

# The Role of Vitamin D in Pregnancy on the Risk of Preeclampsia and Low Birth Weight: A Meta-analysis of Randomised Controlled Trials

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## Abstract

**Objectives:** Preeclampsia (PE), low birth weight (LBW), and preterm birth are major causes of maternal and neonatal morbidity and mortality. Vitamin D supplementation during pregnancy is considered to influence these outcomes. This study aimed to evaluate the effect of maternal vitamin D supplementation during pregnancy on the risk of PE, LBW, and preterm birth.

**Methods:** We systematically searched PubMed, Scopus, and Web of Science using predefined inclusion and exclusion criteria. The study protocol was registered prospectively to the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD420251143323. Risk ratios (RRs) with 95% confidence intervals (CIs) were pooled using fixed- or random-effects models, depending on the level of heterogeneity.

**Results:** Thirteen RCTs involving nearly 4,000 pregnant women were included. Vitamin D supplementation was associated with a significant reduction in the risk of PE (RR 0.53; 95% CI 0.41–0.70;  $p < 0.00001$ ;  $I^2 = 19\%$ ) and preterm birth (RR 0.62; 95% CI 0.50–0.77;  $p < 0.0001$ ;  $I^2 = 31\%$ ). No significant effect was observed on LBW (RR 0.65; 95% CI 0.34–1.27;  $p = 0.21$ ;  $I^2 = 65\%$ ).

**Conclusions:** Vitamin D supplementation during pregnancy significantly reduces the risk of PE and preterm birth. However, the effect on LBW is not statistically significant. These findings support that adequate maternal vitamin D status during pregnancy is essential and emphasize the need for further study on optimal supplementation strategies and the long-term effects on maternal and child health.

**Keywords:** Low birth weight, Meta-analysis, Preeclampsia, Pregnancy, Vitamin D

## Introduction

Preeclampsia (PE) is still one of the major complications of pregnancy and a significant cause of maternal and neonatal morbidity and mortality worldwide. It affects around 2–8% of pregnancies and contributes to roughly 16% of pregnancy-related mortality.<sup>1,2</sup> PE is responsible for around 46,000 maternal and 500,000 fetal deaths annually. Maternal mortality in low- and middle-income countries remains high even though advanced obstetric care has generally improved maternal outcomes.<sup>1–3</sup> PE complications, such as low birth weight (LBW) and preterm birth, represent major clinical and public health challenges.<sup>4</sup> Global estimates from 2020 show that

approximately 19.8 million newborns, equivalent to around 15% of all live births worldwide, were born with LBW. These newborns face a significantly higher risk of early neonatal mortality among survivors and also increased rates of growth problems, neurodevelopmental delays, and long-term chronic diseases in adulthood.<sup>3,5-7</sup>

PE typically develop after mid-gestation and is characterised by new-onset hypertension accompanied by proteinuria or signs of maternal organ dysfunction.<sup>3,8,9</sup> This pregnancy-specific vascular disorder often manifests in the third trimester but may occasionally occur postpartum. The exact mechanisms remain unclear, yet the key initiating events considered are impaired trophoblast invasion and inadequate spiral artery remodelling. These abnormalities lead to reduced placental perfusion, ischemia, oxidative stress, syncytiotrophoblast injury, systemic inflammation, and widespread endothelial dysfunction.<sup>6,10,11</sup> Pre-existing hypertension, diabetes, chronic kidney disease, obesity, nulliparity, multiple pregnancy, immune disorder, and personal or family history of PE or eclampsia are several maternal factors that increase the risk of PE.<sup>8,9</sup> The World Health Organization defined LBW as a weight below 2500 g. The common causes are intrauterine growth restriction, preterm birth, or both, and share overlapping pathways with PE through placental insufficiency.<sup>5,12</sup>

Vitamin D has multiple effects during pregnancy, beyond its well-known role in bone health, calcium and phosphate homeostasis, and cellular function.<sup>13-15</sup> Vitamin D also supports implantation, placental vascular development, angiogenesis, and maternal-fetal immune tolerance. Requirements of maternal vitamin D increase to support fetal skeletal growth and physiological adaptations during pregnancy.<sup>14-16</sup> Several factors increased the risk of vitamin D deficiency during pregnancy, such as women with darker skin pigmentation or limited sun exposure. The prevalence estimates range from 30% to 60%.<sup>13,17,18</sup> The optimal maternal serum 25(OH)D concentration remains debated. The general recommendation suggests at least 20 ng/ml (50 nmol/L), yet some experts suggest a higher threshold, at least 32 ng/ml (80 nmol/L).<sup>17,19,20</sup>

