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Original Article

Shedding light on gestational loss: The role of Vitamin D 25(OH)D deficiency in miscarriage – A systematic review and meta-analysis

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Abstract

Objectives: Miscarriage is a common pregnancy complication with various contributing factors. Recent studies suggest that maternal Vitamin D deficiency may increase the risk of early pregnancy loss. Vitamin D is essential for immune regulation, placental development, and fetal growth. This meta-analysis aimed to evaluate the association between maternal Vitamin D status and miscarriage. **Materials and Methods:** This meta-analysis followed PRISMA 2020 guidelines, including observational studies from PubMed, EMBASE, Scopus, Web of Science, and Cochrane (2018–2025). Eligible studies reported serum 25(OH)D levels and miscarriage outcomes. Data on serum Vitamin D, miscarriage incidence, and odds ratios (ORs) were extracted. Study quality was assessed using the Newcastle–Ottawa Scale. Statistical analyses were performed using Review Manager 5.4 and R, with evaluation of heterogeneity and publication bias. **Results:** Women who experienced miscarriage had significantly lower Vitamin D levels than those with ongoing pregnancies (mean difference: −5.48 ng/mL; 95% confidence interval [CI]: −9.77 to −1.19; $P = 0.02$). The miscarriage rate was higher among Vitamin D-deficient women (34%; 95% CI: 0.21–0.47) than in those with sufficient levels (16%; 95% CI: 0.08–0.24). Deficiency was significantly associated with miscarriage risk (OR: 2.02; 95% CI: 1.37–2.98; $P = 0.0004$). No significant publication bias was observed. **Conclusion:** Maternal Vitamin D deficiency is significantly associated with an increased risk of miscarriage. These findings support the potential benefit of assessing and optimizing Vitamin D status in preconception and antenatal care to improve the pregnancy outcomes.

Keywords: *25(OH)D levels, Maternal health, Miscarriage, Pregnancy loss, Vitamin D deficiency*

Introduction

Miscarriage refers to the spontaneous loss of a pregnancy before fetal viability. Miscarriage, often referred to as spontaneous pregnancy loss, describes the natural termination of a nonviable intrauterine pregnancy before reaching 20 weeks of gestation. It is a common reproductive event, with an estimated 23 million cases occurring globally each year, equivalent to approximately 44 losses per minute. Meta-analytic findings indicate that roughly 15.3% of clinically recognized pregnancies result in miscarriage. The estimated prevalence among women who have experienced a single miscarriage is 10.8%, while 1.9% have had two miscarriages, and approximately 0.7% have experienced three or more [1,2].

Several determinants have been identified as contributing to an increased risk of miscarriage. These include extremes of maternal age, particularly women younger than 20 years or older than 35, and paternal age exceeding 40 years. Abnormal body mass index, whether significantly underweight or obese, has also been linked to elevated miscarriage risk. Additional risk-enhancing factors encompass Black racial background, a prior history of pregnancy loss, tobacco use, alcohol intake, psychological stress, engagement in night shift work, as well as environmental exposures such as air pollution and agricultural pesticides [1,3]. Although the etiology and risk factors of miscarriage are widely acknowledged to be multifactorial and complex, emerging evidence has

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highlighted a potential link between maternal Vitamin D status and the incidence of miscarriage, including recurrent pregnancy loss. Hypovitaminosis D during gestation has been identified as a significant contributor to adverse maternal and neonatal outcomes. In contrast, sufficient Vitamin D supplementation has been associated with improved gestational outcomes and a reduced prevalence of pregnancy-related complications [4,5].

Vitamin D, a lipophilic secosteroid hormone, plays a fundamental role in numerous physiological processes, including the regulation of calcium and phosphate metabolism, immunomodulatory functions, and cellular differentiation. Its significance becomes particularly critical during pregnancy, a period characterized by extensive maternal adaptations to support fetal development. Vitamin D facilitates fetal skeletal mineralization, promotes maternal immunological tolerance toward the semiallogeneic fetus, and supports optimal placental structure and function. As such, adequate maternal Vitamin D status is essential for ensuring a healthy gestational course and favorable maternal and neonatal outcomes [6,7]. Recent studies increasingly indicate that Vitamin D plays an essential role in promoting placental health by facilitating crucial biological processes, including trophoblast invasion, blood vessel formation (angiogenesis), and immune system regulation. All of which are fundamental for normal placental development and function. A deficiency in Vitamin D during pregnancy may disrupt these processes, thereby increasing the risk of complications and unfavorable pregnancy outcomes [8-10].

This meta-analysis presents an updated quantitative and qualitative synthesis of global evidence on the association between maternal Vitamin D status, categorized as sufficient or deficient, and the risk of miscarriage. By integrating the data from diverse populations, it highlights the potential benefit of incorporating routine Vitamin D screening and preconceptional supplementation into standardized antenatal care. These strategies may reduce early pregnancy loss, improve maternal and fetal outcomes, and help bridge a critical gap in reproductive health management.

Materials and methods

Ethics statement

This study is a systematic review and meta-analysis based entirely on previously published research. It does not involve any new studies with human participants or animals performed by the authors. Therefore, ethical approval from an institutional review board and informed consent were not required.

Study design

A comprehensive meta-analysis was conducted to assess the relationship between maternal serum Vitamin D levels and the occurrence of miscarriage. This analysis synthesized evidence from a wide range of observational studies, including retrospective cohort studies, case–control studies, and cross-sectional studies conducted globally. All included studies reported the data on Vitamin D status in relation to miscarriage outcomes, allowing for a more robust understanding of the potential association between Vitamin D deficiency and pregnancy loss. The current research adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and has been officially registered on PROSPERO CRD420251063919 [11]. A comprehensive literature search was conducted from January 2018 to March 2025 across the five major databases from Web of Science, EMBASE, Cochrane, Scopus, and PubMed, utilizing modified search terms to ensure the inclusion of relevant studies. Following study selection and data extraction, methodological quality was assessed using the Newcastle–Ottawa Scale (NOS) to evaluate the rigor and validity of the included studies.

The principal outcome measure of this meta-analysis was the evaluation of the mean difference (MD) in serum 25-hydroxyvitamin D (25[OH]D) concentrations between women who experienced miscarriage and those with viable pregnancies, to determine which group exhibited lower average levels. In addition, Vitamin D status was classified based on established thresholds: deficiency was defined as serum 25(OH)D levels <20 ng/mL (<50 nmol/L), whereas sufficiency was defined as ≥20 ng/mL (≥50 nmol/L). The incidence of miscarriage was quantified within both Vitamin D-deficient and Vitamin D-sufficient cohorts. To further assess the potential association between maternal Vitamin D status and the risk of miscarriage, odds ratios (ORs) were calculated. A pooled proportion analysis was also conducted to estimate the aggregated prevalence of miscarriage among individuals with deficient and sufficient Vitamin D levels across the included studies.

Eligibility criteria

The inclusion criteria for this meta-analysis were established in accordance with the Population, Intervention, Comparison, Outcome, and Study Design framework. Eligible studies were those that reported maternal Vitamin D status, either in the form of serum 25(OH)D concentrations or categorized levels, in relation to the incidence of miscarriage. Included studies were required to provide: (1) data on the number of miscarriage events stratified by Vitamin D status (deficient vs. sufficient), and (2) mean serum Vitamin D levels for both the miscarriage and nonmiscarriage groups. Only the most recent studies published between January 2018 and March 2025 were considered, encompassing research conducted in the diverse geographic regions and clinical settings. Furthermore, eligibility was restricted to all observational studies published in the English language. Studies were excluded if they met any of the following criteria: (1) lack of clear data on Vitamin D levels or miscarriage outcomes; (2) review articles, case reports, letters, editorials, conference abstracts, or animal studies; (3) studies with overlapping populations or duplicate datasets; and (4) studies not reporting sufficient statistical information required for meta-analysis (e.g., missing mean values, standard deviations, or event counts). Non-English publications were also excluded. Information sources: specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.

