

Review article

Effects of maternal vitamin D supplementation during pregnancy and lactation on immune development in offspring: A systematic review

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Abstract

Background: Vitamin D, a fat-soluble prohormone, is essential for skeletal health and plays a key role in immune regulation. Deficiency is common among pregnant and lactating women, raising concerns that fetal and neonatal vitamin D status depends largely on maternal stores. Insufficiency during these periods has been associated with adverse birth outcomes and immune-mediated disorders.

Objective: To examine the effects of maternal vitamin D supplementation during pregnancy and/or lactation on offspring immune development.

Methods: This study followed PRISMA guidelines and was registered with PROSPERO (No. CRD420251117397). Experimental studies published in English between August 2015 and 2025 were eligible. Reviews, *in vitro* examinations, without full text or prenatal vitamin D exposure, and did not assess immune-related offspring outcomes, or included offspring, were excluded. PubMed, ScienceDirect, and EBSCOhost were searched, most recently on August 10, 2025. Risk of bias was assessed with the SYRCLE tool, and findings were synthesized narratively. This study was funded by the Ministry of Higher Education, Science, and Technology, the Republic of Indonesia.

Results: Four studies were included, and evidence was limited to a small number of heterogeneous rodent studies. Maternal vitamin D supplementation enhanced T helper (Th) 1 responses and regulatory T-cell function; suppressed Th2 and Th17 subsets; reduced interleukin (IL)-6, IL-17, and IL-23; and elevated IL-10 and transforming growth factor-beta expression. It also elevated vitamin D receptor and forkhead box P3 levels and interferon-gamma promoter methylation, suggesting epigenetic reprogramming.

Conclusion: Maternal vitamin D may influence early-life immune programming and improve offspring immune resilience. Human studies with standardized protocols and long-term follow-up are needed.

Keywords: Immune system, lactation, pregnancy, rodents, vitamin D.

Vitamin D is a fat-soluble prohormone known for its role in calcium homeostasis and skeletal development. Beyond a classical function in bone health, it exerts broad extra-skeletal effects, modulating cardiovascular, metabolic, respiratory, and immune functions. Vitamin D deficiency remains highly prevalent worldwide, affecting 5.0%–90.0% of women of reproductive age across regions.⁽¹⁾ This is

particularly critical during pregnancy and lactation, as fetal and neonatal vitamin D status depends entirely on maternal stores. Insufficiency during this period has been associated with preterm birth, low birth weight, and increased pediatric morbidity.⁽²⁾

Mechanistically, vitamin D regulates immune responses through the vitamin D receptor (VDR), which is expressed on macrophages, dendritic cells, T and B lymphocytes, and natural killer cells. VDR-mediated signaling influences cytokine production, T-cell differentiation, and immune and immune tolerance.⁽³⁾ Experimental studies in rodents reveal that maternal vitamin D deficiency alters offspring immune composition, suppresses regulatory pathways, and induces aberrant

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inflammatory phenotypes.⁽²⁾ Epigenetic mechanisms, such as promoter methylation of immune-related genes, further support the concept that maternal vitamin D can program offspring immune development during sensitive windows.

Human studies provide complementary evidence; observational data link maternal deficiency to higher risks of childhood asthma, wheezing disorders, and infections, while supplementation trials suggest protection against respiratory and atopic conditions.⁽²⁾ Maternal vitamin D status also shapes neonatal immune function, with deficiency associated with reduced naive CD4 T-cells and other lymphocyte subsets, as well as higher rates of neonatal sepsis.⁽³⁾ Prenatal vitamin D supplementation lowers the risk of asthma or recurrent wheeze by ~25.0% during early childhood, particularly when maternal 25(OH)D concentrations exceed 30 ng/mL.^(4,5) During lactation, maternal supplementation is vital because breast milk contains only ~45 IU/L of vitamin D, far below the infant's requirement of 400 IU/day, and its content depends on maternal status. High-dose maternal supplementation enhances milk vitamin D concentrations and improves infant intake.⁽⁶⁾

Despite growing evidence, uncertainties remain; while animal studies consistently demonstrate robust immunological benefits, results in humans are variable and sometimes modest.⁽⁷⁾ The extent to which maternal availability of vitamin D during pregnancy and lactation influences long-term immune development in the offspring is therefore not fully understood.