The effects of vitamin D supplementation on pregnancy outcomes remain inconsistent in several RCTs. Certain studies demonstrated that vitamin D supplementation reduced the risk of preeclampsia and improved birth weight outcome, while others found no significant correlations.<sup>12,21-24</sup> Synthesising evidence from RCTs is essential to clarify the associations of biological plausibility linking vitamin D with placentation and adverse pregnancy outcomes. Therefore, this systematic review and meta-analysis were conducted to evaluate the effect of vitamin D supplementation during pregnancy on the risk of PE, LBW, and preterm birth, and provide evidence to inform clinical practice guidelines and maternal nutrition policies.

## Methods

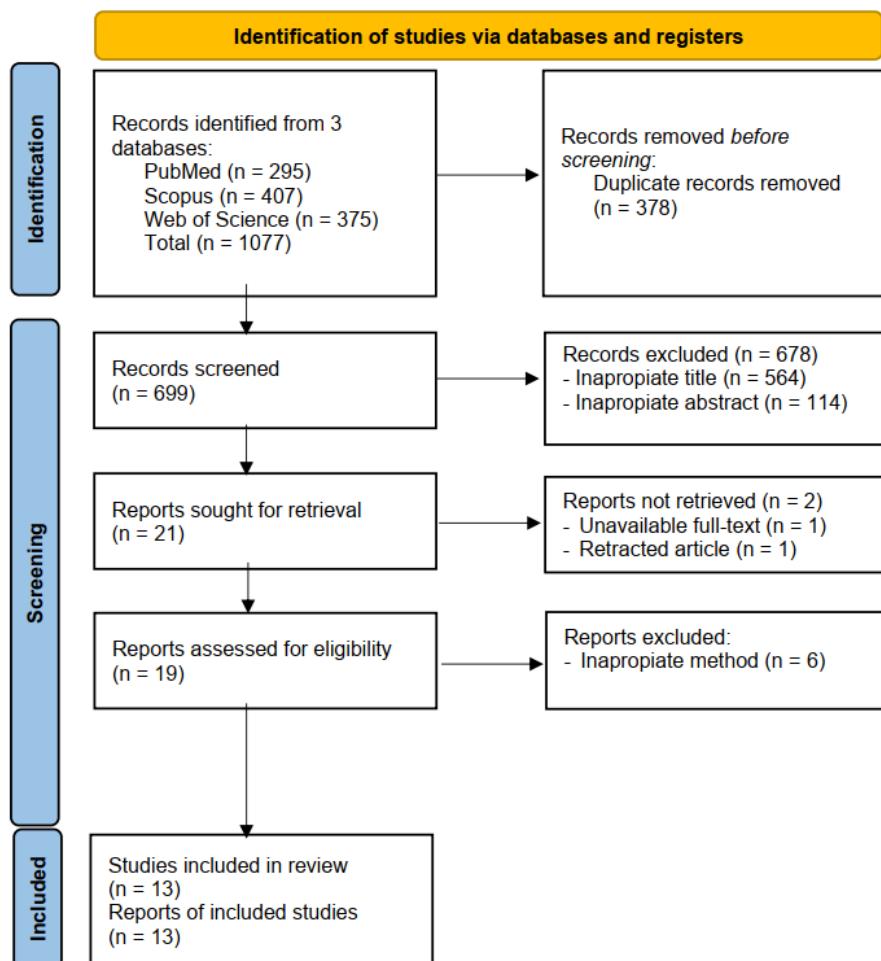
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines were followed for data extraction and synthesis in this systematic review and meta-analysis.<sup>25</sup> The study protocol was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD420251143323.<sup>26</sup>

We systematically searched three databases, PubMed, Scopus, and Web of Science, to identify relevant RCTs. Keywords and Medical Subject Headings (MeSH) were used in this search strategy related to vitamin D, pregnancy, and target outcomes. The searched included terms such as "Vitamin D" OR "ergocalciferol" OR "colecalciferol" OR "calcitriol" OR "calcidiol" OR "Vitamin D 25 OH" OR "25 hydroxy cholecalciferol" AND "pregnancy" OR "pregnant" OR "gestation" OR "maternal" AND "preeclampsia" OR "PE" OR "low birth weight" OR "LBW". Only human studies published in English were considered.