Search strategy

A systematic search was conducted across five major databases, Web of Science, EMBASE, Cochrane, Scopus, and PubMed, on March 1, 2025. The search strategy utilized a combination of Medical Subject Headings terms and modified keywords, with Boolean operators applied to enhance the precision and relevance of the retrieved studies.

Selection process

Duplicates were manually identified and removed on an individual basis. The abstract screening process was carried out by three independent reviewers (C.A.A., F.K., and E.E.), who performed an initial assessment of the titles and abstracts of all studies identified. Any discrepancies or disagreements among the reviewers were addressed through discussion and consensus, with the entire team participating when necessary. Following the initial screening of titles and abstracts, the full-text screening phase commenced to further assess eligibility based on the established inclusion and exclusion criteria.

Data collection process and items

Data extracted from each eligible study included the first author's name and year of publication, the country in which the study was conducted, and the study design. Population characteristics comprised the mean age of participants and the total sample size. Each study provided a clear definition of Vitamin D deficiency, most commonly defined as serum 25(OH)D levels below 20 ng/mL (or <50 nmol/L). Miscarriage was generally defined as spontaneous pregnancy loss before 20 weeks of gestation. Outcome data included the number of miscarriage events among women with deficient and sufficient Vitamin D levels. In addition, summary findings from each study were collected, including calculated ORs, confidence intervals, and key interpretations regarding the association between maternal Vitamin D status and the risk of miscarriage.

Study risk of bias assessment

Three reviewers (C.A.A., F.K., and E.E.) independently assessed the risk of bias in the selected studies using the Newcastle–Ottawa Scale (NOS) [12]. The methodological quality of the included observational studies was rigorously assessed using the Newcastle–Ottawa Scale (NOS), a validated tool specifically designed for evaluating the risk of bias in nonrandomized studies. The NOS evaluates the studies across three core domains: (1) selection of the study groups, including representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study; (2) comparability, which assesses the extent to which the study controlled for potential confounders through design or analysis; and (3) outcome (for cohort studies) or exposure (for case–control studies), which includes evaluation of the assessment method, whether the follow-up was long enough for outcomes to occur, and adequacy of follow-up of cohorts. Each study could receive a maximum of nine stars, with higher scores indicating a lower risk of bias and greater methodological robustness. Studies that received a score of seven or higher were categorized as high quality. To ensure objectivity and reduce potential bias in the evaluation process, two independent reviewers conducted the quality assessment. Any discrepancies in scoring were resolved through consensus-based discussion, and if needed, adjudication by a third reviewer was sought.

Effect measures and synthesis methods

The primary variables examined in this study include maternal serum Vitamin D levels and the occurrence of miscarriage. Serum Vitamin D status was reported either as a continuous variable (mean serum 25-hydroxyvitamin D [25(OH)D] levels) or as a categorical variable based on predefined thresholds typically classified as deficient (<20 ng/mL or <50 nmol/L) and sufficient (≥20 ng/mL or ≥50 nmol/L). Miscarriage was defined across studies as spontaneous pregnancy loss occurring before 20 weeks of gestation. Key outcome variables included the MD in serum Vitamin D levels between women who experienced miscarriage and those with ongoing pregnancies, the proportion of miscarriage events within the Vitamin D-deficient and Vitamin D-sufficient groups, and the calculated ORs with corresponding confidence intervals to assess the strength of the association between Vitamin D status and miscarriage risk. Additional variables collected from the studies included participant age, sample size, and diagnostic criteria for both Vitamin D deficiency and miscarriage. Together, these variables allowed for a comprehensive analysis of both the potential risk relationship and prevalence patterns between maternal Vitamin D status and early pregnancy loss.

Meta-analysis was conducted using Review Manager 5.4 (Cochrane Collaboration, London, United Kingdom) and R statistical software (version 4.4.2), with the meta package used for statistical analyses [13,14]. The primary outcome was assessed using MD, proportion (%), Odd ratio, and 95% confidence interval (CI). Heterogeneity was evaluated using the I^2 statistic, where $I^2 > 50\%$ indicated substantial heterogeneity, necessitating a random-effects model, while $I^2 < 50\%$ suggested homogeneity, allowing for a fixed-effect model. To assess the publication bias, a funnel plot test was performed, supplemented by the Trim-and-Fill method and Egger's test for further analysis.

Results

Study selection

According to the PRISMA diagram, the study identification process began with a comprehensive literature search across multiple databases, including PubMed (n = 167), Scopus (n = 90), EMBASE (n = 731), Web of Science (n = 54), and Cochrane (n = 18), yielding a total of 1060 records. Following the deduplication process, 201 duplicate records were removed, along with 791 records that were either irrelevant to the research topic or inaccessible, resulting in 69 records for the screening phase. During screening, 43 records were excluded for not meeting the predefined selection criteria. Of the 36 reports sought for retrieval, 5 could not be accessed. At the eligibility assessment stage, 31 reports were evaluated, of which 17 were excluded due to being case reports (n = 5), systematic reviews (n = 1), meta-analyses (n = 1), addressing conditions or symptoms unrelated to the research focus (n = 6),

or failing to report relevant outcomes (n = 4). Consequently, 14 studies met the inclusion criteria and were included in the systematic review and meta-analysis [Figure 1].

Study characteristics

Each included study is cited, and its key characteristics are summarized in Supplementary Table 1. These characteristics include the study author and year of publication, country where the study was conducted, and study design. Supplementary Table 1 also presents each study's specific definition of Vitamin D deficiency and miscarriage definition. In addition, it includes the total study population and the number of miscarriage cases stratified by Vitamin D status (i.e., among women with Vitamin D deficiency and those with normal levels).

Risk of bias in studies

This study conducted an assessment of the quality of each study included in the meta-analysis using the NOS, a standardized tool designed to evaluate the methodological quality of observational studies. In conclusion, the overall quality of the studies included in this report is generally high, with the majority demonstrating strong methodological standards across different study designs. Most cohort studies achieved excellent scores, reflecting robust design, thorough control of confounding factors, and adequate follow-up. Although cross-sectional and case–control studies showed some variation, several still scored well, indicating careful execution and reliable data. These results suggest that the body of evidence assessed is of good quality, supporting the credibility and reliability of the findings reported across the included studies [Supplementary Figure 1].

Vitamin D levels based on miscarriage and nonmiscarriage

The provided meta-analysis data indicate a significant relationship between Vitamin D levels and the occurrence of miscarriage. The overall MD in Vitamin D levels between those who experienced a miscarriage and those who did not is −5.48, with a 95% confidence interval of (−9.77, −1.19). This negative MD suggests that individuals who had a miscarriage had lower Vitamin D levels compared to those without miscarriage. The results are statistically significant (P = 0.02), indicating a strong association. However, the high heterogeneity (I^2 = 89%) among the studies suggests variability in results, which may be influenced by different populations or methodologies [Figure 2]. Overall, these findings highlight the potential importance of maintaining adequate Vitamin D levels to reduce the risk of miscarriage.