This systematic review aims to synthesize studies in experimental animals and human from the past decade that investigated maternal vitamin D supplementation during pregnancy and/or lactation, focusing on immunomodulatory outcomes in the offspring. By consolidating these findings, it seeks to clarify the role of maternal vitamin D in immune development during the early stages of life.

Methods

This systematic review used a structured methodology. The research question was defined per the Population, Intervention, Comparison, and Outcome framework⁽⁸⁾, which guided identification of key concepts and search terms. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was prospectively registered in the

PROSPERO database (Registration No. CRD420251117397). The registered protocol was not substantively amended during the review.

Eligibility criteria

Eligible studies included experimental animal studies and randomized controlled trials (RCTs) that met the following criteria: 1) pregnant or lactating rodents (e.g., *Rattus norvegicus*, *Mus musculus*) receiving vitamin D supplementation during only pregnancy or both pregnancy and lactation, or human RCTs of prenatal vitamin D supplementation; 2) use of a control or comparison group (e.g., no supplementation, deficient diets, saline/vehicle injections, or alternative doses of vitamin D); and 3) evaluation of immune-related outcomes in the offspring, including immune cell subsets (e.g., T helper (Th1, Th2, Th17), regulatory T cell (Treg), B cells), cytokine profiles, thymic morphology, or expression of immunoregulatory genes/proteins (e.g., VDR, forkhead box P3 (FOXP3), autoimmune regulator (AIRE)). Only peer-reviewed, original articles published in English between August 2015 and August 2025 were considered.

Outcomes

The primary outcomes were immune cell populations and cytokine levels (e.g., interleukin (IL)-4, IL-10, IL-17, IL-6, interferon-gamma (IFN- γ)). Secondary outcomes included expression of immunoregulatory genes and proteins, B-cell responses, and morphological or histological changes in the thymus. All relevant results within each outcome domain, when available, were extracted across reported measures and assessment time points. If multiple related findings were presented, those most directly aligned with the objectives were prioritized.

Additional data extracted included study characteristics—author, year, and design—subject characteristics, intervention details—form, dose, timing, duration, and route of vitamin D supplementation—comparator characteristics, and main conclusions. Funding information was also recorded when available. For missing or unclear information, data reported in the article were explicitly extracted, and no further assumptions were made.

The findings were synthesized narratively; pooled effect measures were not calculated. For each outcome, the results were presented employing the effect measures reported earlier, including group variations in cytokine levels, immune cell proportions, gene expression or protein levels, and direction of the impact between supplemented and control groups.

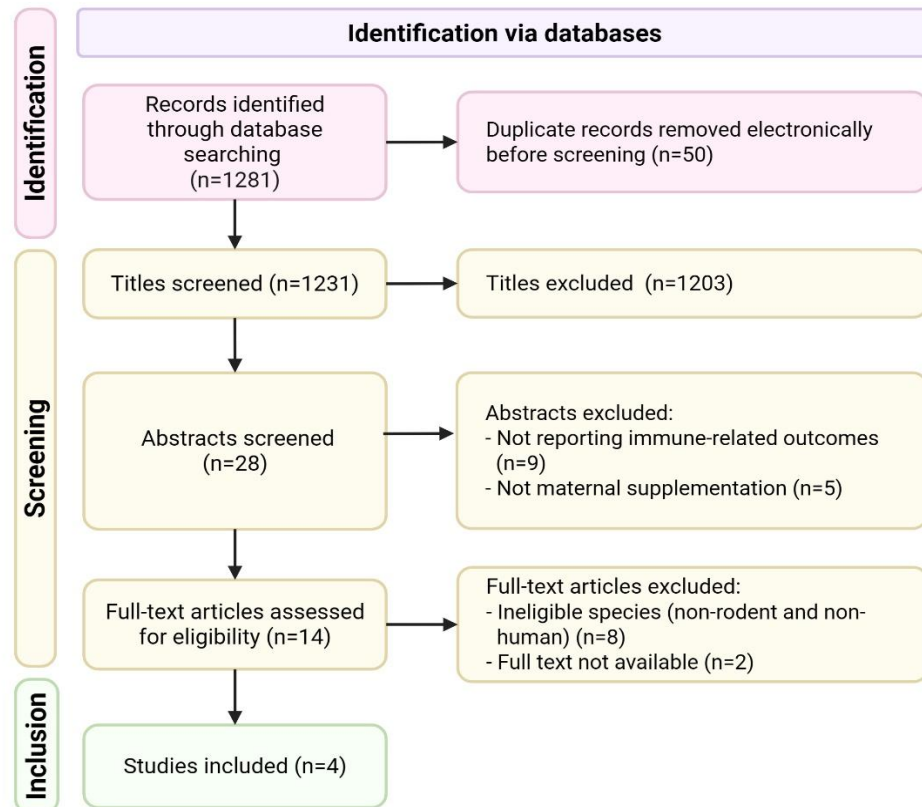


Figure 1. Search strategy using the PRISMA flowchart 2019.