The search covered all records up to August 2025 and was conducted between August 24 and 31, 2025. A total of 1,077 studies were retrieved, consisting of 295 from PubMed, 407 from Scopus, and 375 from Web of Science. We organised the search results using the Rayyan software. Duplicate records were removed, and two reviewers independently screened the remaining citations through successive title, abstract, and full-text assessment. Any disagreements were resolved through discussion. After the duplicates were removed, 699 unique records remained. Title and abstract screening excluded 678 articles, and 21 full-text articles were assessed for eligibility. Finally, we included 13 articles that met the eligibility criteria in the meta-analysis. The selection process is illustrated in the PRISMA 2020 flow diagram (Figure 1).

Our study selection was guided by the PICO framework (Population, Intervention, Comparator and Outcome). Our eligibility criteria focused on pregnant women receiving vitamin D supplementation compared

with placebo, no supplementation, or lower-dose supplementation, as specified in each trial, and reporting outcomes related to PE, LBW, or preterm birth. Our research question was “Among pregnant women, does vitamin D supplementation during pregnancy, compared with placebo or no supplementation or lower-dose vitamin D, reduce the risk of PE and LBW?”, in which the population is pregnant women of any age, parity, or gestational stage, regardless of geographical setting. The intervention is vitamin D supplementation during pregnancy in any form ( $D_2$  or  $D_3$ ), at any dosage, frequency, route or timing of administration. Comparator groups include placebo, no supplementation, or lower-dose vitamin D, as defined by each study. Outcomes include PE (new-onset hypertension  $\geq 140/90$  mmHg after 20 weeks of gestation with proteinuria or maternal organ dysfunction) and LBW (birth weight  $< 2,500$  g) as primary outcome, and preterm birth (delivery before 37 completed weeks of gestation) as secondary outcome.



**Figure 1:** Literature search and screening strategy for candidate studies.

We included RCTs evaluating the association between maternal vitamin D supplementation during pregnancy and the risk of PE or LBW. Exclusion criteria comprised animal or in vitro studies, case reports or series, cross-sectional, case-control, cohort studies, and duplicate publications derived from the same dataset.

Pooled estimates were calculated using Review Manager (RevMan) version 5.4 (Cochrane Collaboration). We generated the pooled risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes. We assessed heterogeneity with Cochran's Q ( $\chi^2$ ) test, with a p-value  $< 0.10$  considered significant and quantified with  $I^2$  statistic. A fixed-effect model was applied when heterogeneity was low ( $I^2 < 50\%$ ), whereas a random-effects model (DerSimonian-Laird method) was used for moderate or high heterogeneity ( $I^2 \geq 50\%$ ). Statistical significance was set at p-value  $< 0.05$  for all analyses.

The risk of bias of the included studies was evaluated using the revised Cochrane Risk of Bias tool for randomised trials (RoB 2).<sup>27</sup> Two reviewers independently assessed each study across multiple domains, including randomisation process, deviations from intended interventions, completeness of outcome data,

measurement of outcomes, and selective reporting. Each domain was rated as low risk, some concerns, or high risk. We resolved discrepancies through discussion to reach a consensus. We evaluated potential publication bias by visual inspection of the funnel plot. In addition, publication bias for preeclampsia outcomes was quantitatively assessed using Egger's regression test.

## Results

The initial database search identified a total of 1,077 records. After removing 378 duplicates, 699 unique articles remained for screening. Based on titles and abstracts, 564 were removed based on the title alone and another 114 after reviewing the abstract. We then retrieved 21 full-text articles for further assessment. Two reports could not be included, one because the full-text was inaccessible and another because it had been retracted. Six of the remaining 19 full-text articles were excluded because they did not meet our eligibility criteria. In the end, 13 RCTs fulfilled all inclusion criteria and were incorporated into the final analysis. The PRISMA 2020 flow diagram (Figure 1) illustrates the screening process.

