth Risk and Maternal-Neonatal Outcomes: A Systematic Review and Meta-Analysis of 38 Randomized Controlled Trials

Graphical abstract



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Brief statement

This systematic review and meta-analysis evaluates randomized evidence on prenatal vitamin D supplementation in relation to preterm birth and maternal-neonatal outcomes, emphasizing cautious interpretation according to baseline 25(OH)D status, supplementation dose, and timing of initiation.

Highlights

- Prenatal vitamin D supplementation was evaluated using randomized controlled trial evidence.
- The review focused on preterm birth and maternal-neonatal secondary outcomes.
- Subgroup interpretation considered baseline 25(OH)D status, dose, and timing of initiation.
- Current evidence does not support universal vitamin D supplementation specifically for preterm birth prevention.
- Individualized interpretation should consider baseline vitamin D status, clinical context, and local guidelines.

Effects of Vitamin D Supplementation During Pregnancy on Preterm Birth Risk and Maternal-Neonatal Outcomes: A Systematic Review and Meta-Analysis of 38 Randomized Controlled Trials

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Abstract

Background and objective: Preterm birth complications are among leading causes of mortality in neonates and children under 5 years of age worldwide. The association between prenatal vitamin D supplementation and risk of preterm birth is controversial based on randomized controlled trials (RCTs). We aimed to determine the effect of vitamin D supplementation during pregnancy on preterm birth and maternal and neonatal secondary outcomes, and to ascertain whether the effects of vitamin D supplementation on preterm birth differed by baseline 25(OH)D status, supplementation dose, and timing of initiation.

Data sources: PubMed, Web of Science, Medline, Cochrane Library, and Embase were searched from inception to April 2023 with no language restrictions.

Study selection: RCTs comparing vitamin D supplementation with placebo, no treatment, or standard low-dose vitamin D (≤ 600 IU/day) in pregnant women were included. The primary outcome was preterm birth (<37 weeks' gestation) and secondary outcomes included maternal adverse events and neonatal anthropometric indicators.

Results: Thirty-eight RCTs involving 17,392 pregnant women were included. Nineteen RCTs involving 7959 pregnant women reported preterm birth. Vitamin D supplementation was associated with a borderline increase in preterm birth risk in the primary analysis (RR, 1.13; 95% CI, 1.01–1.26; $P = 0.04$; $I^2 = 0\%$) but this association was modest and largely driven by one large RCT among women living with HIV. An increased preterm birth signal was noted among participants with a baseline 25(OH)D ≥ 30 nmol/L (OR, 1.25; 95% CI, 1.05–1.48) in exploratory subgroup analyses presented as ORs and this signal was entirely derived from the same HIV trial. No significant subgroup associations were detected in the < 30 nmol/L subgroup or by supplementation dose or initiation timing. No significant effects were noted for maternal or neonatal secondary outcomes.

Limitations: The main study limitations included incomplete reporting of preterm births across trials, reliance on the risk signal on a single population-specific risk signal, dichotomization of baseline 25(OH)D status, and lack of individual participant data for refined subgroup analyses.

Conclusions: Current evidence does not support universal vitamin D supplementation to prevent preterm birth. A possible increased risk of preterm birth among participants with a baseline 25(OH)D ≥ 30 nmol/L should be interpreted cautiously because this finding was driven by a single trial in HIV-positive pregnant women and should not be generalized to healthy pregnant women. Further large-scale RCTs and individual participant data meta-analyses are warranted to clarify whether baseline vitamin D status modifies effects of vitamin D supplementation.

Keywords

Maternal outcomes, neonatal outcomes, pregnancy, preterm birth, randomized controlled trials, vitamin D.

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Introduction

Preterm birth, which is defined by the World Health Organization as a birth before 37 completed weeks of gestation or fewer than 259 days from the first day of the last menstrual period, remains a

major contributor to neonatal morbidity and mortality worldwide [1]. Preterm infants are at increased risk of short-term complications, including respiratory distress syndrome, necrotizing enterocolitis, and sepsis, as well as long-term sequelae, such as neurodevelopmental impairment, chronic lung disease, and metabolic

disorders, which impose substantial clinical, economic, and psychological burdens on families and healthcare systems [2–7]. Despite extensive research, the etiology of preterm birth is multifactorial and incompletely understood, and effective preventive strategies are limited [5, 8].

Vitamin D insufficiency and deficiency are common among pregnant women worldwide. Maternal vitamin D status has been investigated as a potentially modifiable factor related to adverse pregnancy outcomes [9]. Vitamin D is a fat-soluble secosteroid hormone, the active form of which [1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃)] acts through the vitamin D receptor (VDR), which is expressed in placental trophoblasts, uterine smooth muscle, and immune cells. Vitamin D may contribute to maternal-fetal immune tolerance, placental trophoblast invasion and angiogenesis, and calcium homeostasis in uterine smooth muscle through these pathways [10]. Observational studies have linked lower maternal 25-hydroxyvitamin D (25(OH)D) concentrations with increased risks of adverse pregnancy outcomes, including preeclampsia, gestational diabetes, and preterm birth [11–15]. However, observational associations do not establish causality and findings from randomized controlled trials (RCTs) and meta-analyses evaluating prenatal vitamin D supplementation have been inconsistent with some studies reporting potential benefit, others showing neutral effects, and a few suggesting possible harm signals.

Several evidence gaps in the association between vitamin D and preterm birth remain. First, many meta-analyses have evaluated vitamin D supplementation using a “one-size-fits-all” approach, despite evidence suggesting that baseline maternal 25(OH)D status may modify the effects of supplementation on pregnancy outcomes. This issue is clinically relevant because baseline nutrient status is a key determinant of response to nutritional interventions and is central to precision nutrition frameworks [16]. Second, pooled analyses have included trials conducted in special populations, such as women living with human immunodeficiency virus (HIV), without fully examining how population-specific factors may influence pooled estimates or subgroup findings. Third, although recent evidence syntheses have updated overall effects of vitamin D supplementation during pregnancy, the extent to which supplementation effects differ by baseline 25(OH)D status, dose, and gestational age at initiation has not been established [17].

To address these gaps, we performed a systematic review and meta-analysis of 38 RCTs to evaluate the effect of vitamin D supplementation during pregnancy on preterm birth risk and secondary maternal and neonatal outcomes [18, 19]. We further performed prespecified subgroup analyses according to baseline 25(OH)D status, supplementation dose, and timing of initiation to explore potential effect modification and to facilitate more individualized interpretation of prenatal vitamin D supplementation evidence.

Materials and methods

This systematic review and meta-analysis were performed and reported in accordance with the Preferred Reporting Items

for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (**Supplementary Table S1**). The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42022328941). The eligibility criteria were defined according to the PICOS framework, including population, intervention, comparison, outcome, and study design.

Data source and search strategy

We systematically searched five electronic databases, including PubMed, Web of Science, Medline, Cochrane Library, and Embase, from database inception to April 2023 with no language restrictions. The search combined MeSH terms and free-text terms related to “vitamin D,” “pregnancy,” and “randomized controlled trial.” The full search strategy for each database is provided in **Supplementary Material 1**. We also manually screened reference lists of included studies and relevant systematic reviews to identify additional eligible trials.

Eligibility criteria

Trials were eligible for inclusion if the following criteria were met: (1) [study design] parallel-group RCTs, including cluster-randomized RCTs; (2) [population] pregnant women enrolled before or during pregnancy and followed up until delivery; (3) [intervention] vitamin D supplementation, either alone or in combination with other micronutrients, with no restriction on dose, frequency, or duration; (4) [comparison] placebo, no treatment, or standard low-dose vitamin D supplementation defined as ≤ 600 IU/d and treated as a background or standard-care comparator rather than therapeutic-dose supplementation; and (5) [outcomes] at least one primary or secondary outcome. The primary outcome was preterm birth, defined as birth before 37 completed weeks of gestation. The secondary outcomes included stillbirth, spontaneous abortion, preeclampsia, gestational hypertension, birth length, birth weight, head circumference at birth, and low birth weight.

Non-randomized studies, secondary analyses of RCTs, animal studies, *in vitro* studies, conference abstracts without extractable data, duplicate reports without additional eligible outcomes, or studies with no extractable or derivable data for any prespecified outcome were excluded. Missingness was not defined by a fixed percentage of loss to follow-up but by the absence of usable outcome-level summary data required for quantitative synthesis. The most complete report was used when multiple reports described the same trial population and additional reports were only reviewed for supplementary outcome or intervention information.

Study selection and data extraction

Three reviewers (ZLL, WJJ, and LQ) independently screened titles and abstracts to identify potentially eligible studies. Then, two reviewers (ZQY and PM) independently assessed full-text articles for final inclusion. Disagreements at any stage were resolved by discussion with a third senior reviewer.