Search strategy

As a strategy, three major databases: PubMed (MEDLINE), ScienceDirect, and EBSCOhost were comprehensively searched, finally on August 10, 2025. It combined Medical Subject Headings and free-text terms related to vitamin D supplementation, pregnancy, immune development, and rodent models. The Boolean queries were “Vitamin D supplementation” OR “cholecalciferol” OR “calcitriol” AND “pregnancy” OR “prenatal” OR “maternal” AND “lactation” OR “breastfeeding” AND “immune development” OR “immune function” OR “immunity” OR “cytokine” OR “Treg” OR “Th1” OR “Th2” OR “Th17” AND “offspring” OR “neonate” OR “newborn” OR “rats” OR “rodent” OR “*Rattus norvegicus*.” The search was limited to full-text, peer-reviewed articles published in English between August 2015 and August 2025. Reference lists of included studies were also manually screened for additional relevant articles. The detailed search strings used for each database are presented in **Supplementary Table S1**.

Study selection

All records were imported into Mendeley® reference management software (<https://www.mendeley.com/>), and duplicates were automatically removed. Two

reviewers independently screened titles and abstracts, followed by full-text assessment of potentially eligible studies. Discrepancies were resolved through discussion or consultation with a third reviewer. The selection process was documented as a PRISMA flow diagram (**Figure 1**).

Selection and data collection process

All retrieved records were imported into Mendeley, and duplicates were removed before screening. Two reviewers independently screened titles, abstracts, and full texts against the predefined eligibility criteria. Data were extracted independently by two reviewers using a standardized data extraction form. Any disagreements were resolved through discussion and re-examination of the original reports, with consultation from a third reviewer when necessary. No automation tools were used for selection, and no additional data were requested from study investigators.

Risk of bias and quality assessment

The methodological quality of the included studies was assessed using Systematic Review Centre for Laboratory Animal Experimentation’s (SYRCLE) Risk of Bias tool, which evaluates selection, performance, detection, attrition, and reporting. Two reviewers independently evaluated each included study

across the relevant bias domain. Any disagreements were resolved through discussion, with consultation with a third reviewer when necessary. No automation tools were used in the assessment process.

Synthesis methods

Studies were included in the synthesis if they met the eligibility criteria and reported immune-related outcomes relevant to the objective. Study characteristics, interventions, comparators, and outcome domains were tabulated to determine their suitability for narrative synthesis. Data were presented as originally reported in the articles, with no statistical conversion. Results were summarized into evidence tables and described narratively. Meta-analysis was avoided due to substantial heterogeneity among animal models, supplementation regimens, and outcome measures. Potential sources of heterogeneity were explored descriptively based on differences in species, dose, timing of supplementation, and reported immune outcomes. Sensitivity was not formally analyzed; however, the findings were interpreted in light of methodological variations and results of bias across studies.

Reporting bias assessment

Reporting bias was not formally assessed. The potential influence of missing results was assumed to be qualitative due to the small number of studies and the possibility of selective reporting or publication of only positive findings.

Certainty assessment

No formal method was used to assess the credence of the evidence for each outcome. The overall confidence was narrative based on the number of studies included, consistency of findings, methodological limitations, and risk of bias.

Results

This review first outlined the characteristics of the included studies and then synthesized their key immunological outcomes. Maternal vitamin D supplementation was associated with changes in Th cell balance, Treg responses, cytokine regulation, and molecular pathways in the offspring. No meta-analysis was performed because of this variability; therefore,

no pooled estimates or statistical measures of heterogeneity were generated.