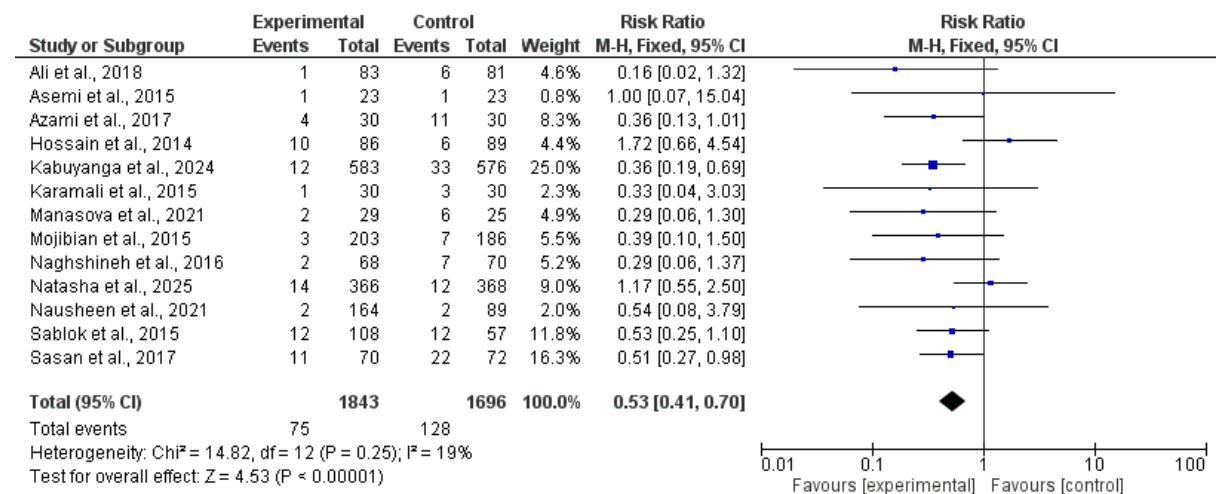
**Table 1:** Characteristics of included RCTs on vitamin D supplementation and pregnancy outcomes.

Author (Year, Country)	Eligibility for Pregnant Women	Gestational Weeks of Sampling	Sample Size	Vitamin D Supplementation Doses	
				Intervention	Control
Naghshineh et al. (2016, Iran) <sup>24</sup>	Primigravida, mean age 25 ± 4.1 years	16 weeks	140	600 IU daily until the delivery	Placebo
Natasha et al. (2025, UK) <sup>21</sup>	Women >18 years, baseline 25(OH)D with Vitamin D External Quality Assessment Scheme (DEQAS) standards	14–17 weeks	734	1,000 IU daily until delivery	Placebo
Kabuyanga et al. (2024, DRC) <sup>12</sup>	Primigravida, not exceeding 16 weeks	≤16 weeks	1,300	60,000 IU monthly, total six doses until delivery	Placebo
Manasova et al. (2021, Ukraine) <sup>28</sup>	Women in the 1 <sup>st</sup> trimester, mean age 27.4 ± 4.4 years for intervention and 28.2 ± 4.6 years for the control group, with vitamin D deficiency and PE risk factors	10–12 weeks	54	4,000 IU until 16 weeks, then 2,000 IU daily until term	Multivitamin with 500 IU vitamin D
Nausheen et al. (2021, Pakistan) <sup>29</sup>	Pregnant women, ≥25 years	<16 weeks	350	Group A 4,000 IU daily, group B 2,000 IU daily	400 IU daily
Ali et al. (2018, Saudi Arabia) <sup>30</sup>	Pregnant women, <20 or >40 years, baseline 25(OH)D <25 nmol/L	≤13 weeks	179	4,000 IU daily	400 IU daily
Azami et al. (2017, Iran) <sup>31</sup>	Pregnant women, mean age 31.63 ± 6.13 years,	>20 weeks	90	Multimineral with vitamin D containing, 400	Ferrous sulfate only