Two reviewers (ZZK and XXY) independently extracted data using a standardized, pre-piloted data extraction form. The extracted data included the following: (1) study characteristics, including first author, publication year, country, study design, and sample size; (2) participant characteristics, including baseline 25(OH)D concentration, age range, and inclusion/exclusion criteria; (3) intervention and comparator details, including vitamin D dose, frequency, timing of initiation, duration, co-interventions, and control conditions; and (4) outcome data, including number of events and total participants for binary outcomes, and mean, standard deviation, and sample size for continuous outcomes.

The means and standard deviations were extracted when available for continuous outcomes. Outcomes were converted to means and standard deviations using established statistical methods when reported as the median with interquartile ranges or ranges. Data were extracted as the number of events and number of participants analyzed in each group for binary outcomes. Participants lost to follow-up were excluded from outcome-specific denominators unless the original study reported intention-to-treat data. Calculated values were included if missing summary statistics could be derived from other reported information. Studies reporting at least one prespecified outcome with usable data were retained and included only in the corresponding outcome-specific meta-analyses.

Risk of bias, publication bias, and certainty of evidence assessment

Two independent reviewers (WJJ and HJY) assessed risk of bias of included RCTs using Cochrane risk-of-bias tool. Assessment covered random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Each domain was rated as low risk, unclear risk, or high risk of bias. Disagreements were resolved by consensus or consultation with a third reviewer.

Two reviewers (ZZK and ZLL) independently assessed certainty of evidence for each outcome using Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Evidence certainty was evaluated across domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias. Certainty of evidence was rated as high, moderate, low, or very low.

Publication bias and small-study effects were assessed for the primary outcome (preterm birth) by visual inspection of a funnel plot. Funnel plots were not formally interpreted for other outcomes because of limited numbers of studies or limited interpretability.

Data synthesis and statistical analysis

All meta-analyses were performed using Review Manager 5.4 (Cochrane Collaboration, Copenhagen, Denmark). Pooled relative risks (RRs) with 95% confidence intervals

(CIs) were calculated for primary overall analysis and other binary outcomes. Pooled standardized mean differences (SMDs) with 95% CIs were calculated for continuous outcomes. All statistical tests were two-sided and *P* values < 0.05 were considered statistically significant. Forest plots were used to display study-specific and pooled effect estimates.

Only trials reporting extractable data for that specific outcome were included in corresponding meta-analysis for each outcome. Therefore, the number of included trials and participants differed across outcomes. A random-effects model using the DerSimonian-Laird method was applied as the primary analytical model to account for potential between-study heterogeneity. Statistical heterogeneity was quantified using an I^2 statistic with I^2 values of 0–25%, 26–50%, 51–75%, and > 75% interpreted as negligible, moderate, substantial, and considerable heterogeneity, respectively. Cochran's Q test and τ^2 were also considered when interpreting between-study heterogeneity.

Prespecified subgroup analyses were performed for the primary outcome (preterm birth) according to baseline 25(OH)D status (< 30 nmol/L vs. $\geq$ 30 nmol/L), daily vitamin D supplementation dose (< 2000 IU/day, 2000–4000 IU/day, and $\geq$ 4000 IU/day), and gestational age at supplementation initiation (first trimester vs. second trimester). For these subgroup analyses, odds ratios (ORs) with 95% CIs were estimated using Mantel-Haenszel fixed-effect models. ORs were used as a standard effect measure for binary outcomes and are suitable for stratified comparisons across subgroups, particularly when the number of trials and events differed across strata. OR-based subgroup analyses were used to explore whether the association differed across predefined subgroups and were interpreted alongside rather than in place of the primary RR-based overall analysis. Tests for subgroup differences were used to evaluate whether pooled estimates differed across strata.

Sensitivity analyses were performed to examine robustness of pooled effect estimates. These included sequential exclusion of studies rated as high overall risk of bias, use of a fixed-effect model as an alternative to primary random-effects model, and exclusion of a single large trial conducted among women living with HIV that appeared to drive main subgroup signal.

Results

Search results and characteristics of the included studies

A total of 6454 records were identified and screened based on a predefined search strategy. After title and abstract screening, 363 full-text articles were assessed for eligibility and 38 RCTs were ultimately included in the systematic review and meta-analysis. The main reasons for exclusion were non-vitamin D intervention ($n = 262$), non-randomized design ($n = 25$), and absence of extractable or derivable data for any prespecified outcome ($n = 38$; **Figure 1**).

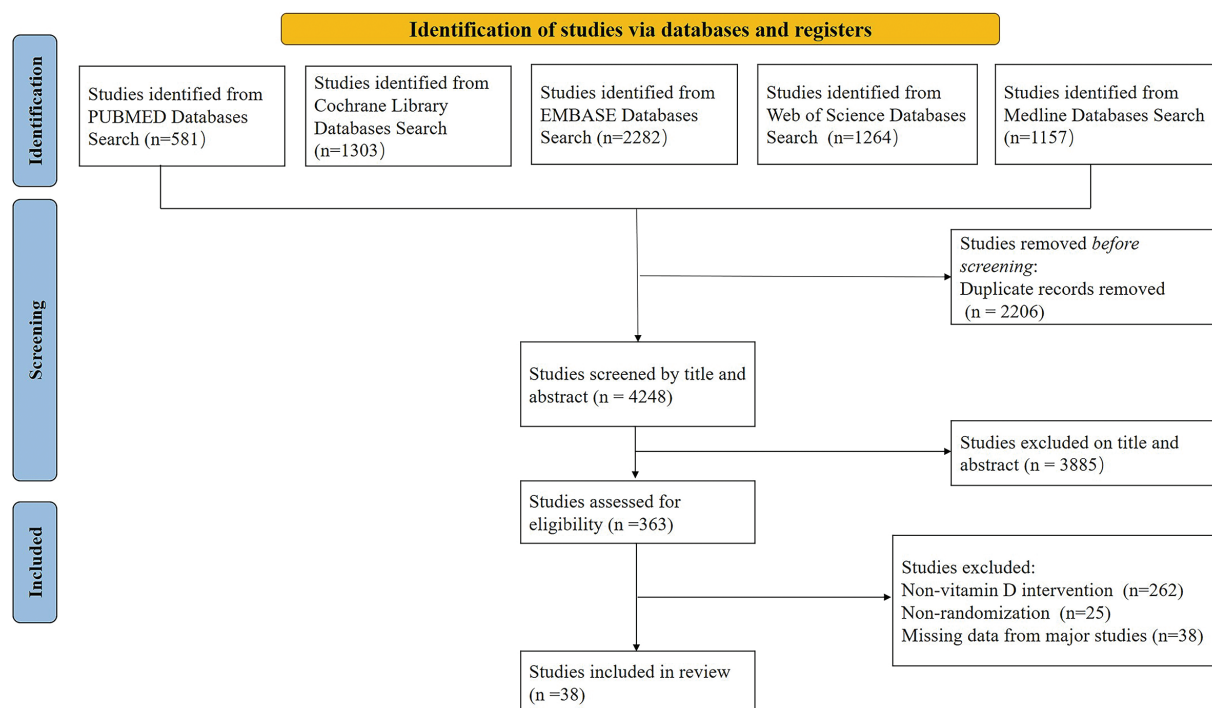


Figure 1 PRISMA flow diagram of study selection for meta-analysis. Flow diagram showing process of literature searching, screening, eligibility assessment, and final inclusion of randomized controlled trials.

The characteristics of included trials are summarized in **Table 1**. A total of 38 RCTs involving 17,392 pregnant women were included. Among these studies, 17 were placebo-controlled, 11 compared two different vitamin D doses, and 10 compared multiple vitamin D doses. Most trials enrolled generally healthy pregnant women, whereas one large trial was conducted among HIV-positive pregnant women. Twenty-five trials were published in or after 2016 (**Table 1**).

Risk of bias and publication bias assessment

The risk of bias assessment is shown in **Figure 2**. All studies included were randomized trials. Three trials were judged to be at high overall risk of bias, whereas most trials were assessed as having a low or moderate risk of bias. Thirty trials used double-blind designs and 30 trials reported allocation concealment methods. However, reporting of selective outcome reporting was incomplete in several studies, which may have introduced uncertainty in interpretation of the pooled estimates.

The funnel plot for the primary outcome (preterm birth) was visually symmetric, suggesting no obvious evidence of publication bias or small-study effects (**Figure 3**).

Effects on primary outcome

Nineteen of the 38 included RCTs reported extractable data on preterm births and were included in the primary meta-analysis involving 7959 pregnant women. The

remaining 19 trials did not report preterm births and were therefore not included in this outcome-specific analysis. Overall, prenatal vitamin D supplementation was associated with a borderline increase in preterm birth risk compared to control conditions (RR = 1.13; 95% CI, 1.01–1.26; $P = 0.04$; $I^2 = 0\%$; **Figure 4**). The between-study heterogeneity was negligible for this outcome ($\tau^2 = 0.00$; Cochran's $Q = 9.08$; $df = 18$; $P = 0.96$; $I^2 = 0\%$).