Study characteristics

Four experimental animal studies, comprising murine (*M. musculus*) and rat (*R. norvegicus*) models, met the inclusion criteria. Notably, no human RCTs on prenatal vitamin D supplementation were identified. Sample sizes ranged from 25 to 60 pregnant dams, with immunity-related outcomes evaluated in offspring between post-natal days (PNDs) 21 and 54, corresponding to the late juvenile stage of immune development. Across studies, these methodologies demonstrated significant variability in routes of administration and the concentrations of Vitamin D₃ used, necessitating a standardized approach for comparative analysis. Administration protocols ranged from non-invasive dietary supplementation providing 800 IU/kg to more precise systemic interventions via subcutaneous (100–400 IU/kg) and intraperitoneal (10–160 IU/kg) injections, as well as localized intrauterine delivery (400 IU/kg). Thus, to facilitate a coherent comparison across different metric units—such as µg/kg, µmol/kg, and IU/kg—dosages were normalized based on the established conversion factor, where 1 µg of cholecalciferol corresponds to 40 IU. Across studies, immune assessments included T helper (Th1, Th2, Th17) and regulatory T cell (Treg) profiling, cytokine quantification (e.g., IL-4, IL-10, IL-17, IFN-γ, transforming growth factor-beta (TGF-β)), and molecular analyses such as FOXP3 expression, VDR mRNA, and cytokine-related promoter methylation (Table 1).

Risk of bias studies

Based on the SYRCLE Risk of Bias tool, the following qualitative assessment summarizes the four studies for methodological rigor and potential for bias (Table 2). Overall, the included studies were judged to have a moderate risk of bias, mainly due to insufficient assessment of sequence generation, allocation concealment, random housing, and blinding of outcome analysis. Most studies showed a low risk of bias for incomplete outcome data and selective outcome reporting, as the findings were generally consistent with the study objectives. However, several domains were rated as posing an unclear risk because methodological details were not adequately described.

Table 1. Study characteristics.

No	Author (year)	Study design	Species and sample	Intervention (dose and duration)	Control group	Primary outcomes	Key findings	Proposed mechanism
1	Jiao X, <i>et al.</i> (2019) ⁽⁹⁾	Experimental study in pregnant rats	48 offspring from 3 maternal diet groups (deficient, control, supplemented), with 4 offspring randomly selected from each dam and offspring sex assigned randomly	Vitamin D ₃ diet (800 IU/kg) during pregnancy until parturition	Deficient and control diets	Th1/Th2 ratio, IFN- γ , IL-4, IL-10, IL-13, methylation of IFN- γ /IL-4; assessed at PND28	Supplementation increased the Th1/Th2 ratio, reduced IL-4/IL-13, and decreased IFN- γ gene methylation. Deficiency promoted Th2 dominance	Epigenetic regulation via IFN- γ promoter methylation; skewing immune balance toward Th1
2	Wang G, <i>et al.</i> (2020) ⁽¹⁰⁾	Experimental study with BPA exposure	60 pregnant mice, with 2 offspring randomly selected from each dam and offspring sex assigned randomly	Intraperitoneal vitamin D ₃ (0.25–4 μ g/kg BW) with BPA during pregnancy until PND21	Blank and vehicle controls	Splenic VDR mRNA, Th17, IL-6, IL-23, IL-17, IL-21, TGF- β ; assessed at PND21 & PND42	Vitamin D reduced Th17 cells and cytokines in a dose-dependent manner, and increased VDR expression. No significant effect on TGF- β .	VDR-mediated suppression of the Th17 axis; attenuation of BPA-induced inflammation.
3	Zhang L, <i>et al.</i> (2021) ⁽¹¹⁾	Experimental study in an allergic rhinitis model	25 pregnant BALB/c mice, 5 groups; the number of offspring per dam was not specified, and offspring sex was not reported	Subcutaneous vitamin D ₃ (100–400 IU/kg/day) during pregnancy until parturition	0.9% saline injection	Serum IgE, IL-4, IL-17, IFN- γ , IL-10, TGF- β , Tregs (CD4 ⁺ , CD25 ⁺ , FoxP3z); assessed at PND54	Vitamin D reduced IgE, IL-4, and IL-17; increased IFN- γ , IL-10, and TGF- β . Treg counts rose dose-dependently. Indicated suppression of Th2/Th17 and support for Th1 immunity.	Promotion of immune tolerance via Treg induction and cytokine rebalancing (IL-10, TGF- β).
4	Zhang Q, <i>et al.</i> (2022) ⁽¹²⁾	Experimental study in an intrauterine inflammation model	Pregnant C57BL/6 mice at embryonic day 12.5, with one male offspring selected from each dam	Intrauterine vitamin D ₃ (400 IU/kg BW) $\pm$ LPS; single dose injection at GD12	PBS control	Gene expression in Th1, Th17, Treg (CD4 ⁺); assessed at PND28	Vitamin D reversed LPS-induced changes and reduced Th17 cell levels. No significant effect on Th1 or Treg numbers.	Downregulation of inflammation through suppression of Th17 pathways.