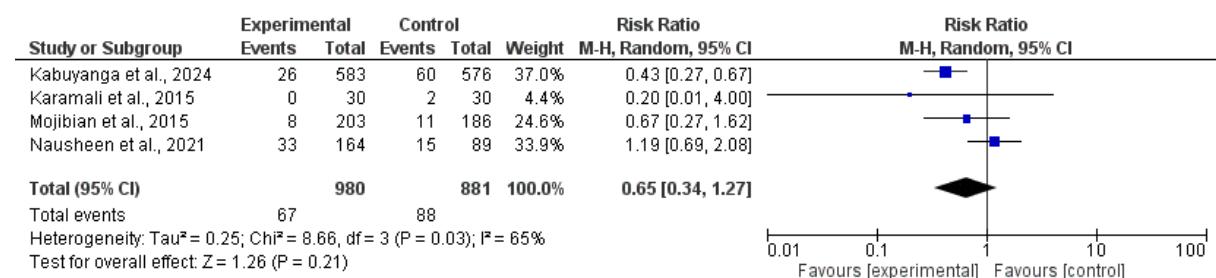
	with PE risk factors, received ferrous sulfate			IU Vitamin D3, 800mg calcium, 200mg magnesium, and 8mg zinc daily	
Sasan et al. (2017, Iran) <sup>9</sup>	Pregnant women, mean age $32.04 \pm 5.901$ for the intervention and $29.77 \pm 5.21$ for the control group, with prior PE history	~14 weeks	142	50,000 IU every 2 weeks until 36 weeks	Placebo
Mojibian et al. (2015, Iran) <sup>32</sup>	Pregnant women, mean age $27.8 \pm 5$ for intervention and $27.3 \pm 4.9$ for control group with serum 25(OH)D $<30$ ng/ml	12–16 weeks	500	50,000 IU every 2 weeks until delivery	400 IU daily
Sablok et al. (2015, India) <sup>33</sup>	Primigravida, who received vitamin D supplementation in dosages depending on serum 25(OH)D level for the intervention group and no prior vitamin D supplementation for the control group	14–20 weeks	180	60,000–120,000 IU at scheduled intervals until delivery	No supplementation
Asemi et al. (2015, Iran) <sup>34</sup>	Primigravida, at their third trimester at PE risk with positive roll over test, aged 18–40 years	27 weeks	46	Multi-mineral Vitamin D, containing 400 IU Vitamin D3, 800 mg calcium, 200 mg magnesium, and 8 mg zinc	Placebo
Karamali et al. (2015, Iran) <sup>23</sup>	Pregnant women at PE risk, according to abnormal uterine Doppler	18–20 weeks	60	50,000 IU every 2 weeks from 20 to 32 weeks	Placebo
Hossain et al. (2014, Pakistan) <sup>17</sup>	Pregnant women, singleton pregnancy, normoglycemic and normotensive	$\leq 20$ weeks	207	4,000 IU daily until delivery	Ferrous sulfate 200 mg twice daily and calcium lactate 600mg daily

This systematic review and meta-analysis included 13 RCTs with a total sample size of 3983 pregnant women. The trials were published between 2014 and 2025. These represented a broad range of geographical regions, including Asia (e.g., Iran), Europe (e.g., the United Kingdom, Ukraine), and Africa (e.g., the Democratic Republic of Congo). Most of the studies were conducted in the Asian population in Iran. All studies' populations recruited pregnant women with singleton pregnancies. Four studies recruited primigravida women, and five studies specifically targeted women at increased risk of preeclampsia. Three studies recruited women with documented vitamin D deficiency or insufficiency, whereas two studies tailored supplementation based on baseline serum 25(OH)D levels. Vitamin D supplementation generally began in the first or early second trimester (10–17 weeks of gestation). Intervention strategies differed considerably, with vitamin D supplementation ranging from daily doses of 600 to 4,000 IU to intermittent high doses, such as 50,000 IU every two weeks, 60,000 IU monthly, and 120,000 IU two to four doses during pregnancy. Supplementation was

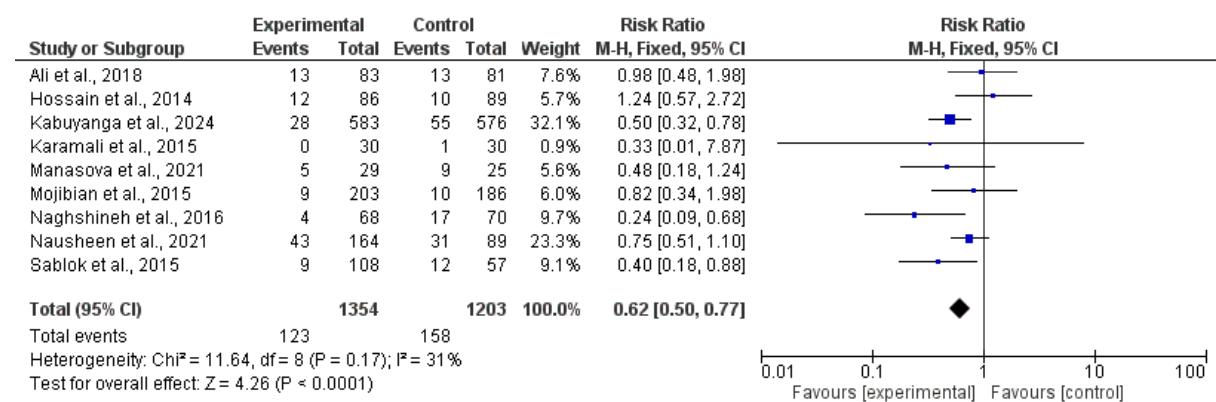
typically continued until delivery. Control groups were assigned either a placebo, low-dose vitamin D (e.g., 400 IU daily), or vitamin D-free supplementation.