Exploratory subgroup analyses of preterm birth were presented as ORs using Mantel-Haenszel fixed-effect models (**Figure 5**). No significant association was detected among participants with a baseline 25(OH)D < 30 nmol/L in the subgroup analysis stratified by baseline 25(OH)D status (OR = 1.02; 95% CI, 0.80–1.30). In contrast, an increased preterm birth signal was noted among participants with a baseline 25(OH)D ≥ 30 nmol/L (OR = 1.25; 95% CI, 1.05–1.48). However, this subgroup result was derived entirely from one large RCT conducted among HIV-positive pregnant women and should therefore be interpreted with caution (**Figure 5B**).

Subgroup analyses by supplementation dose showed no significant association in the < 2000 IU/d subgroup (OR = 1.01; 95% CI, 0.72–1.41; $I^2 = 0\%$), the 2000–4000 IU/d subgroup (OR = 1.14; 95% CI, 0.97–1.34; $I^2 = 0\%$), or the ≥ 4000 IU/d subgroup (OR = 0.99; 95% CI, 0.80–1.23; $I^2 = 0\%$; **Figure 5A**). Similarly, the subgroup analyses by timing of supplementation initiation had no significant association when supplementation was initiated in the first trimester (OR = 1.15; 95% CI, 0.98–1.35; $I^2 = 0\%$) or second trimester (OR = 1.18; 95% CI, 0.89–1.57; $I^2 = 0\%$; **Figure 5C**). Tests for subgroup differences were not statistically significant for supplementation dose, baseline 25(OH)D status, or timing of initiation.

Table 1 Summary of Studies Included

Study	Region	Study Design	Sample Size	Interventions	Timing of Vitamin D Supplementation (Gestational Weeks)
Ali et al. 2019 [32]	Saudi Arabia	Randomized controlled trial	164	400 IU/d vs. 4000 IU/d	13 weeks
Litonjua et al. 2020 [33]	United States of America	Randomized double-blind placebo-controlled trial	806	400 IU/d vs. 4400 IU/d	10–18 weeks
Litonjua et al. 2016 [34]	United States of America	Randomized, double-blind, placebo-controlled trial	881	400 IU/d vs. 4400 IU/d	10–18 weeks
Chawes et al. 2016 [35]	Denmark	Double-blind, single-center, randomized clinical trial	623	400 IU/d vs. 2800 IU/d	24 weeks
Hollis et al. 2011 [36]	United States of America	Single center, randomized, controlled, double-blinded study	516	400 IU/d vs. 2000 IU/d vs. 4000 IU/d	12–16 weeks
Grant et al. 2014 [37]	New Zealand	Randomized, double-blind, placebo-controlled trial	404	Placebo vs. 1000 IU/d vs. 2000 IU/d	27 weeks
Wagner et al. 2013 [38]	United States of America	Randomized controlled trial	504	400 IU/d vs. 2000 IU/d vs. 4000 IU/d	12–16 weeks
Sudfeld et al. 2022 [25]	Tanzania	Randomized, triple-blind, placebo-controlled trial	2167 (HIV-positive pregnant women)	Placebo vs. 3000 IU/d	12–27 weeks
Wall et al. 2016 [39]	Auckland, New Zealand	Randomized, double-blinded, placebo-controlled trial	75	Placebo vs. 1000 IU/d vs. 2000 IU/d	27 weeks
Yap et al. 2014 [40]	Australia	Double-blind randomized controlled trial	203	400 IU/d vs. 5000 IU/d	< 20 weeks
Cooper et al. 2016 [41]	UK	Multicenter, double-blind, randomized placebo-controlled trial	965	Placebo vs. 1000 IU/d	14–17 weeks
Enkhmaa et al. 2019 [42]	Mongolia	Randomized, controlled, double-blind trial	512	600 IU/d vs. 2000 IU/d vs. 4000 IU/d	12–16 weeks
Roth et al. 2013 [43]	Bangladesh	Randomized double-blind placebo-controlled trial	147	Placebo vs. 5000 IU/d	26–29 weeks
Roth et al. 2018 [28]	Bangladesh	Randomized, double-blind, placebo-controlled trial	1298	Placebo vs. 600 IU/d vs. 2400 IU/d vs. 4000 IU/d	17–24 weeks
Roth et al. 2013 [44]	Bangladesh	Randomized controlled trial	147	Placebo vs. 5000 IU/d	26 and < 30 weeks
Curtis et al. 2021 [45]	UK	Randomized, double-blind, placebo-controlled trial	965	Placebo vs. 1000 IU/d	14 weeks
Hornsby et al. 2018 [46]	United States of America	Multicenter, randomized, double-blind, placebo-controlled clinical trial	876	400 IU/d vs. 4400 IU/d	10–18 weeks
Mutlu et al. 2014 [47]	Turkey	Randomized controlled trial	51	600 IU/d vs. 1200 IU/d vs. 2000 IU/d	13–32 weeks
Xiaomang et al. 2021 [48]	China	Randomized controlled trial	450	400 IU/d vs. 1500 IU/d vs. 4000 IU/d	13 weeks
March et al. 2015 [49]	Canada	Double-blind randomized controlled trial	249	400 IU/d vs. 1000 IU/d vs. 2000 IU/d	13–24 weeks
O'Callaghan et al. 2022 [50]	Dhaka, Bangladesh	Double-blind, dose-ranging trial	1300	Placebo vs. 600 IU/d vs. 2400 IU/d vs. 4000 IU/d	17–24 weeks
Sass et al. 2020 [51]	Denmark	Randomized double-blind placebo-controlled trial	623	400 IU/d vs. 2800 IU/d	24 weeks
Chen et al. 2020 [52]	United States of America	Randomized controlled trial	92	Placebo vs. 4000 IU/d	10–14 weeks
Karamali et al. 2015 [53]	Iran	Randomized double-blind placebo-controlled trial	60	Placebo vs. 3571 IU/d	20 weeks
Valizadeh et al. 2016 [54]	Iran	Randomized controlled trial	84	Placebo vs. 14,286 IU/d	12 and 32 weeks
Razavi et al. 2017 [55]	Iran	Randomized, double-blind, placebo-controlled trial	120	Placebo vs. 3571 IU/d	24–28 weeks
Hjelmsø et al. 2020 [56]	Denmark	Nested, factorial, double-blind, placebo-controlled, randomized trial	736	400 IU/d vs. 2800 IU/d	24 weeks
Zerofsky et al. 2016 [57]	United States of America	Randomized controlled trial	57	400 IU/d vs. 2000 IU/d	< 20 weeks
Hossain et al. 2014 [58]	Pakistan	Randomized controlled trial	175	Placebo vs. 4000 IU/d	20 weeks
Alhomaidd et al. 2021 [59]	Northern Ireland	2-arm parallel double-blind randomized trial	240	400 IU/d vs. 800 IU/d	12 weeks

Table 1 Continued

Study	Region	Study Design	Sample Size	Interventions	Timing of Vitamin D Supplementation (Gestational Weeks)
Corcoy et al. 2020 [60]	Spain	Multicenter randomized controlled trial	140	Placebo vs. 1600 IU/d	20 weeks
El-Heis et al. 2022 [61]	UK	Multicenter, double-blind, randomized, placebo-controlled trial	703	Placebo vs. 1000 IU/d	14 weeks
Sahoo et al. 2017 [62]	India	Randomized double-blind placebo-controlled trial	300	Placebo vs. 1071 IU/d vs. 2143 IU/d	14–20 weeks
Morris et al. 2021 [63]	Bangladesh	Randomized double-blind placebo-controlled trial	1174	Placebo vs. 600 IU/d vs. 2400 IU/d vs. 4000 IU/d	17–24 weeks
Naushee et al. 2021 [64]	Pakistan	Double-blinded, randomized controlled trial	350	400 IU/d vs. 2000 IU/d vs. 4000 IU/d	12–16 weeks
Motamed et al. 2019 [65]	Iran	Randomized controlled trial	73	1000 IU/d vs. 2000 IU/d	First trimester
Goldring et al. 2013 [66]	United Kingdom	Randomized controlled trial	158	Placebo vs. 800 IU/d vs. 200,000 IU	27 weeks
Asemi and Esmailzadeh 2015 [67]	Iran	Double blind randomized controlled clinical trial	45	Placebo vs. 4762 IU/d	24–28 weeks

Effects on secondary maternal outcomes

Vitamin D supplementation had no statistically significant effect on the following maternal secondary outcomes: still-birth (RR = 0.94; 95% CI, 0.67–1.32; $I^2 = 0\%$); spontaneous abortion (RR = 1.11; 95% CI, 0.67–1.84; $I^2 = 0\%$); preeclampsia (RR = 0.78; 95% CI, 0.59–1.04; $I^2 = 18\%$); or gestational hypertension (RR = 1.04; 95% CI, 0.71–1.54; $I^2 = 46\%$; **Figure 4**). Statistical heterogeneity was moderate for gestational hypertension and negligible or low for other maternal outcomes.