BPA, bisphenol A; BW, body weight; FoxP3, forkhead box P3; IFN- γ , interferon-gamma; IgE, immunoglobulin E; IL, interleukin; LPS, lipopolysaccharide; PND, postnatal day; TGF- β , transforming growth factor-beta; Th1/Th2/Th17, T helper cell type 1/2/17; Treg, regulatory T cell; VDR, vitamin D receptor.

Table 2. Risk of bias assessment of included studies using SYRCLE's tool

Bias Domain	Jiao X, <i>et al.</i> (2019)	Wang G, <i>et al.</i> (2020)	Zhang L, <i>et al.</i> (2021)	Zhang Q, <i>et al.</i> (2022)
Selection bias (sequence generation)	Low	Unclear	Low	Unclear
Selection bias (baseline characteristics)	Low	Low	Low	Low
Selection bias (allocation concealment)	Unclear	Unclear	Unclear	Unclear
Performance bias (random housing)	Unclear	Unclear	Unclear	Unclear
Performance bias (assessor blinding)	Unclear	Unclear	Low	Unclear
Detection bias (random outcome assessment)	Unclear	Unclear	Unclear	Unclear
Detection bias (blinding)	Unclear	Unclear	Unclear	Unclear
Attrition bias (incomplete outcome)	Low	Low	Low	Low
Reporting bias (selective reporting)	Low	Low	Low	Low
Overall judgment	Moderate	Moderate	Moderate	Moderate

Low risk, domain adequately reported and unlikely to introduce bias; Unclear risk, insufficient methodological detail; High risk, methods likely introduced bias or key safeguards such as blinding were absent

Th cell modulation

Across studies, maternal vitamin D supplementation had similar immunomodulatory impacts, particularly on T helper cell differentiation. Offspring from vitamin D-supplemented dams exhibited a Th1 bias with concurrent suppression of Th2 and Th17 subsets. Jiao X, *et al.* (2019) and Zhang L, *et al.* (2021) demonstrated increased IFN- γ expression alongside reduced Th2 cytokines (IL-4 and IL-13), indicating enhanced Th1 responses.^(9, 11) Wang G, *et al.* (2020) and Zhang Q, *et al.* (2022) reported marked reductions in Th17 frequency and related cytokines (IL-17, IL-21, and IL-23), particularly under inflammatory challenges such as exposure to bisphenol A (BPA) or lipopolysaccharide (LPS) (**Figure 2**).^(11, 12)

Regulatory T cells (Tregs)

Effects on Treg were variable. Zhang L, *et al.* observed a dose-dependent increase in CD4⁺, CD25⁺, FoxP3⁺, and Tregs with enhanced suppressive function. In contrast, Zhang Q, *et al.* (2022) did not detect proportional changes in Treg numbers, though suppression of Th17-mediated inflammation was evident.^(11, 12)

Cytokine profiles

Cytokine patterns corroborated these cellular shifts. Pro-inflammatory mediators—IL-6, IL-17, IL-21, IL-23—were generally downregulated across studies,

while anti-inflammatory cytokines such as IL-10 and TGF- β were upregulated. This cases suggesting that maternal vitamin D supplementation supports a more balanced cytokine milieu, potentially reducing susceptibility to immune dysregulation in offspring.

Molecular and epigenetic effects

At the molecular level, vitamin D exposure was associated with an upregulation of VDR and FOXP3. Wang G, *et al.* (2020) demonstrated a dose-dependent increase in splenic VDR mRNA and protein levels. In contrast, Jiao X, *et al.* (2019) reported reduced methylation of the IFN- γ promoter, highlighting an epigenetic mechanism underpinning the Th1 bias.^(9, 10)

Collectively, these findings demonstrate that maternal vitamin D supplementation during pregnancy and/or lactation exerts multi-level immunomodulatory effects in offspring by enhancing Th1 responses, suppressing Th2 and Th17 pathways, variably modulating Treg activity, balancing pro- and anti-inflammatory cytokine production, and regulating immune gene expression through both transcriptional and epigenetic mechanisms.