(a)



(b)



(c)

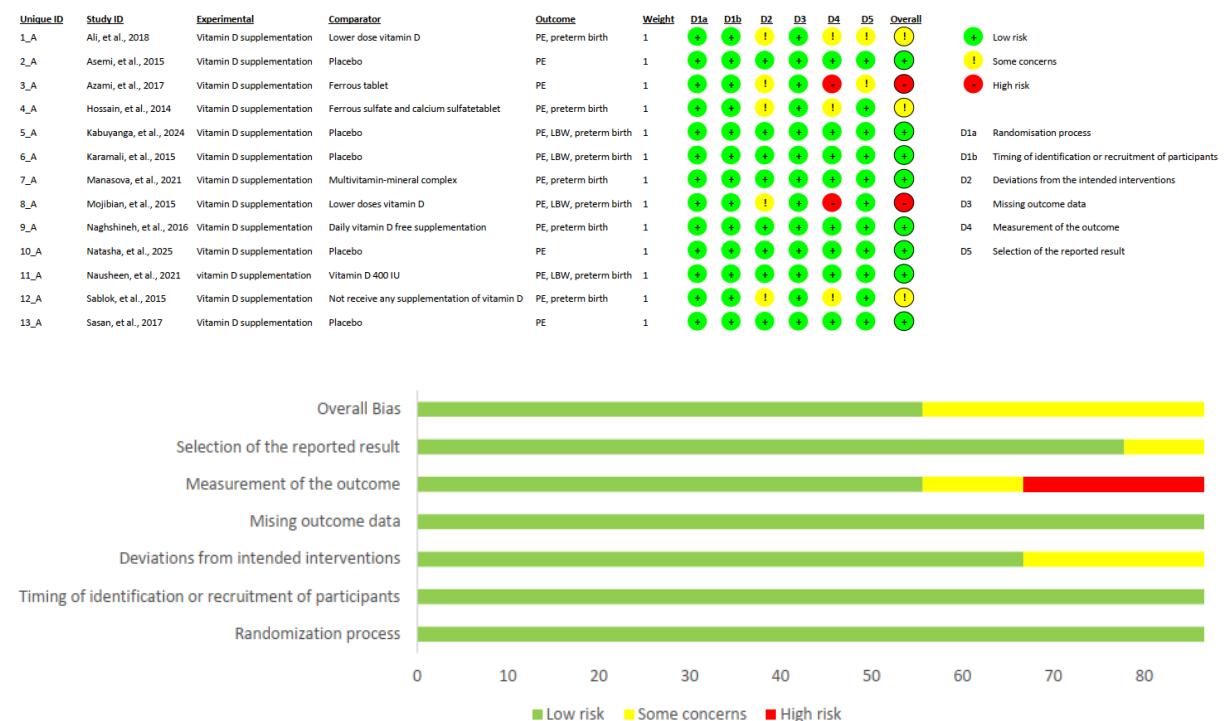
**Figure 2:** Forest plot (a) vitamin D supplementation versus control on preeclampsia, (b) vitamin D supplementation versus control on low birth weight, (c) vitamin D supplementation versus control on preterm birth

The meta-analysis using a fixed-effect model demonstrated that the vitamin D supplementation was associated with a 47% lower risk of PE compared to control (RR 0.53, 95% CI 0.41–0.70,  $P < 0.00001$ ) (Figure 2a). The largest weight comes from Kabuyanga et al. (25%) and Sasan et al. (16.3%). Some studies (e.g.,

Hossain, Natasha, Nausheen) are not individually statistically significant since they have wide confidence intervals that cross 1. Between-study heterogeneity was low ( $I^2 = 19\%$ ).