Effects on secondary neonatal outcomes

No significant differences were detected between vitamin D supplementation and control groups for the following neonatal outcomes: birth length (SMD = 0.02; 95% CI = -0.06, 0.10; $I^2 = 22\%$); birth weight (SMD = 0.02; 95% CI = -0.02, 0.07; $I^2 = 17\%$); head circumference at birth (SMD = 0.01; 95% CI = -0.06, 0.09; $I^2 = 19\%$); and low birth weight (RR = 1.07; 95% CI, 0.89–1.28; $I^2 = 0\%$; **Figure 6**).

Discussion

Prenatal vitamin D supplementation was not associated with a reduction in preterm birth or in assessed maternal and neonatal secondary outcomes in this systematic review and meta-analysis of 38 RCTs involving 17,392 pregnant women. Nineteen RCTs involving 7959 participants reported extractable data on preterm birth (the primary outcome). Primary RR-based overall analysis revealed a borderline increase in preterm birth risk but the magnitude

of the association was modest, the CI was close to a null value, and the between-study heterogeneity was negligible. Importantly, the OR-based subgroup signal noted in participants with a baseline 25(OH)D ≥ 30 nmol/L was derived entirely from a single large RCT conducted among HIV-positive pregnant women, whereas no significant association was detected among participants with a baseline 25(OH)D < 30 nmol/L or in subgroups stratified by supplementation dose or timing of initiation. These findings indicate that the apparent subgroup signal should be interpreted cautiously and should not be generalized to healthy pregnant women or interpreted as evidence of causality.

Preterm birth remains a major cause of neonatal morbidity and mortality, and the etiology is complex and multifactorial, involving maternal, fetal, placental, infectious, inflammatory, anatomic, and socioeconomic factors [20]. Vitamin D has been investigated as a potentially modifiable factor because of its roles in immune regulation, placental function, and calcium homeostasis during pregnancy [10, 21]. Observational studies have reported associations between low maternal 25(OH)D concentrations and adverse pregnancy outcomes, including preterm birth, preeclampsia, and fetal growth impairment [22]. However, observational associations are vulnerable to residual confounding and cannot determine whether vitamin D supplementation alone prevents preterm birth. Consistent with this distinction, previous randomized evidence and recent evidence syntheses have generally reported neutral or inconsistent effects of prenatal vitamin D supplementation on preterm birth in general pregnant women [23]. Our findings are broadly consistent with this randomized evidence because no protective effect on preterm birth was noted overall or among participants with a baseline 25(OH)D < 30 nmol/L.

A key feature of the present analysis was stratification by baseline maternal 25(OH)D status. Baseline nutrient status is biologically and clinically relevant because response to supplementation may differ between individuals below

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aisha Mansoor Ali 2019	+	+	+	+	+	+	?
Augusto A. Litonjua 2020	+	+	+	+	+	+	?
Augusto A Litonjua 2016	+	+	+	+	+	+	?
Bo L. Chawes 2016	+	+	+	+	+	+	?
Bruce W Hollis 2011	+	+	+	+	+	+	?
Cameron C Grant 2014	+	+	+	+	+	+	?
Carol L. Wagner 2013	+	+	+	+	+	+	?
Christopher R Sudfeld 2022	+	+	+	+	+	+	?
Clare R Wall 2016	+	+	+	+	+	+	?
Constance Yap 2014	+	+	+	+	+	+	?
Cyrus Cooper 2016	+	+	+	+	+	+	?
D.E. Roth 2018	+	+	+	+	+	+	?
Daniel E. Roth 2013.12	+	+	+	+	+	+	?
Daniel E Roth 2013.4	+	+	+	+	+	+	?
D Enkhmaa 2019	+	+	+	+	+	+	?
Elizabeth M Curtis 2021	+	+	+	+	+	+	?
Eve Hornsby 2018	+	+	+	+	+	+	?
Gul Yesiltepe Mutlu 2014	+	+	+	+	+	+	?
Jiang Xiaomang 2020	+	+	+	+	+	+	?
Kaitlin M March 2015	+	+	+	+	+	+	?
Karen M O'Callaghan 2022	+	+	+	+	+	+	?
Laerke Sass 2020	+	+	+	+	+	+	?
Li Chen 2020	+	+	+	+	+	+	?
M. Karamali 2015	+	+	+	+	+	+	?
Majid Valizadeh 2016	+	+	+	+	+	+	?
Maryamalsadat Razavi 2017	+	+	+	+	+	+	?
Mathis H Hjelms 2020	+	+	+	+	+	+	?
Melissa S Zerofsky 2016	+	+	+	+	+	+	?
Nazil Hossain 2014	+	+	+	+	+	+	?
Raghad M Alhomaidd 2021	+	+	+	+	+	+	?
Rosa Corcoy 2019	+	+	+	+	+	+	?
Sarah El-Heis 2022	+	+	+	+	+	+	?
Saroj Kumar Sahoo 2017	+	+	+	+	+	+	?
Shaun K. Morris 2021	+	+	+	+	+	+	?
Sidrah Nausheen 2021	+	+	+	+	+	+	?
Soudabe Motamed 2019	+	+	+	+	+	+	?
Stephen T. Goldring 2013	+	+	+	+	+	+	?
Z. Asemi 2015	+	+	+	+	+	+	?

Figure 2 Summary of risk of bias for each included study. Risk of bias was assessed according to Cochrane Collaboration tool. Green dots (+) indicate low risk of bias, red dots (−) indicate high risk of bias, and yellow dots (?) indicate unclear risk of bias.

and above the prespecified 30 nmol/L threshold, which is a central concept in precision nutrition [24]. Vitamin D supplementation was not significantly associated with preterm

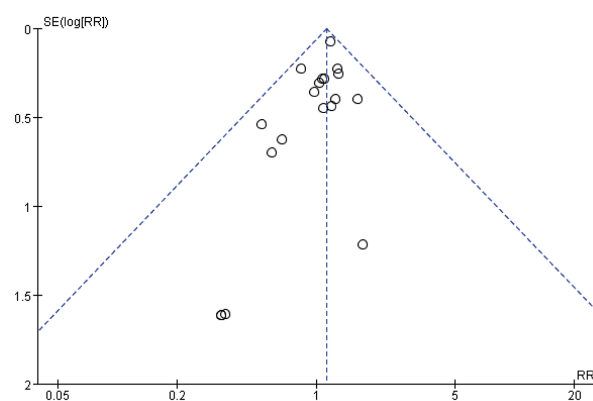


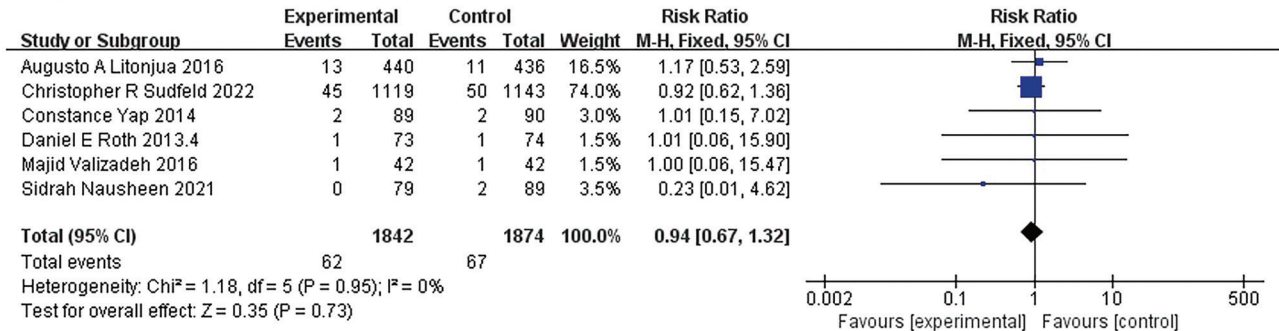
Figure 3 Funnel plot for preterm birth to assess potential publication bias. The funnel plot was visually inspected to assess potential publication bias and small-study effects for preterm birth. No obvious funnel plot asymmetry was observed but visual inspection alone cannot exclude publication bias.

birth risk in the subgroup with a baseline 25(OH)D < 30 nmol/L. This finding does not exclude the possible benefits in more narrowly defined deficient populations but indicates that the currently available RCT data do not provide clear evidence that supplementation reduces preterm birth among women classified as vitamin D deficient using this threshold. The OR-based pooled estimate suggested an increased preterm birth signal in the subgroup with a baseline 25(OH)D ≥ 30 nmol/L. However, this result was based entirely on one large trial among women living with HIV and therefore may reflect population-specific factors rather than a general effect of vitamin D supplementation in pregnant women with a baseline 25(OH)D ≥ 30 nmol/L [25]. Women living with HIV may differ from general obstetric populations in immune status, infection burden, antiretroviral therapy exposure, nutritional status, and baseline risk of adverse pregnancy outcomes [26, 27]. Accordingly, this subgroup finding should be considered hypothesis-generating rather than definitive.