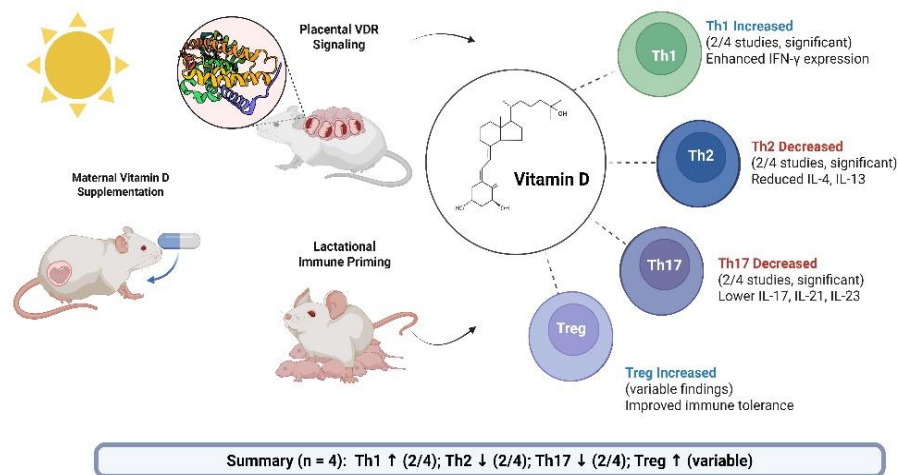


Figure 2. Effect of maternal vitamin D supplementation on offspring T-cell differentiation. Arrows indicate the direction of change, and annotations denote the number of studies reporting statistically significant impacts. Across the four included studies, the Th1 response showed variable findings (created with BioRender.com[®]). IFN- γ , interferon-gamma; IL, interleukin; Th, T helper cell; Treg, regulatory T cell; VDR, vitamin D receptor.

Discussion

This review synthesized evidence from four experimental animal studies investigating the immunomodulatory effects of maternal vitamin D₃ administration during pregnancy and/or lactation. The included studies consistently showed that maternal vitamin D supplementation promoted a more balanced immune profile in offspring. Across the reviewed rodent studies, supplementation was associated with a shift toward a Th1-dominant response, suppression of Th2 and Th17 subsets, and enhancement of regulatory T-cell (Treg) activity. In particular, offspring from vitamin-supplemented dams exhibited increased IFN- γ expression and reduced IL-4, IL-13, and IL-17, indicating improved T helper cell differentiation and a less pro-inflammatory immune milieu. In addition, maternal vitamin D supplementation during pregnancy and lactation was associated with lower levels of pro-inflammatory cytokines such as IL-1 β and IL-6 in offspring, further supporting its anti-inflammatory effect.^(9–12) Collectively, these findings suggest that maternal vitamin D exposure may contribute to the establishment of immune homeostasis early in life.

Supporting external evidence further strengthens the biological plausibility of these findings. Supplementation induced a Th1-dominant bias, suppressed Th2 and Th17 subsets, and enhanced

Tregs. In a rat model, prenatal vitamin D supplementation similarly shifted the Th1/Th2 balance toward a Th1 profile in offspring, characterized by increased IFN- γ and suppressed IL-4, IL-13, and IL-17 expression, supporting our findings at the cell and cytokine levels.⁽¹³⁾ A study similarly reported that maternal vitamin D supplementation during pregnancy and lactation suppressed IL-1 β and IL-6 levels in rat offspring.⁽¹⁴⁾ A large Japanese birth cohort noted that adequate maternal dietary vitamin D intake during pregnancy is hypothesized to correct fetal Th1/Th2 balance and suppress Th17 responses; they cite animal data showing that third-trimester vitamin D deficiency increases fetal Th2 cells while reducing Tregs.^(15, 16) These experimental and epidemiological observations not only support our findings and are consistent with broader immunology reviews indicating that vitamin D signaling promotes Treg development and restrains excessive Th1 and Th17 activity, thereby limiting the risk of allergic, autoimmune, and chronic inflammatory disorders in later stages of life.^(3, 17)

Mechanistically, these effects are mediated *via* VDR activation and epigenetic modifications, including reduced methylation of the IFN- γ promoter, facilitating transcriptional reprogramming toward Th1 responses.⁽¹⁸⁾ Beyond IFN- γ , active vitamin D influences the broader epigenetic landscape in CD4⁺ T-cells by modulating methionine metabolism and maintaining global DNA methylation, thereby stabilizing lineage-specific transcriptional programs.⁽¹⁹⁾ In parallel,

several *in vitro* and *in vivo* studies demonstrate that 1,25-dihydroxyvitamin D₃ directly constrains Th17 differentiation via VDR, down-regulating ROR γ t and suppressing IL-17 and inflammatory Th17 responses.^(20,21) These findings are consistent with Wang, *et al.* (2020), who demonstrated that maternal vitamin D₃ supplementation significantly inhibited BPA-induced Th17 proliferation and upregulated splenic VDR expression in a dose-dependent manner in offspring.⁽¹⁰⁾