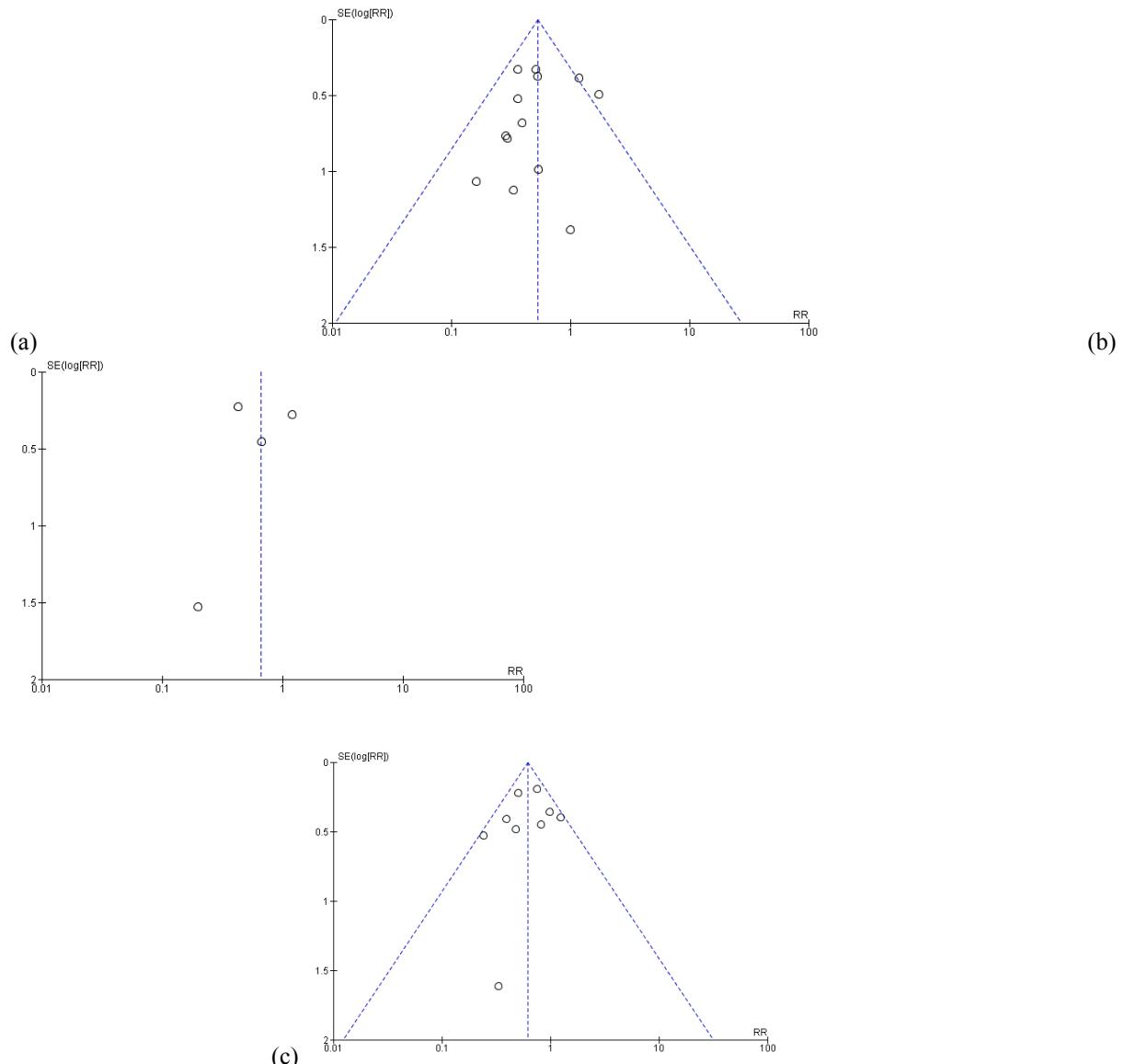
Four RCTs assessed LBW as an outcome, including 1861 participants (980 in the intervention group and 881 in the control group). The pooled random-effects analysis revealed no statistically significant association between the vitamin D supplementation and LBW (RR 0.65, 95% CI 0.34–1.27;  $p = 0.21$ ) (Figure 2b). Kabuyanga et al. reported a significant reduction in risk among individual studies, while other studies showed non-significant findings. Between-study heterogeneity was substantial ( $I^2 = 65\%$ ,  $p = 0.03$ ), reducing confidence in the pooled estimate.

Vitamin D supplementation was associated with a reduction in preterm birth risk by 38% compared with the control (Figure 2c). The pooled risk ratio (RR 0.62, 95% CI 0.50–0.77) and the result is statistically significant ( $p < 0.0001$ ). The low between-study variability ( $I^2 = 31\%$ ) strengthens the reliability of this finding.



**Figure 3: (a) risk of bias, (b) risk of bias summary.**

The risk of bias assessment of the 13 included studies, performed using Cochrane Risk of Bias 2 tools (RoB 2), is summarised in Figure 3. Overall, most trials showed low risk of bias, particularly in randomisation, outcome measurement, and reporting. The primary limitation was related to blinding. As several studies were conducted in an open-label designs, raising potential performance bias. Nevertheless, missing data were minimal, attrition rates were low, and the outcomes were largely objective. Thus, the overall quality of evidence was considered acceptable and reliable.