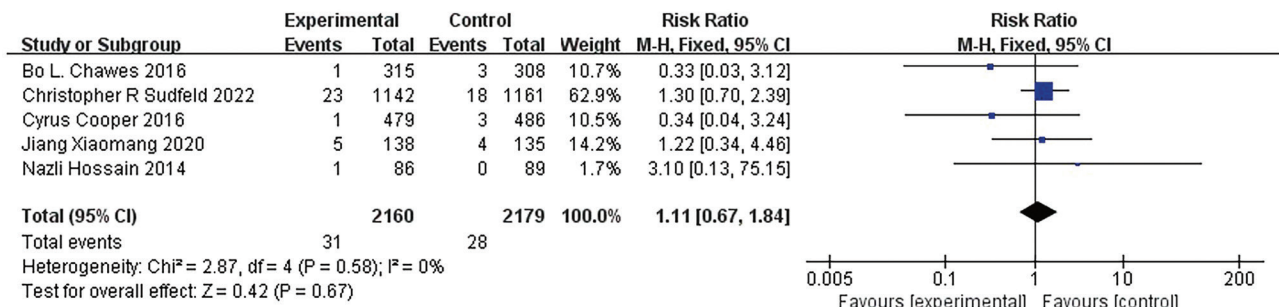
Absence of a clear dose-response pattern further supports cautious interpretation of the apparent subgroup signal. No significant association with preterm birth was noted in any OR-based supplementation-dose subgroup, including < 2000 IU/d, 2000–4000 IU/d, or ≥ 4000 IU/d. Similarly, supplementation initiated in the first or second trimester was not significantly associated with preterm birth risk. If vitamin D supplementation had a strong and consistent causal effect on preterm birth, a clearer pattern by dose or timing might be expected. A discrepancy between the baseline 25(OH)D subgroup results and dose-stratified results suggests that the association is unlikely to be explained by supplementation dose alone. Instead, the discrepancy may reflect baseline status, population characteristics, trial-specific factors, or chance. Therefore, the present findings cannot support dose-based recommendations for preterm birth prevention.

Vitamin D supplementation had no statistically significant effect on maternal secondary outcomes (stillbirth, spontaneous abortion, preeclampsia, or gestational hypertension). Previous mechanistic evidence suggests that vitamin D may influence immune and inflammatory regulation,

Stillbirth



Abortion



Preterm birth

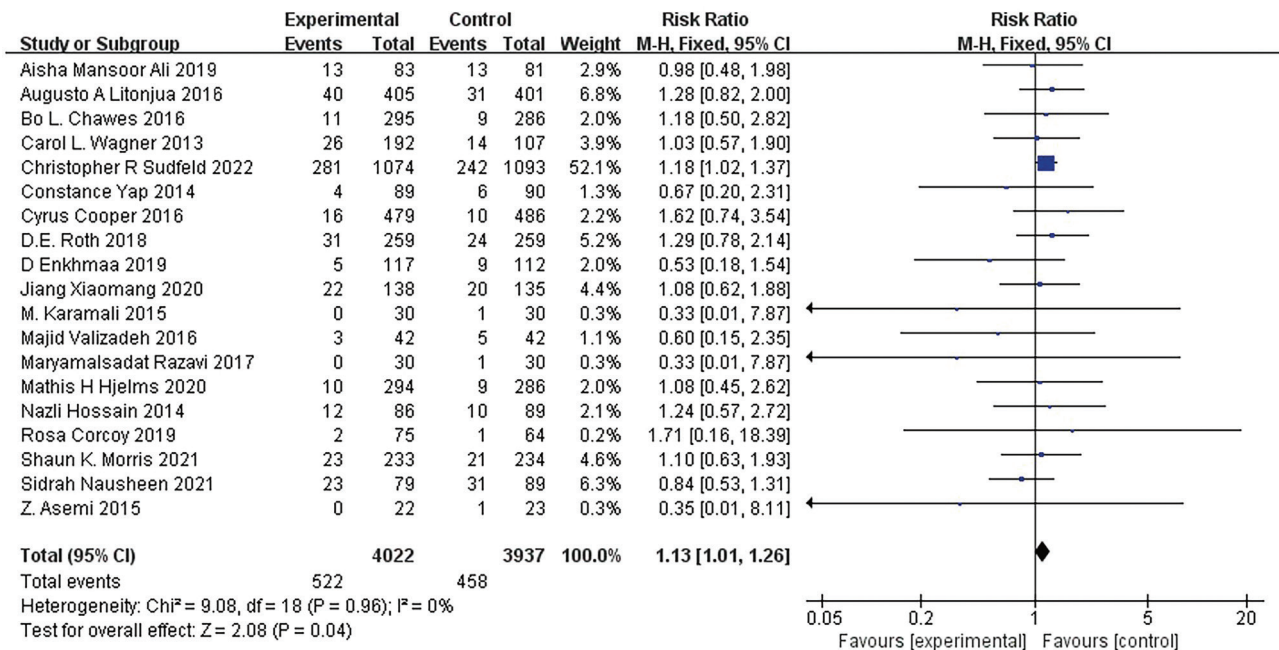
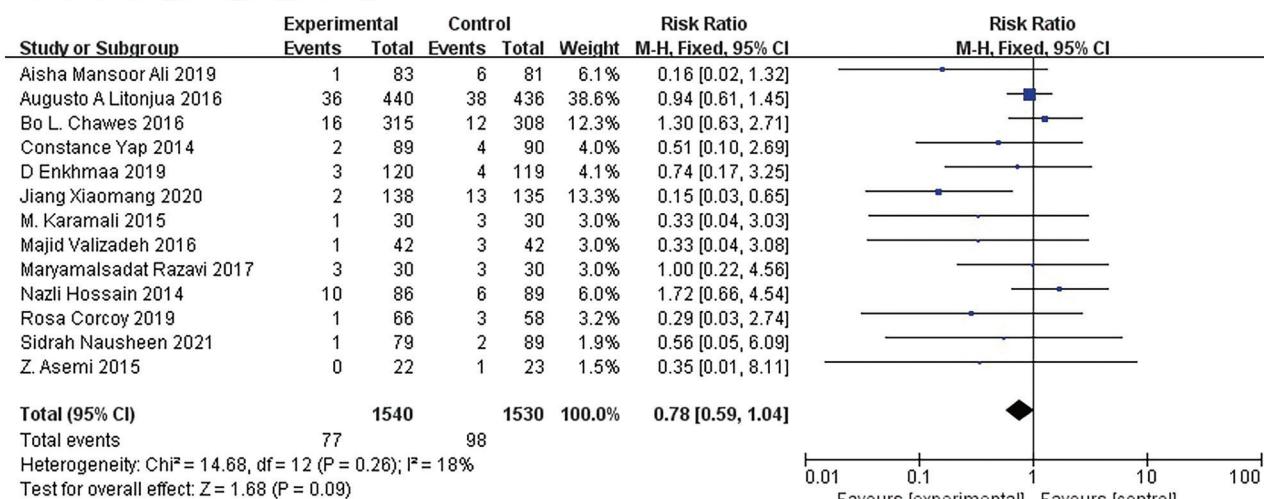


Figure 4 (continued)

endothelial-related angiogenic pathways, and placental function, all of which are implicated in the pathophysiology of preeclampsia [9]. Nevertheless, the present pooled RCT evidence did not demonstrate a significant clinical benefit for these maternal outcomes. The direction of effect for preeclampsia was toward a potential benefit but the CI

crossed the null value. Therefore, this result should be interpreted as inconclusive rather than as evidence of a protective effect. Future trials may need to evaluate whether effects differ among participants with severe vitamin D deficiency, low calcium intake, high baseline risk of preeclampsia, or other clinically relevant subgroups.