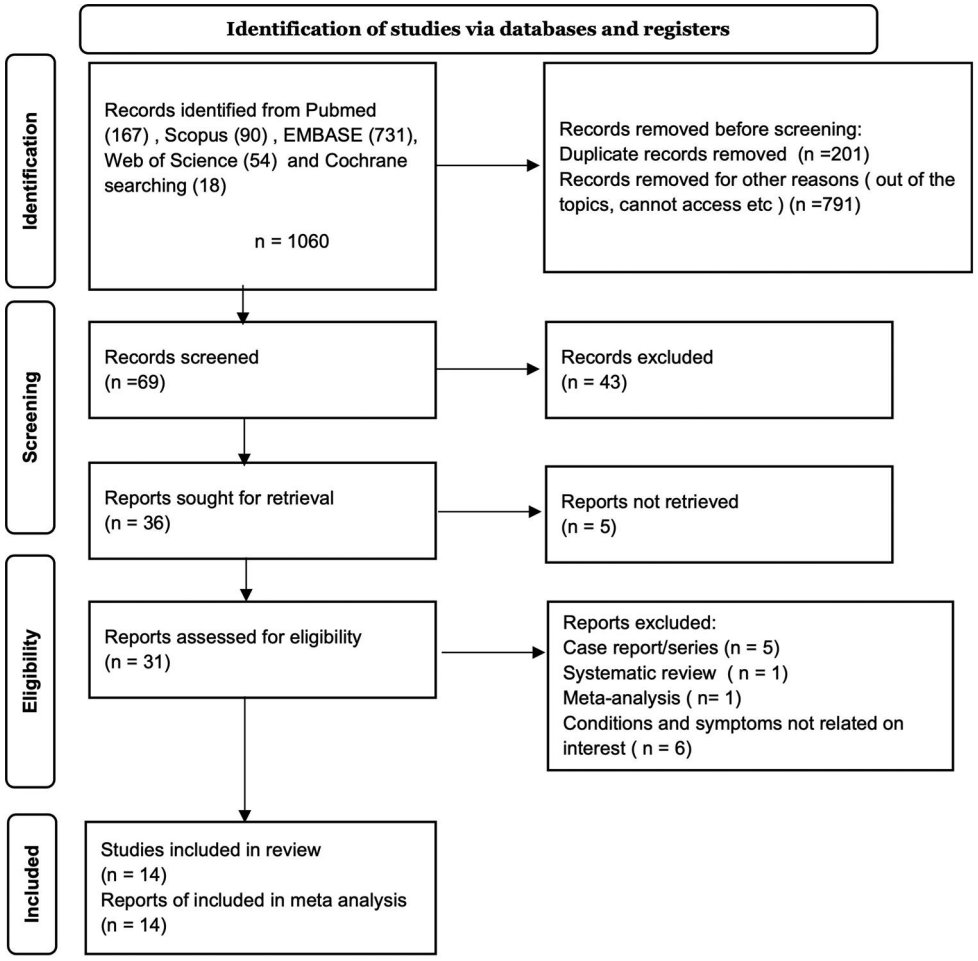

Figure 1: PRISMA flow diagram illustrating the study selection process

Pooled proportion of miscarriage with deficient Vitamin D

The forest plot focuses on the pooled proportion of miscarriage associated with deficient Vitamin D levels, specifically highlighting the random effects model. This model estimates the proportion of miscarriage at 34% with a 95% confidence interval of [0.21; 0.47] [Figure 3]. The high heterogeneity statistics (I^2 = 98.6%) indicates substantial variability among the studies included, suggesting that the results may differ significantly due to the factors such as study design and population characteristics. While the findings indicate a notable association between deficient Vitamin D levels and miscarriage rates, the high variability underscores the necessity for further research to clarify these associations and understand the underlying factors contributing to the observed differences. The Linear regression test of funnel plot asymmetry (t = 0.94, df = 10, P = 0.3714), there is no statistically significant indication of publication bias in the data [Supplementary Figure 2].

Pooled proportion of miscarriage with normal Vitamin D

The forest plot highlights the pooled proportion of miscarriage associated with normal Vitamin D levels, specifically focusing on the random effects model, which estimates the proportion at 16% with a 95% confidence interval of 0.08; 0.24. [Figure 4]. This suggests a significant association, although the high heterogeneity statistics (I^2 = 96.9%) indicates considerable variability among the studies included. This variability may stem from differences in study design, population characteristics, or measurement methods. While the findings suggest a potential link between normal Vitamin D levels and miscarriage rates, the variability emphasizes the need for further research to better understand these associations. Linear regression test of funnel plot asymmetry showed the following results: t = −2.56, df = 10, P value = 0.0284. However, in the trim and fill analysis, two studies were added, and the P value after adjustment remained < 0.05 [Supplementary Figure 3]. This indicates that the association between Vitamin D deficiency and the occurrence of miscarriage can still be considered statistically significant.

Association between Vitamin D and miscarriage

The meta-analysis reveals a statistically significant association between Vitamin D deficiency and increased risk of miscarriage (OR: 2.02; 95% CI: 1.37–2,98; P = 0.0004) [Figure 5]. However, substantial heterogeneity (I^2 = 76%) exists across studies,

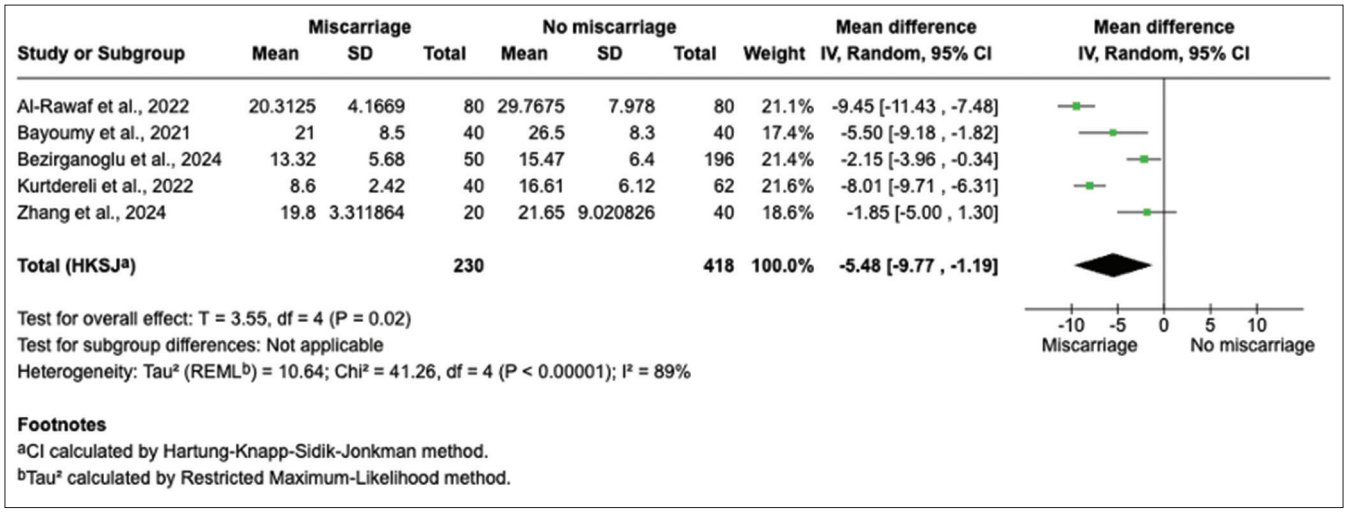

Figure 2: Forest plot of Vitamin D levels among miscarriage and nonmiscarriage

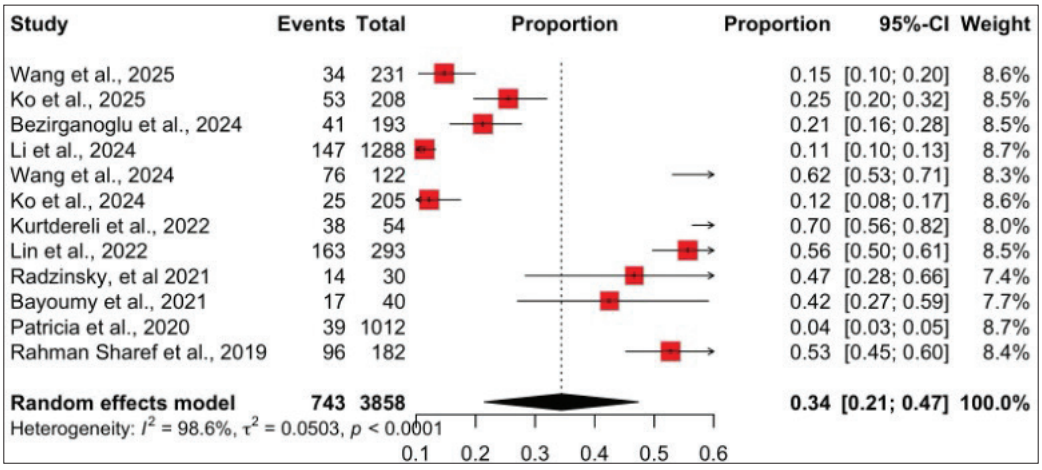

Figure 3: Forest plot of the pooled proportion of miscarriage with deficient Vitamin D