**Figure 4:** Funnel plot (a) preeclampsia, (b) low-birth weight, (c) preterm birth.

The funnel plot for preeclampsia is symmetric. Egger's regression test did not demonstrate evidence of funnel plot asymmetry ( $z = -0.5560$ ,  $p = 0.5782$ ), and that indicates there were no statistically significant small-study effects or publication bias. Due to the small number of studies ( $n=4$ ), funnel plot asymmetry for LBW cannot be reliably assessed. Most studies are clustered around the pooled estimate near  $RR = 1$  for preterm birth. The funnel plot shows even distribution around the pooled effect, meaning most of the studies show significant effect with preterm birth..

## Discussion

This systematic review and meta-analysis of 13 RCTs with nearly 4,000 participants found that vitamin D supplementation during pregnancy was associated with a reduced risk of PE and preterm birth. Nevertheless, no statistically significant association between vitamin D supplementation and LBW was observed. Adequate vitamin D status is biologically known to support placental function, modulate immune tolerance, and reduce systemic inflammation. These mechanisms are central to the pathogenesis of PE and fetal growth restriction. The findings of several other studies also support this mechanism.<sup>15,35-39</sup>

The beneficial effects of vitamin D on PE and preterm birth are attributed to its facilitation of early placental development. Adequate vitamin D levels support trophoblast invasion and spiral artery remodelling.

This support enables uteroplacental blood flow improvement and limits placental hypoxia.<sup>6,19</sup> Vitamin D is a key pathway of vascular regulation by stimulating VEGF expression and suppressing anti-angiogenic mediators such as sFlt-1. This can protect endothelial function and reduce the likelihood of maternal hypertension.<sup>6,19,40,41</sup> Vitamin D also helps immune modulation during pregnancy by regulating T-cell activity and decreasing pro-inflammatory cytokines, which support maternal-fetal tolerance and reduce systemic inflammation.<sup>37,39,42</sup> Besides its vascular and immunological effects, the evidence also supports that vitamin D reduces inflammatory signalling and influences myometrial contractility.<sup>37,38</sup> Those mechanisms may reduce the risk of premature labour and preterm birth.<sup>12,24,35,36</sup>

The 46% reduction in PE risk mirrors the findings of earlier meta-analyses by Palacios et al. and Wei et al., which also demonstrated that vitamin D supplementation was associated with decreased hypertensive disorders of pregnancy.<sup>18,36</sup> Vitamin D enhances trophoblast invasion, regulates angiogenic factors, and mitigates endothelial dysfunction. These can impair placentation and maternal hypertension. Our study heterogeneity for LBW was substantial ( $I^2 = 65\%$ ), hence reduced the confidence of the pooled estimate. This variability is probably due to study design, supplementation dosage, timing of intervention, and maternal vitamin D status. Some individual trials, such as Kabuyanga et al., reported beneficial effects, but other large-scale studies from the UK and Pakistan found no significant effects.<sup>12,21,29</sup> This inconsistency indicates that vitamin D may have stronger effects on maternal vascular function and gestational duration than fetal growth outcome.

Our analysis showed that preterm births among pregnant women with vitamin D supplementation were 38% lower than those with placebo or low-dose vitamin D. These findings align with evidence from previous RCTs and reviews, which show that vitamin D supplementation reduces preterm birth by maintaining uterine quiescence and modulating inflammatory pathways.<sup>12,29,35,39</sup> Given that preterm birth is still one of the leading causes of neonatal mortality worldwide, this result has meaningful public health implications.

The strengths of this study include the inclusion of only RCTs, which minimises confounding compared to observational study designs, and the application of a pre-registered protocol, which gives assurance of transparency in the research process. We pooled a large sample size to enhance the generalizability of the findings. In general, our risk of bias assessment indicated acceptable methodological quality. Our study has several limitations, including considerable heterogeneity in supplementation protocols. The factors may influence the outcomes, such as vitamin D form (D<sub>2</sub> vs D<sub>3</sub>), regimen (daily vs intermittent high-dose), and maternal vitamin D status. Performance bias was also present in some open-label studies. In addition, several included trials in a population with a high prevalence of vitamin D deficiency may limit extrapolation to the general population. The limited number of trials that evaluate LBW could also restrict conclusions for this outcome.

Finally, these findings suggest that vitamin D supplementation may have a preventive role against PE and preterm birth. Future high-quality RCTs with standardised dosing regimens and adequate power are needed to determine optimal supplementation strategies and to clarify their role in improving birth weight outcomes.

## Conclusion

Vitamin D supplementation during pregnancy significantly reduces the risk of PE and preterm birth. However, the effect on LBW is not statistically significant. These findings reinforce the importance of maintaining adequate maternal vitamin D status during pregnancy and highlight the need for further RCTs to determine optimal supplementation strategies and the long-term effects on maternal and child health.

## Disclosure

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