Preeclampsia pregnancy



Hypertension of pregnancy

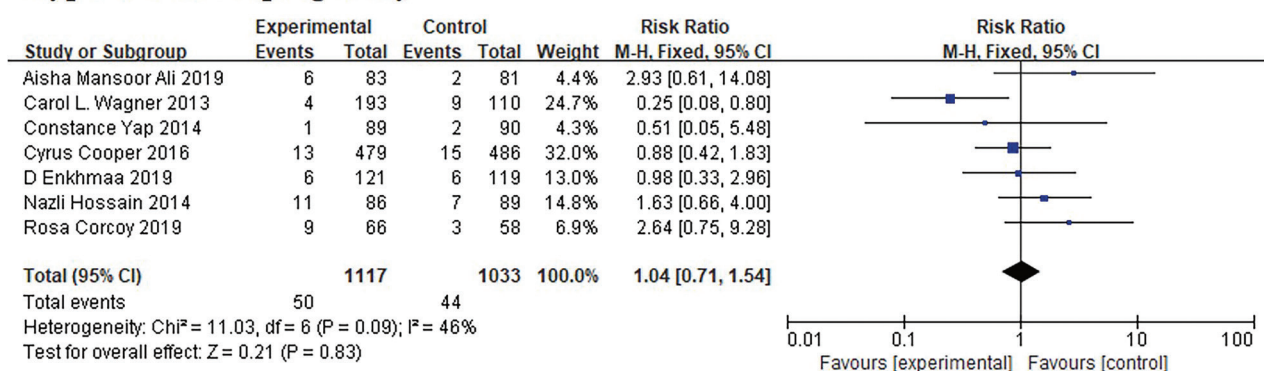


Figure 4 Forest plot from meta-analysis examining effect of vitamin D supplementation during pregnancy on maternal outcomes. Forest plots show the effect of vitamin D supplementation on stillbirth, abortion, preterm birth, preeclampsia, and hypertension of pregnancy. The results are presented as a risk ratio (RR) and 95% confidence interval (CI).

Vitamin D supplementation was not associated with significant differences in neonatal outcomes (birth length, birth weight, head circumference at birth, or low birth weight). This finding is consistent with several randomized studies reporting limited, neutral, or inconsistent effects of prenatal vitamin D supplementation on fetal growth and infant anthropometric outcomes [28, 29]. Although vitamin D may affect skeletal development and neonatal vitamin D status, available trial evidence does not indicate a meaningful effect on birth-size outcomes assessed in this meta-analysis. These findings suggest that routine prenatal vitamin D supplementation should not be expected to substantially improve neonatal anthropometric indicators in unselected pregnant women.

Several biological mechanisms may explain why baseline vitamin D status could modify responses to supplementation but these mechanisms remain speculative in relation to clinical outcomes observed in this meta-analysis. Vitamin D may support maternal-fetal immune tolerance through VDR-mediated immunomodulatory mechanisms, including regulation of cytokine production, inflammatory responses, and T-cell tolerance. Vitamin D may also influence placental

function through effects on trophoblast invasion and angiogenic pathways involving sFlt-1 and VEGF, which are relevant to placental development, fetal growth, and pregnancy maintenance [9]. In addition, vitamin D contributes to calcium homeostasis and may influence uterine myometrial contractile profiles through regulation of inflammation-related and contraction-associated pathways [30, 31]. These pathways provide biological plausibility for studying vitamin D status in pregnancy but do not prove that supplementation prevents or causes preterm birth. Specifically, the potential harm signal noted among participants with a baseline $25(\text{OH})\text{D} \geq 30 \text{ nmol/L}$ should not be attributed to over-supplementation or hypercalcemia without direct supporting biomarker evidence. Future RCTs should incorporate mechanistic biomarkers, such as achieved $25(\text{OH})\text{D}$ concentrations, calcium status, inflammatory markers, VDR-related measures, and placental function indicators, to clarify whether these pathways mediate clinical outcomes.

The clinical implications of this study should be conservative. Current evidence does not support universal vitamin D supplementation specifically for prevention of preterm birth. At the same time, the present findings do not justify

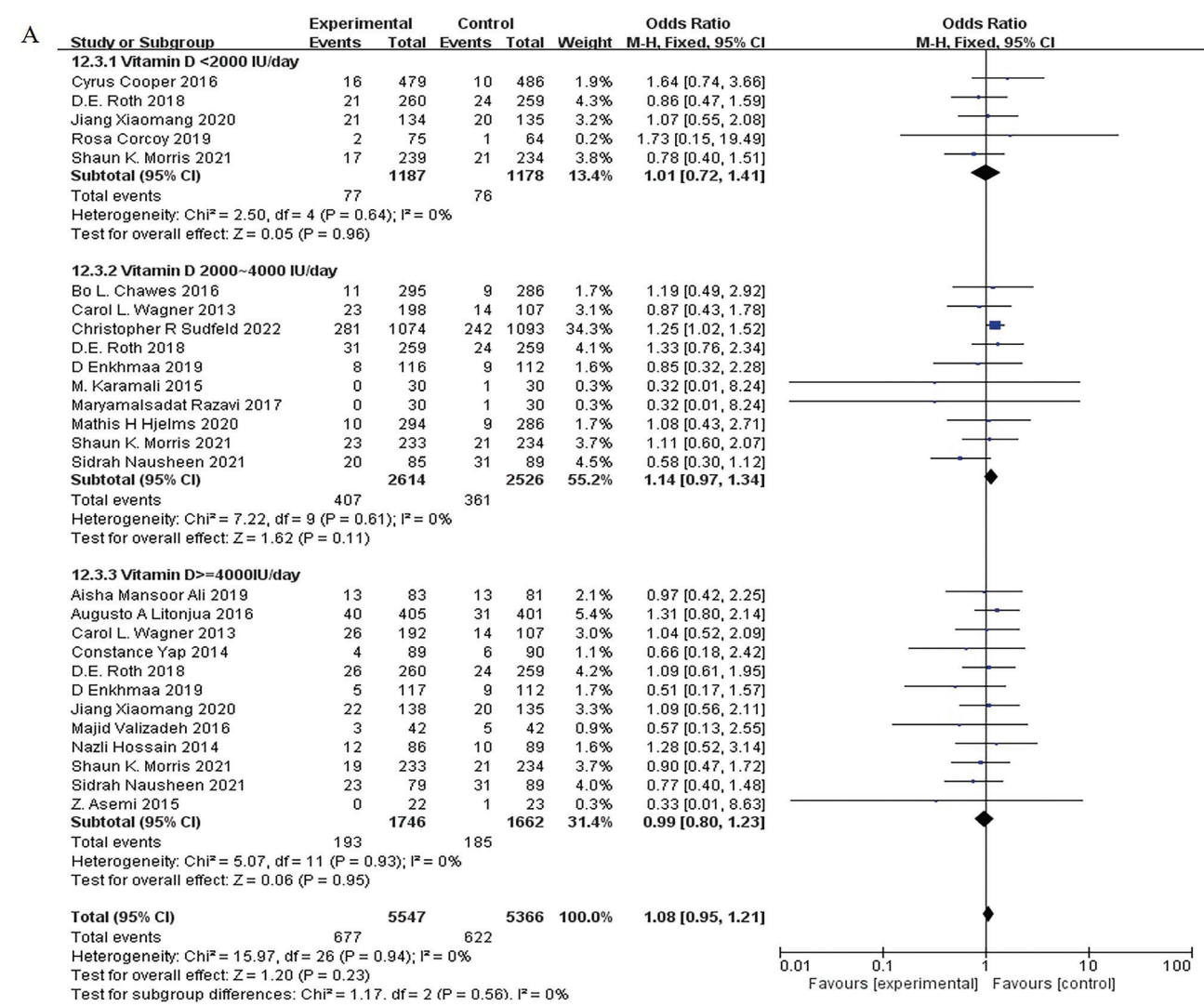


Figure 5 (continued)

contraindicating vitamin D supplementation in pregnant women who require vitamin D supplementation for deficiency correction or bone-health-related indications. A more appropriate interpretation is that the baseline 25(OH)D status may be important for individualized interpretation of supplementation effects but current trial evidence is insufficient to define clear subgroup-specific clinical recommendations. No consistent benefit was observed for women with a baseline 25(OH)D ≥ 30 nmol/L and a possible increase in preterm birth risk was limited to a single population-specific trial. Thus, decisions about prenatal vitamin D supplementation may consider baseline 25(OH)D status when clinically indicated and in accordance with local guidelines, together with clinical context, dietary intake, sun exposure, calcium status, and safety monitoring, rather than assuming universal benefit for preterm birth prevention.

This study had several strengths. First, only RCTs were included, which reduced confounding compared to observational evidence. Second, the review included 38 RCTs and incorporated recent trials, which provided an updated synthesis of prenatal vitamin D supplementation evidence. Third, we conducted prespecified subgroup analyses by baseline 25(OH)D status, supplementation dose, and timing

of initiation, which allowed exploration of potential effect modification. Fourth, the primary outcome had negligible statistical heterogeneity and the funnel plot for preterm birth did not suggest obvious publication bias. Together, these features improve transparency and interpretability of pooled estimates.