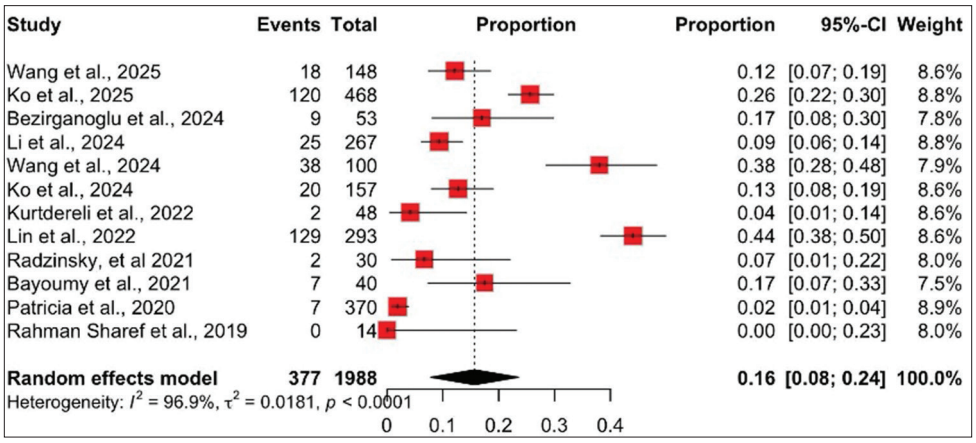

Figure 4: Forest plot of the pooled proportion of miscarriage with normal Vitamin D

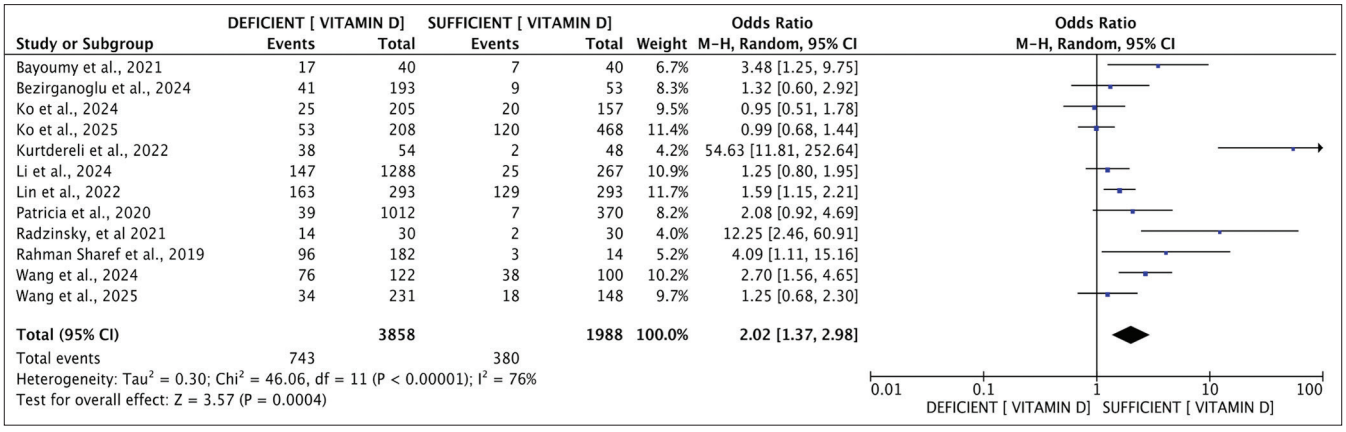

Figure 5: Forest plot of the association between Vitamin D and risk of miscarriage

suggesting that other factors may influence this relationship and highlighting the need for further research to confirm these findings and explore potential confounding variables. From the results of the Regression Test for Funnel Plot Asymmetry, it was found that t = 3.2093, df = 10, P = 0.0093. However, in the trim and fill analysis, no missing or added studies were detected, and the P value after adjustment remained < 0.05 [Supplementary Figure 4]. This indicates that the association between Vitamin D deficiency and the occurrence of miscarriage can still be considered statistically significant.

The meta-analysis showed that Vitamin D deficiency significantly increased the risk of miscarriage (OR = 2.02; 95% CI: 1.25–3.26; P = 0.004; I^2 = 85%). In subgroup analysis by the region, the association was significant in non-Asian countries (OR = 4.14; 95% CI: 1.19–14.43; P = 0.03; I^2 = 84%) but not in Asian countries (OR = 1.52; 95% CI: 0.93–2.51; P = 0.10; I^2 = 84%). However, the subgroup difference was not significant (Ch I^2 = 2.12; P = 0.15). By the study design, the association remained significant in both cohort (OR = 2.20; 95% CI: 1.18–4.09; P = 0.01; I^2 = 85%) and case–control studies (OR = 2.28; 95% CI: 1.20–4.32; P = 0.01; I^2 = 45%), with no significant difference between them (Ch I^2 = 0.01; P = 0.93). Subgroup analysis by miscarriage definition showed a significant overall association (OR = 1.99; 95% CI: 1.38–2.88; P = 0.0002). For studies using <20 weeks or <500 g, the association was modest but significant (OR = 1.39; 95% CI: 1.01–1.91; P = 0.04; I^2 = 55%), while studies with broader definitions showed stronger effects (OR = 3.43; 95% CI: 1.59–7.39; P = 0.002; I^2 = 77%). Subgroup difference was significant (Ch I^2 = 4.53; P = 0.03). By trimester, Vitamin D deficiency was linked to increased miscarriage risk in both the first (OR = 1.57; 95% CI: 1.28–1.91; P < 0.0001; I^2 = 78%) and second trimesters (OR = 1.83; 95% CI: 1.39–2.42; P < 0.0001; I^2 = 62%). No significant subgroup difference was observed (I^2 = 0.81; P = 0.37). For miscarriage risk status, the association was significant in both low-risk (OR = 2.15; 95% CI: 1.23–3.76; P = 0.007; I^2 = 80%) and high-risk groups (OR = 1.99; 95% CI: 1.06–3.73; P = 0.03; I^2 = 76%), with no difference between subgroups (I^2 = 0.04; P = 0.85; I^2 = 0%) [Supplementary Figure 5]. In summary, these findings consistently support a significant association between *Vitamin D deficiency* and increased miscarriage risk, across regions, study designs, miscarriage definitions, gestational loss timing, and risk categories [Supplementary Table 2].

Discussion

Interpretation and comparison with previous studies

Vitamin D deficiency has emerged as a significant factor in reproductive health, particularly in relation to pregnancy

outcomes such as miscarriage. While traditionally recognized for its role in calcium homeostasis and musculoskeletal integrity, Vitamin D is now known to influence a range of reproductive and immunological processes. Its active form, calcitriol, binds to the Vitamin D receptor (VDR), which is expressed in various reproductive tissues, including the endometrium, decidua, and placenta. This widespread distribution suggests that Vitamin D plays a crucial role in maintaining a successful pregnancy [29,30].