Beyond offspring T-cell responses, VDR-mediated pathways at the maternal–fetal interface likely contribute to early immune priming. Tamblyn, *et al.* (2015) highlighted that vitamin D signaling in decidual cells and trophoblasts modulates local cytokine production and tolerance pathways, suggesting that placental immune regulation is an integral component of vitamin D-driven programming.⁽²²⁾ Such a concept is reinforced by studies showing clear expression of VDR and vitamin D-metabolizing enzymes (CYP27B1 and VDBP) in human placenta and decidua, where vitamin D regulates trophoblast function and placental inflammation, potentially shaping the intrauterine immune milieu.^(23,24) More recently, maternal vitamin D status has been linked to chromatin accessibility and the transcriptional rewiring of offspring CD4⁺T cells and hematopoietic progenitors, further supporting a role for vitamin D in long-term immune programming *via* VDR-driven epigenetic mechanisms.^(2,7) These findings align with our results, demonstrating Th17 suppression and cytokine modulation, underscoring a conserved role of maternal vitamin D in shaping offspring immunity.⁽²⁵⁾

Evidence also points to the consequences of deficiency. Huang F, *et al.* (2020) reported that maternal vitamin D deficiency impaired Treg and Breg responses in offspring, exacerbating allergic airway inflammation induced by elevated pro-inflammatory cytokine levels.⁽²⁶⁾ These findings reinforce the notion that sufficient maternal vitamin D exposure not only enhances Treg function but also prevents exaggerated immune activation, thereby protecting offspring against dysregulated inflammatory responses.

From a broader perspective, maternal vitamin D emerged as a critical factor in early immune programming, particularly during prenatal and early post-natal windows when immune development is most sensitive to environmental and nutritional cues. Across animal and human studies, vitamin D recalibrates

immune responses in offspring exposed to pro-inflammatory or allergenic stimuli, suggesting potential utility in mitigating risks of allergy, autoimmunity, and chronic inflammation.^(9–12) Mailhot and White summarized evidence that vitamin D shapes T-cell differentiation, cytokine production, and antimicrobial responses in infants and children, emphasizing its capacity to modulate Th1/Th2/Th17 balance and support regulatory pathways during critical developmental periods.⁽²⁷⁾ More recently, Zhu B, *et al.* demonstrated in a rodent model that maternal vitamin D status can reshape offspring intestinal and immune phenotypes *via* changes in chromatin accessibility and metabolic reprogramming, providing direct mechanistic support for vitamin D-driven immune programming across generations.⁽⁷⁾ Together, these findings reinforce the concept that maternal vitamin D acts at the cellular and epigenetic levels to calibrate immune trajectories from fetal life onward.

Across animal and human studies, vitamin D appears to recalibrate immune responses in offspring exposed to pro-inflammatory or allergenic stimuli, with potential implications for allergy, autoimmunity, and a risk of chronic inflammation. Prospective cohort and meta-analytic data suggest that low maternal 25(OH)D concentrations during pregnancy are associated with higher risks of childhood eczema and allergic outcomes; however, results were not entirely uniform across studies.^(28, 29) Randomized trials and pooled analyses, such as the VDAART and COPSAC combination reported by Wolsk HM, *et al.*, indicate that prenatal vitamin D supplementation can reduce the risk of asthma or recurrent wheeze in early childhood, particularly when maternal vitamin D levels are sufficient at baseline.^(4, 5) More recent work has extended these findings to atopic dermatitis: in the MAVIDOS trial, El-Heis S, *et al.* found that antenatal cholecalciferol supplementation reduced the risk of atopic eczema in offspring; Zhang Q, *et al.* reported that adequate maternal vitamin D status and supplementation lowered eczema risk in infants in a contemporary birth cohort.^(30, 31) Although effect sizes vary and not all outcomes are consistently protective, the overall pattern from these animal and human studies supports the idea that maternal vitamin D can help temper excessive Th2/Th17-skewed responses and enhance regulatory pathways in offspring, thereby offering a promising avenue to mitigate long-term susceptibility to allergic, autoimmune, and chronic inflammatory diseases.