Several limitations should also be acknowledged. First, the effective evidence base for primary outcome was limited. Only 19 of the 38 included RCTs reported extractable data on preterm birth and the database search was conducted up to April 2023. Although recent evidence remains mixed and does not consistently demonstrate a clear reduction in preterm birth, a fully updated systematic search and quantitative synthesis will be needed to confirm currency and robustness of present findings. Second, the apparent increased risk among participants with a baseline 25(OH)D ≥ 30 nmol/L was driven entirely by one large trial conducted among HIV-positive pregnant women, which limited generalizability to healthy pregnant women. Third, some included trials lacked placebo controls or used low-dose vitamin D as a comparator, which may have attenuated between-group differences and selective outcome reporting was incompletely described in several studies. Fourth, the subgroup analyses were

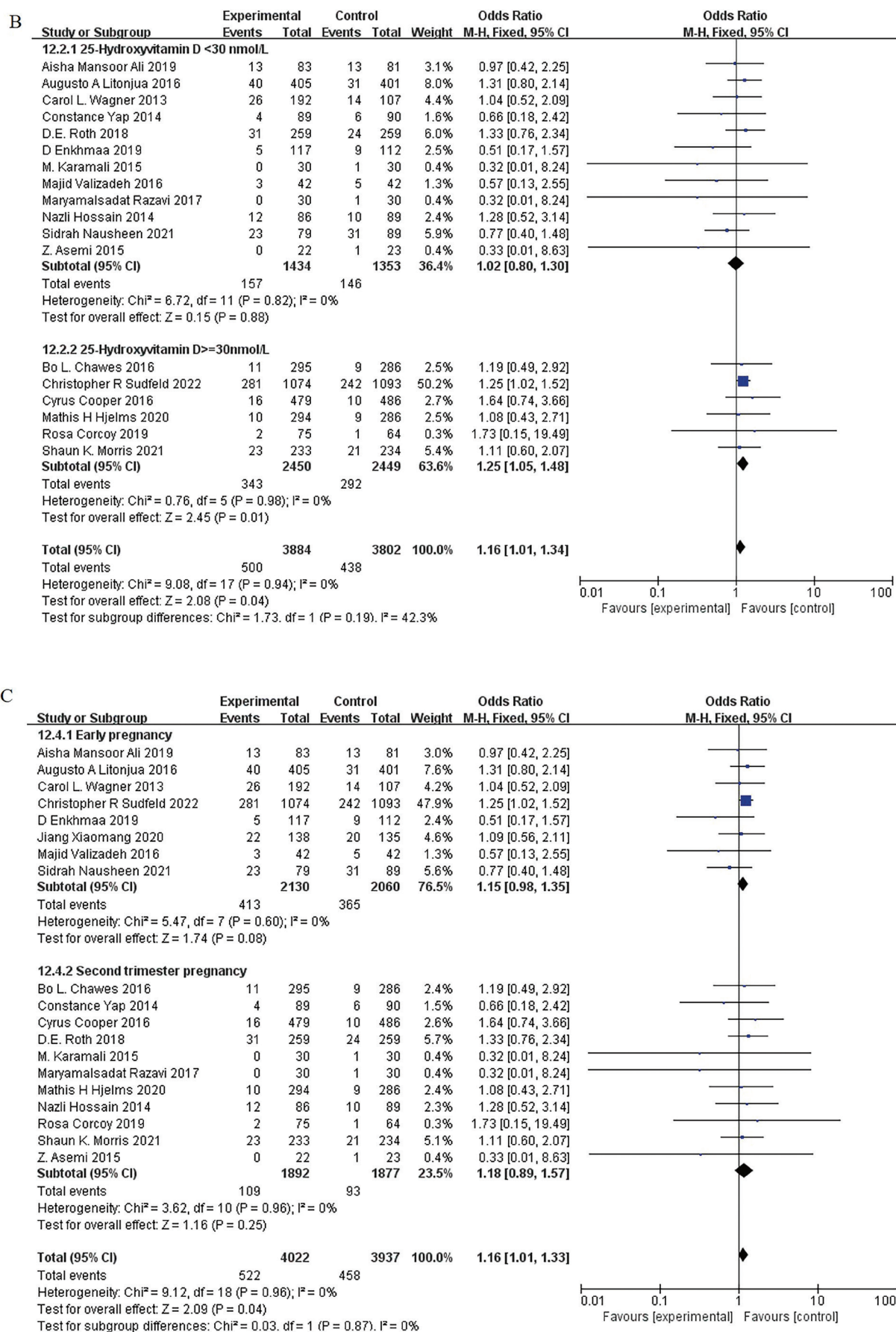
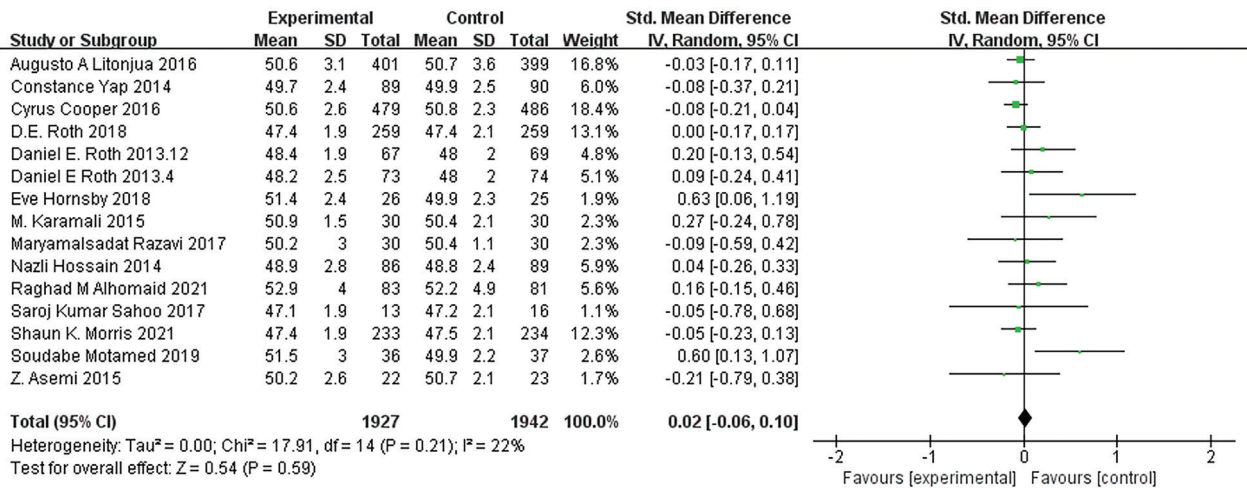


Figure 5 Subgroup analysis of effect of vitamin D supplementation during pregnancy on preterm birth. (A) Subgroup analyses stratified by dosage of vitamin D; (B) Subgroup analyses stratified by 25-hydroxyvitamin D level; (C) Subgroup analyses stratified by timing of vitamin D supplementation. The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs) using Mantel-Haenszel fixed-effect models.