In the present meta-analysis, a comprehensive comparison of mean serum Vitamin D concentrations was conducted between individuals who experienced miscarriage and those with ongoing pregnancies. The analysis revealed a statistically significant association between Vitamin D levels and the incidence of miscarriage, with a reported MD of −5.48 ng/mL. This negative MD clearly indicates that women who experienced miscarriage had substantially lower serum Vitamin D concentrations compared to their counterparts with viable pregnancies. These findings reinforce the hypothesis that Vitamin D deficiency may play a contributory role in the pathophysiology of early pregnancy loss, possibly through mechanisms involving impaired immune tolerance, disrupted placental development, and altered inflammatory responses at the maternal–fetal interface. In addition to evaluating continuous measures of Vitamin D levels, we analyzed the pooled proportions of miscarriage occurrences within Vitamin D-deficient and nondeficient populations. The data demonstrated that approximately 34% of women classified as Vitamin D-deficient experienced miscarriage. This figure is clinically significant, suggesting that over one-third of miscarriages in the studied populations occurred in individuals with suboptimal Vitamin D status. In comparison, the pooled proportion of miscarriage among women with sufficient Vitamin D levels was substantially lower, at approximately 16%. These findings suggest that a considerable number of pregnancy losses could potentially be preventable through the identification and correction of maternal Vitamin D deficiency before or during early gestation.

To further quantify the strength of association between Vitamin D deficiency and the risk of miscarriage, an OR analysis was conducted. The current meta-analysis revealed an OR: 2.02; 95% CI: 1.37–2,98; $P = 0.0004$. This statistically significant finding suggests that individuals with Vitamin D deficiency are more than twice as likely to experience miscarriage compared to those with sufficient Vitamin D levels. The observed elevated risk highlights the critical need for routine Vitamin D screening in women of reproductive age, especially during the preconception period and early stages of pregnancy, where early intervention may be most effective.

This meta-analysis revealed substantial heterogeneity overall and across several subgroups, with an overall I^2 of 85%, indicating that most variability in effect estimates stems from real differences rather than chance. This justified the use of a random-effects model. Subgroup analyses were conducted to explore the possible sources of heterogeneity, but high I^2 values remained in many groups. Both Asian and non-Asian studies showed high heterogeneity (I^2 = 84%), suggesting geographical factors alone do not explain the variability, possibly influenced by the differences in baseline Vitamin D levels, genetics, or public health strategies. By study design, cohort studies had higher heterogeneity (I^2 = 85%) than case–control studies (I^2 = 45%), likely due to variations in follow-up time, exposure measurement, and outcome determination. Stratification by miscarriage definitions showed moderate heterogeneity in studies using standard definitions (I^2 = 55%) and higher heterogeneity in studies with broader definitions (I^2 = 77%), reflecting inconsistencies in outcome classification. By pregnancy trimester, heterogeneity was moderate to high (I^2 = 78% in the first and 62% in the second trimester), possibly due to the timing of Vitamin D measurement or gestational differences. Finally, heterogeneity by miscarriage risk status was substantial in both low-risk (I^2 = 80%) and high-risk groups (I^2 = 76%), potentially due to unmeasured factors such as comorbidities or treatment differences. Despite the persistent heterogeneity, the consistent direction of association supports a robust link between Vitamin D deficiency and miscarriage. These findings underscore the need for standardized definitions, methods, and reporting in future studies.

These findings are consistent with those reported by Tamblyn *et al*., who also investigated the association between Vitamin D status and miscarriage through a meta-analytical approach. Their study found that both Vitamin D deficiency and insufficiency were significantly associated with an increased risk of miscarriage, with a pooled OR of 1.60 (95% CI: 1.11–2.30) across six studies involving a total sample size of 6,338 participants and a moderate level of heterogeneity (I^2 = 35%). Although the magnitude of the association reported by Tamblyn *et al*. was somewhat lower than that found in our analysis, the consistency in directionality reinforces the potential role of Vitamin D in early pregnancy maintenance. Moreover, Tamblyn *et al*. acknowledged an important knowledge gap regarding the effectiveness of preconceptional Vitamin D supplementation in reducing miscarriage risk, particularly among women already identified as high risk. These converging lines of evidence suggest that while a clear association between Vitamin D deficiency and miscarriage exists [29].

Numerous clinical investigations have explored the relationship between maternal Vitamin D levels both before conception and during pregnancy and various adverse outcomes for mothers and their offspring. A deficiency in Vitamin D has been linked to several pregnancy-related complications, such as miscarriage, preeclampsia, gestational diabetes, intrauterine growth restriction, low birth weight, premature labor, stillbirth, and other gestational disorders. Among these, miscarriage is particularly concerning due to its significant physical and emotional toll. In addition to its well-established role in supporting the normal function of the skeletal and muscular systems, Vitamin D has been shown to contribute to several key reproductive processes. Recent findings have highlighted the impact of Vitamin D on trophoblast function, immune tolerance at the maternal–fetal interface, and vascular remodeling, particularly the transformation of spiral arteries.

These processes are essential for proper placental development and fetal nourishment. A deficiency in Vitamin D may impair these mechanisms, thereby increasing the risk of pregnancy loss. Specifically, low levels of Vitamin D are associated with dysregulation of the immune system, leading to elevated Th1 responses and increased natural killer (NK) cell activity, both of which have been implicated in early pregnancy failure [31].

Vitamin D sufficiency during pregnancy is linked to improved placental health, characterized by better vascular integrity, reduced expression of antiangiogenic markers (e.g., sFlt-1), enhanced villous structure, reduced inflammation, and better mitochondrial function. These improvements contribute to favorable neonatal outcomes. Conversely, Vitamin D deficiency disrupts placental function by impairing angiogenesis, immune regulation, and nutrient transport. It lowers VEGF expression in the labyrinth zone vital for maternal–fetal exchange, leading to conditions such as intrauterine growth restriction (IUGR) and preeclampsia. In addition, Vitamin D is crucial for proper trophoblast invasion and placental attachment. Deficiency also alters glucocorticoid signaling by reducing 11β-HSD2 expression, resulting in increased fetal exposure to maternal stress hormones, which can impair fetal development and promote placental inflammation [32].

Vitamin D deficiency during pregnancy has detrimental effects on both placental function and fetal development. Experimental studies in mice have shown that deficiency leads to reduced fetal weight and crown-rump length, key indicators of intrauterine growth restriction (IUGR). This condition is associated with smaller placental size, reduced cell proliferation, and impaired development of the labyrinth zone, which is critical for maternal–fetal nutrient and oxygen exchange. Key nutrient transporters (GLUT1, SNAT2, and FATP4) were downregulated, impairing the transfer of glucose, amino acids, and fatty acids. In addition, vital angiogenic and growth factors (VEGF-α, PlGF, and IGF2) were also decreased, further limiting placental vascularization and development. Vitamin D deficiency also triggered placental inflammation, marked by elevated pro-inflammatory cytokines (TNF-α, IL-17α, and IFN-γ) and chemokines (MCP-1, MIP-2, and KC), along with increased activation of the NF-κB signaling pathway. Human studies confirmed these findings, reporting increased inflammation and smaller placental diameters in Vitamin D-deficient pregnancies. Notably, supplementation with active Vitamin D [$1\alpha,25(OH)_2D_3$] reversed many of these effects, improving placental growth, nutrient transport, and reducing inflammation [32].

Vitamin D plays a vital role in the metabolism of various elements, including calcium and phosphorus. Beyond its metabolic functions, it serves as a key regulator of essential biological processes, particularly immune system regulation and hormone secretion, through its interaction with the VDR. It influences both the innate and adaptive immune responses and has a suppressive effect on components of the adaptive immune system. Specifically, Vitamin D downregulates pro-inflammatory cytokines produced by T-helper 1 (Th1) cells, such as interferon-gamma (IFN-γ), while promoting T-helper 2 (Th2) responses by reducing IFN-γ and increasing interleukin-4 (IL-4) expression. Given that VDR is expressed in placental tissue, Vitamin D is believed to play a significant role in maintaining immune tolerance at the maternal–fetal interface through immunomodulatory mechanisms. Clinically, many individuals experiencing recurrent pregnancy loss (RPL) are found to have Vitamin D deficiency. This deficiency is associated with impaired cellular immune function, including elevated peripheral natural killer (NK) cell levels, increased NK cytotoxic activity, and a higher Th1/Th2 ratio. In addition, women with low Vitamin D levels appear to be more susceptible to autoimmune disturbances, as indicated by the increased presence of autoantibodies such as antiphospholipid antibodies (APA), antinuclear antibodies (ANA), antisingle-stranded DNA antibodies, and thyroid peroxidase antibodies (anti-TPO) in patients with RPL [33].

This study did not evaluate the timing or dosage of Vitamin D supplementation, as it focused solely on the association between Vitamin D deficiency and miscarriage. However, based on the findings from other studies, clinical recommendations regarding dosage and initiation of supplementation can still be cautiously discussed. For example, Liu and Huang implemented a regimen where Vitamin D3 supplementation was initiated between 12 and 16 weeks of gestation for pregnant women with Vitamin D deficiency, beginning with 2000 IU/day until serum 25(OH)D levels reached ≥20 ng/mL, then continuing with a maintenance dose of 800 IU/day until delivery [34,35].

Globally, clinical guidelines such as those from the World Health Organization (WHO) recommend daily Vitamin D intake during pregnancy of 200–600 IU. However, many experts argue that higher doses may be needed, particularly for deficient individuals. Pilz *et al*. propose a safe range of 800–1000 IU/day starting from preconception or early pregnancy to ensure adequate maternal and fetal Vitamin D levels. Randomized controlled trials further support the safety and efficacy of supplementation up to 2000 IU/day, showing benefits such as reduced risk of infants being small for gestational age and improved early growth, without increasing fetal or neonatal mortality or congenital anomalies. In comparison, countries such as Singapore provide only 400 IU/day through standard antenatal multivitamins, which may be inadequate for women with existing deficiencies. The regimen from Liu and Huang's study reflects a more proactive and adaptive approach, starting supplementation in the second trimester with higher corrective doses followed by maintenance dosing. While this strategy was not specifically evaluated for miscarriage prevention, it offers a clinically sound model for achieving and sustaining sufficient Vitamin D levels during pregnancy. Nevertheless, since our study did not assess the supplementation outcomes and the causal link with miscarriage remains unconfirmed, randomized controlled trials are needed to validate the effectiveness of such an approach in reducing miscarriage risk [36-38].

Limitations and implications

This meta-analysis provides important insights into the association between Vitamin D deficiency and miscarriage, but

several limitations should be noted. First, substantial variability across the included studies, in terms of design, population characteristics, Vitamin D assessment methods, and gestational timing, may have affected the pooled estimates. Second, since most of the studies were observational, causality cannot be established. While a consistent association was observed, it remains unclear whether Vitamin D deficiency directly contributes to miscarriage or simply reflects other underlying factors such as poor nutrition, limited sunlight exposure, or inflammatory and endocrine conditions. Potential confounders such as body mass index, ethnicity, socioeconomic status, and comorbidities were not uniformly controlled for, which could influence the observed associations. In addition, variations in geographic location and the season of Vitamin D measurement, along with nonstandardized assays and reference ranges, may limit the generalizability of the findings.

Other limitations include selection bias, particularly in case–control studies, and information bias due to inconsistent definitions of miscarriage or methods of measuring Vitamin D levels. Reverse causation is also a concern, where low Vitamin D may result from early pregnancy complications rather than cause them. Although statistical adjustments were applied, residual confounding remains likely. Despite these issues, the association between Vitamin D deficiency and miscarriage risk was consistently observed across multiple subgroups. However, the high heterogeneity seen in many of these analyses reflects differences in methodology, populations, and outcome definitions, making causal interpretation challenging. Therefore, while the association appears robust, it should be interpreted cautiously. Future research should prioritize randomized controlled trials and rigorous causal inference approaches to clarify the true nature of this relationship.

This meta-analysis offers several strengths that enhance its validity and clinical relevance. It synthesizes diverse studies across various regions, ethnicities, and healthcare settings, improving generalizability. Rigorous methodology, including both continuous and categorical analyses, strengthens interpretation. The use of statistical indicators such as ORs: 2.02 and MDs (−5.48 ng/mL) provides strong evidence linking Vitamin D deficiency to miscarriage. Underscores the public health importance of Vitamin D screening in reproductive-aged women. Finally, it highlights the need for further research on supplementation and screening protocols.

Conclusions

This meta-analysis demonstrates a significant association between maternal Vitamin D deficiency and increased risk of miscarriage. However, as the evidence is based solely on observational studies, causal inferences cannot be drawn. While the association is consistent across populations and study designs, no conclusions can yet be made regarding the optimal dose, timing, or duration of Vitamin D supplementation for miscarriage prevention. The absence of randomized controlled trials specifically addressing this issue limits clinical applicability. Nonetheless, the biological plausibility of Vitamin D in immune regulation, placental development, and pregnancy maintenance, combined with consistent observational findings, supports routine monitoring and early correction of deficiency during pregnancy. Although the current WHO guidelines recommend 200–600 IU per day, studies suggest that 800 to 2000 IU daily may be more effective, particularly for those at risk of deficiency. Until more definitive interventional data are available, individualized supplementation strategies may aid in reducing miscarriage risk. Future randomized trials are urgently needed to establish causality and inform the clinical guidelines.

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Data availability statement

The datasets generated during and/or analyzed during the current study are publicly available.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary material

Supplementary Table 1: Characteristics of the included studies

Study author and publication year	Study country	Study type	Definition of Vitamin D deficiency	Miscarriage definition	Total populations of the study	Miscarriage (deficient Vitamin D)		Miscarriage (normal Vitamin D)	
						E	T	E	T
Wang *et al*., 2025 [15]	China	Retrospective cohort	Deficient (<20 ng/mL; <50 nmol/L)	Expulsions <20 weeks/<500 g	1459	34	231	18	148
Ko *et al*., 2025 [16]	China	Retrospective cohort	Deficient (<20 ng/mL; <50 nmol/L)	Expulsions <20 weeks/ <500 g	10,489	53	208	120	468
Bezirganoglu *et al*., 2024 [17]	Turkey	Retrospective cross-sectional study	Deficient (<20 ng/mL; <50 nmol/L)	Expulsions <20 weeks/ <500 g	246	41	193	9	53
Li *et al*., 2024 [18]	China	Retrospective cohort	Deficient (<20 ng/mL; <50 nmol/L)	Expulsions <20 weeks/ <500 g	3397	147	1288	25	267
Wang *et al*., 2024 [19]	China	Retrospective cohort	Deficient (<20 ng/mL; <50 nmol/L)	Spontaneous abortions <28 weeks	292	76	122	38	100
Zhang *et al*., 2024 [20]	China	Retrospective study	Deficient (<20 ng/mL; <50 nmol/L)	Gestational age of delivery of <24 weeks	60	NA	NA	NA	NA
Ko *et al*., 2024 [21]	Hongkong	Retrospective study	Deficient (<20 ng/mL; <50 nmol/L)	Miscarriage before 20 weeks	406	25	205	20	157
Kurtdereli *et al*., 2022 [22]	Turkey	Retrospective study	Deficient (<12.5 ng/mL)	Absence heartbeat 2 weeks 11 days or more	102	38	54	2	48
Lin *et al*., 2022 [23]	China	Case–control	Deficient (<12.5 ng/mL)	Expulsions <20 weeks/<500 g	789	163	293	129	293
Al-Rawaf *et al*., 2022 [24]	Iraq	Prospective case–control	Deficient (<12.5 ng/mL)	Expulsion s<20 weeks/< 500 g	160	NA	NA	NA	NA
Radzinsky, *et al*., 2021 [25]	Russia	Prospective cohort study	Deficient (<12.5 ng/mL)	Expulsions <20 weeks/<500 g	60	14	30	2	30
Bayoumy *et al*., 2021 [26]	Egypt	Case–control	Deficient (<12.5 ng/mL)	Expulsions <20 weeks/< 00 g	80	17	40	7	40
Christoph *et al*., 2020 [27]	Switzerland	Retrospective observational cross-sectional study	Deficient (<12.5 ng/mL)	Expulsions <20 weeks/< 500 g	1382	39	1012	7	370
Sharef *et al*., 2019 [28]	Iraq	Retrospective case–control	Deficient (<12.5 ng/mL)	Expulsions <20 weeks/<500 g	NA	96	182	0	14