Length at birth



Weight at birth

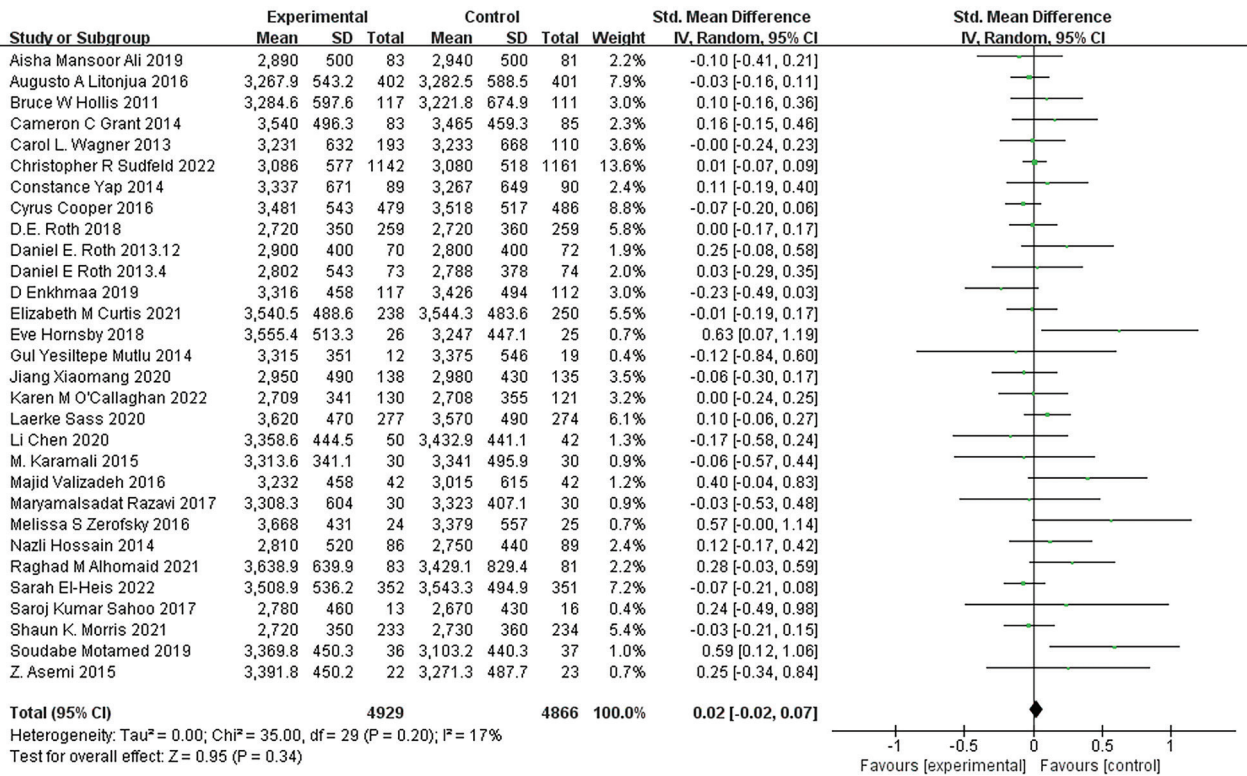
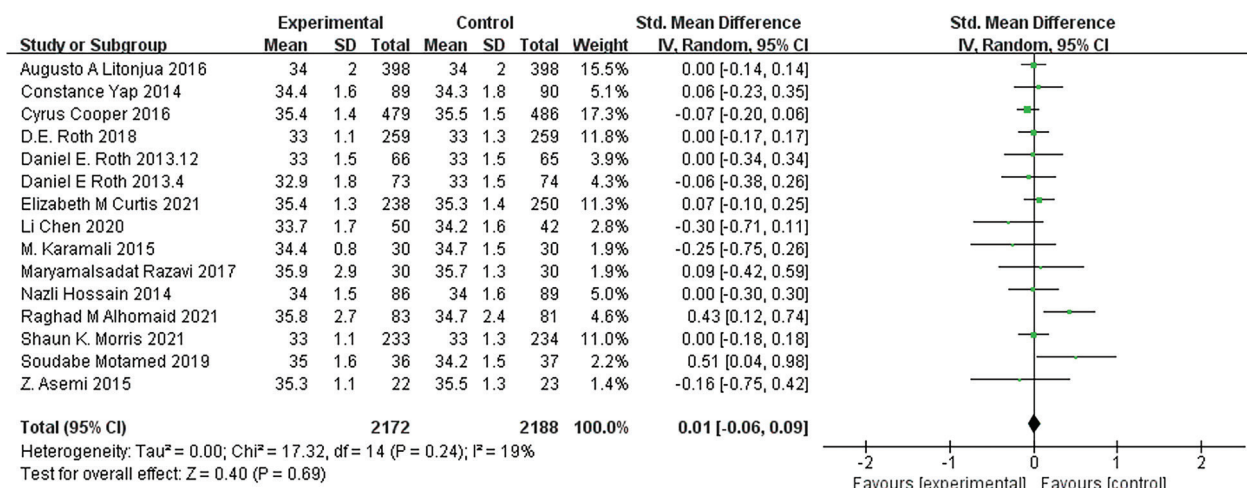


Figure 6 (continued)

limited by dichotomization of baseline 25(OH)D status, limited number of trials and events within some strata, and use of aggregate published data rather than individual participant data. These factors limited our ability to evaluate more granular 25(OH)D categories and to adjust for participant-level factors, such as achieved 25(OH)D concentration, calcium intake, body mass index, ethnicity, season, sun exposure, comorbidities, and adherence. Finally, preterm birth was analyzed as a single outcome and we could not distinguish spontaneous, medically indicated, inflammatory, infectious, or placental subtypes of preterm birth, which may have different relationships with vitamin D biology [2].

Future research should prioritize large, well-designed RCTs in diverse but clearly defined populations of pregnant women. Trials should stratify or randomize participants according to baseline 25(OH)D status, measure achieved 25(OH)D concentrations during follow-up, and report safety outcomes, including hypercalcemia and other adverse events. Future studies should also distinguish spontaneous from medically indicated preterm birth and consider mechanistic biomarkers related to immune regulation, placental function, calcium metabolism, and inflammation. Individual participant data meta-analyses of existing RCTs would be particularly valuable because

Head circumference at birth



Low birth weight

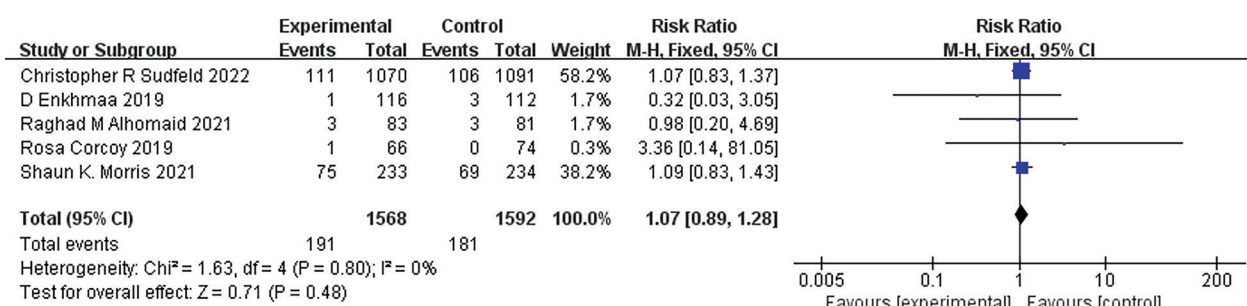


Figure 6 Forest plots examining effects of prenatal vitamin D supplementation on neonatal anthropometric outcomes. (A) Length at birth; (B) Weight at birth; (C) Head circumference at birth; (D) Low birth weight. The continuous outcomes are presented as standardized mean differences (SMDs) and 95% confidence intervals (CIs); binary outcomes are presented as risk ratios (RRs) and 95% CIs.

such meta-analyses could evaluate dose-response relationships, baseline-status modification, achieved vitamin D levels, and clinically relevant subgroups more precisely than aggregate-data analyses. Such evidence is needed before definitive precision-nutrition recommendations for prenatal vitamin D supplementation can be made.

be important for interpreting supplementation effects but current aggregate trial evidence remains insufficient to support definitive stratified clinical recommendations. Future large-scale RCTs in diverse healthy pregnant women and individual participant data meta-analyses are needed to clarify whether baseline vitamin D status modifies effect of supplementation on pregnancy outcomes.

Conclusions

Prenatal vitamin D supplementation showed no evidence of reducing preterm birth risk or improving assessed maternal and neonatal outcomes in this systematic review and meta-analysis of 38 RCTs involving 17,392 pregnant women. Although a borderline increase in preterm birth risk was noted in the primary overall analysis and an OR-based subgroup signal was noted among participants with a baseline $25(\text{OH})\text{D} \geq 30$ nmol/L, this signal was largely driven by a single large trial among women living with HIV and should not be interpreted as causal evidence or generalized to healthy pregnant women. Current evidence does not support universal vitamin D supplementation specifically for prevention of preterm birth. Baseline $25(\text{OH})\text{D}$ status may

Abbreviations

RCTs, randomized controlled trials; $25(\text{OH})\text{D}$, 25-hydroxyvitamin D; RR, risk ratio; CI, confidence interval; HIV, human immunodeficiency virus; $1,25(\text{OH})_2\text{D}_3$, 1,25-dihydroxyvitamin D_3 ; VDR, vitamin D receptor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; PICOS, population, intervention, comparison, outcome, and study design; MeSH, Medical Subject Headings; GRADE, Grading of Recommendations Assessment, Development and Evaluation; SMD, standardized mean difference; OR, odds ratio.

Data availability statement

All data analyzed in this study were extracted from previously published articles cited in the References. The extracted datasets used for the current systematic review and meta-analysis are available from the corresponding author upon reasonable request.

Ethics statement

No direct interactions with human or animal subjects were involved. Therefore, ethical approval and informed consent were not required.

Author contributions

Lulu Zuo, Jiaojiao Wang, and Qiong Lu conceptualized and designed the study, drafted the initial manuscript, and critically reviewed and revised the manuscript. Xinyan Xie and Mei Peng designed the data collection instruments, collected data, carried out the initial analyses, and critically reviewed and revised the manuscript. Zhaokai Zhou critically reviewed and revised the manuscript. Qiyue Zheng conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Not applicable.

Conflict of interest

The authors declare that there are no conflicts of interest.

Supplementary materials

Supplementary Material can be downloaded from https://bio-integration.org/wp-content/uploads/2026/07/bioi20250224_Supplemental.zip.

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