NA: Not available

Supplementary Table 2: Summary findings of subgroup analysis

Subgroup category	Subgroup	OR (95% CI)	*P*	Heterogeneity (I^2)	Test for subgroup differences	Interpretation
Geographical region	Non-Asian	4.14 (1.19–14.43)	0.03*	84%	χ^2=2.12, *P*=0.15	Significant in non-Asian countries; not in Asian. However, *P*=0.15 indicates no statistically significant difference between regions
	Asian	1.52 (0.93–2.51)	0.10	84%		
Study design	Cohort	2.20 (1.18–4.09)	0.01*	85%	χ^2=0.01, *P*=0.93	Both designs show significant results; *P*=0.93 indicates no significant subgroup difference by study design
	Case-control	2.28 (1.20–4.32)	0.01*	45%		
Miscarriage definition	<20 weeks or <500 g	1.39 (1.01–1.91)	0.04*	55%	χ^2=4.53, *P*=0.03*	Both definitions show significant results; *P*=0.03 indicates significant difference in effect based on miscarriage definition
	Other definitions	3.43 (1.59–7.39)	0.002*	77%		
Trimester of pregnancy	First trimester	1.57 (1.28–1.91)	<0.0001*	78%	χ^2=0.81, *P*=0.37	Significant in both trimesters; *P*=0.37 shows no significant difference in effect between the first and second trimester
	Second trimester	1.83 (1.39–2.42)	<0.0001*	62%		
Miscarriage risk status	Low risk (first-time miscarriage)	2.15 (1.23–3.76)	0.007*	80%	χ^2=0.04, *P*=0.85	Both groups show significant associations; *P*=0.85 suggests no difference in effect based on miscarriage history
	High risk (>1 miscarriage)	1.99 (1.06–3.73)	0.03*	76%		

CI: Confidence interval, OR: Odds ratio. *: Statistically significant results

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (Adapted for cross sectional studies)

Study	Selection				Comparability	Outcome		Quality Score
	Representativeness of the cases	Sample size	Non-Response rate	Ascertainment of the screening / surveillance tool	The potential confounders were investigated by subgroup analysis or multivariable analysis	Assessment of the outcome	Statistical test	
Bezirganoglu et al., 2024	*			*	*	*	*	5/10
Patricia et al., 2020	*			**	**	**	*	8/10

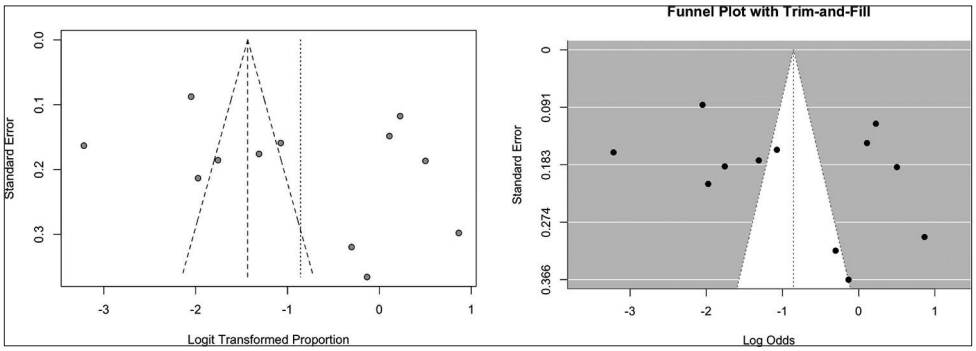
NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (Cohort studies)

Study	Selection				Comparability		Outcome		Quality Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis controlled for confounders	Assessment of the outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Wang et al., 2025	*	*	*	*	**	*	*	*	9/9
Ko et al., 2025	*	*	*	*	**	*	*	*	9/9
Li et al., 2024	*	*	*	*	**	*	*	*	9/9
Wang et al., 2024	*	*	*	*	**	*	*	*	9/9
Zhang et al., 2024		*	*	*		*	*	*	6/9
Ko et al., 2024	*	*	*	*	*	*	*	*	8/9
Kurtdereli et al., 2022	*	*	*	*	*	*	*		7/9
Radzinsky, et al 2021	*	*	*	*	**	*	*	*	9/9

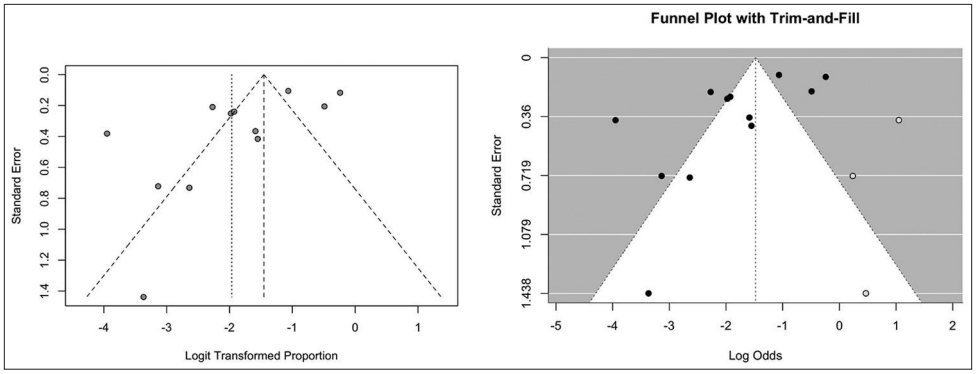
NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (Case-control)

Study	Selection				Comparability		Outcome		Quality Score
	Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Lin et al., 2022	*	*	*	*	**	*	*		8/9
Al-Rawaf et al., 2022	*	*	*	*	*	*	*		7/9
Bayoumy et al., 2021	*	*	*	*	**	*	*	*	9/9
Rahman Sharef et al., 2019	*	*	*	*		*	*		6/9

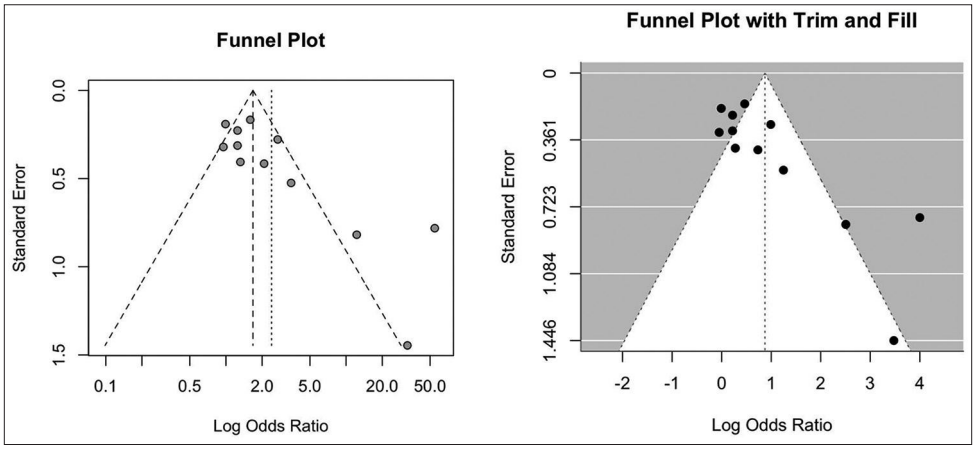
Supplementary Figure 1: Risk of bias evaluation of the included studies using the (Newcastle–Ottawa Quality Assessment Scale) NOS



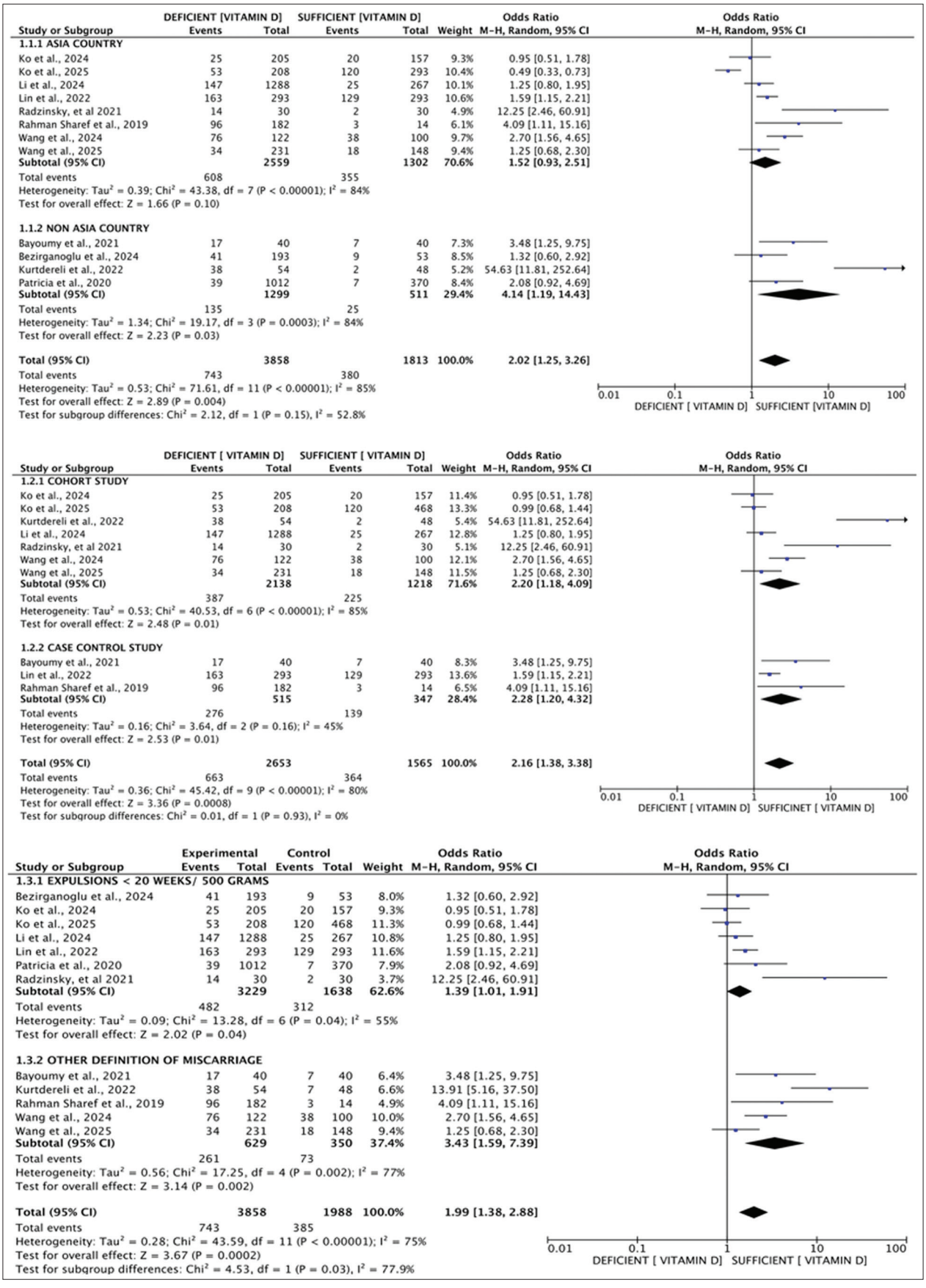
Supplementary Figure 2: Funnel plot with trim and fill pooled proportion of miscarriage with deficient Vitamin D



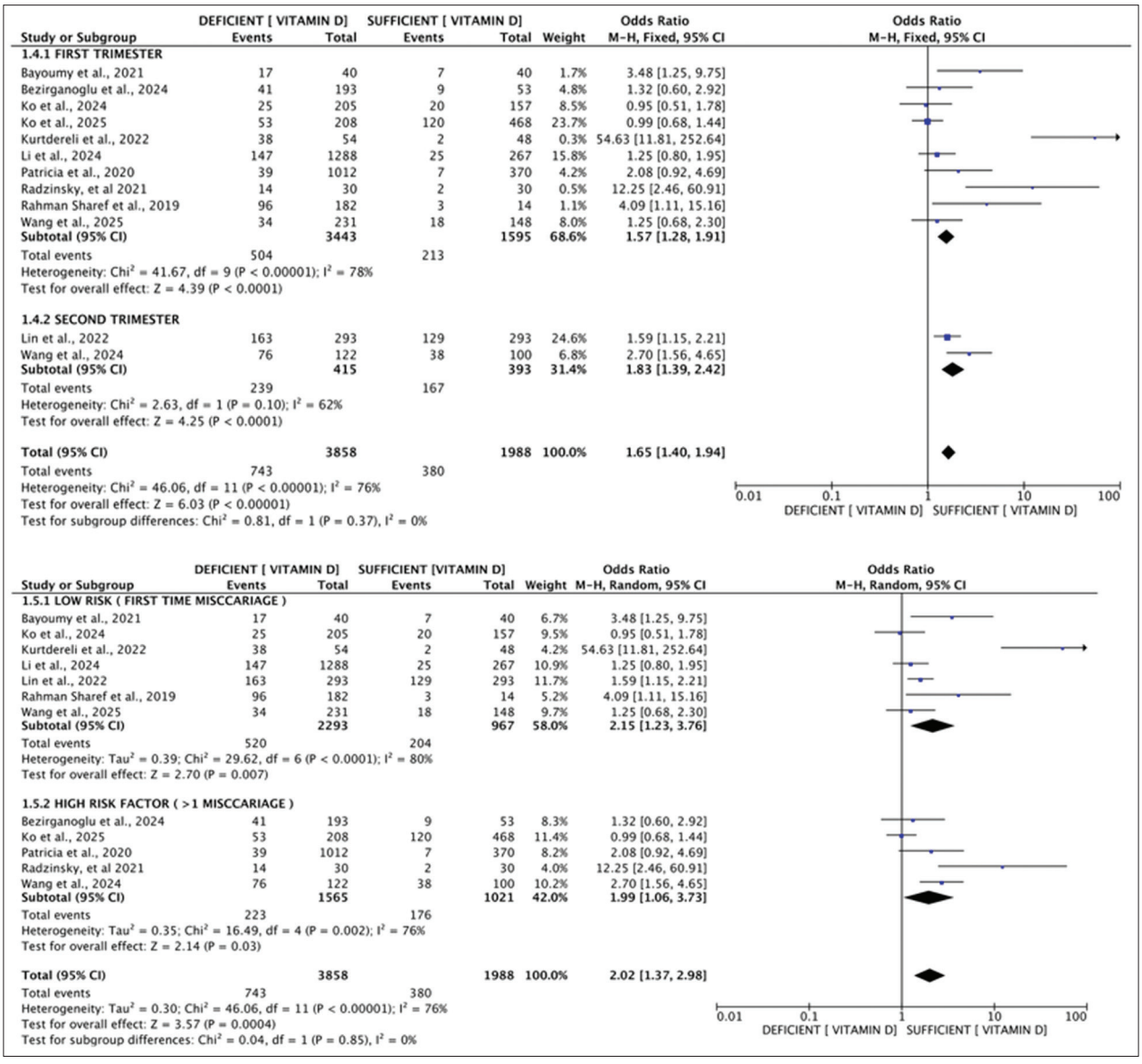
Supplementary Figure 3: Funnel plot with trim and fill pooled proportion of miscarriage with normal Vitamin D



Supplementary Figure 4: Funnel plot with trim and fill association between Vitamin D and risk of miscarriage



Supplementary Figure 5: Contd...



Supplementary Figure 5: Forest plot of subgroup analysis of the association between vitamin D and the risk of miscarriage