Clinically, prenatal vitamin D supplementation represents a low-cost, accessible strategy to enhance fetal and neonatal immune health. Evidence from animal studies suggests that maternal vitamin D influences Th balance, Treg function, and cytokine modulation, with potential implications for reducing the risk of allergic, autoimmune, and inflammatory disorders in offspring. Although clinical data remain limited, the current evidence base supports its use in maternal nutrition guidelines. Future human intervention studies should move beyond perinatal outcomes to incorporate standardized immune phenotyping, long-term follow-up, and integration of molecular and epigenetic analyses, which will be essential in clarifying mechanistic pathways and strengthening translational applicability.^(9–12)

According to the WHO antenatal care recommendations, routine vitamin D supplementation during pregnancy does not improve maternal and perinatal outcomes, and supplementation is generally reserved for women with suspected or confirmed deficiency.⁽³²⁾ However, emerging evidence suggests that maternal vitamin D may also exert immunomodulatory effects, potentially influencing offspring immune development and susceptibility to immune-related conditions. These findings highlight an area of growing scientific interest, as current guidelines primarily focus on skeletal outcomes, while additional biological roles of vitamin D continue to be explored. Given that much of the current evidence is derived from animal models, interpretation of these findings in the context of human physiology should be approached with caution. Further, well-designed human studies are needed to clarify the clinical relevance, optimal dosing, and timing of supplementation.

Most evidence on maternal vitamin D and offspring immunity comes from rodent models, which may not fully reflect immune development in humans. Heterogeneity among species, dosing, timing (pregnancy vs. pregnancy plus lactation), route of administration, and outcome measures limits comparability. Additionally, only a few studies assessed long-term effects, leaving persistence, and clinical relevance unclear.

The evidence included in this review was limited by the small number of studies, all of which were in rodent models. In addition, they showed substantial heterogeneity across species, experimental conditions, vitamin D regimens, and immune-related outcomes,

which limited direct comparability. Several also had an unclear to moderate risk of bias because of insufficient methodological reporting, particularly regarding randomization, allocation concealment, and blinding. This review also has methodological limitations. The search was restricted to English-language articles published within the last 10 years; thus, it may exclude a few relevant studies. Furthermore, the limited number of studies included and their heterogeneity precluded quantitative synthesis. Reporting bias or certainty of evidence was not formally assessed.

Despite limitations, the findings suggest that maternal vitamin D may play a crucial role in early immune programming and may help promote a more balanced immune profile in offspring. From a practice and policy perspective, these findings support further consideration of maternal vitamin D status as part of prenatal nutritional care. However, current evidence remains insufficient to justify changes to existing recommendations based solely on immune outcomes. Future research should prioritize well-designed human studies with standardized supplementation protocols, detailed immune phenotyping, and longer follow-up durations to clarify the translational relevance of these findings.

Addressing these gaps requires standardized protocols and integration of immune phenotyping with molecular and epigenetic analyses. Well-designed human trials with longitudinal follow-up are essential. Maternal vitamin D supplementation is a low-cost intervention that enhances Treg cells, modulates Th2/Th17 responses, and shapes cytokine profiles, suggesting a key role in early immune programming. Evidence-based guidelines on dosing and timing during pregnancy could have a marked clinical and public health impact, supporting both skeletal and immune health in offspring.

Conclusion

Maternal vitamin D supplementation during pregnancy and lactation critically shapes offspring immune development. Rodent studies show enhanced Treg function, suppressed Th2/Th17 responses, and altered expression of key cytokines and genes (FOXP3, VDR, IFN- γ), supporting immune tolerance and reduced early-life susceptibility to immune-mediated diseases. Human data remains limited despite available mechanistic evidence. Well-controlled clinical trials

with longitudinal follow-up and standardized molecular analyses are needed. As a low-cost, accessible intervention, maternal vitamin D holds promise for optimizing early immune programming and preventing allergic and autoimmune diseases in future generations.

Author contributions

KMH contributed substantially to the concept and design of the study, supervision, funding acquisition, materials preparation, and data collection and processing, as well as data analysis and interpretation. GK contributed to the study concept, materials preparation, and drafting the manuscript. LZ contributed to the study concept, supervision, funding acquisition, and drafting the manuscript. WS contributed substantially to the concept and design of the study, supervision, funding acquisition, materials preparation, and data collection and processing, and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Conflicts of interest statement

The authors hereby declare no conflict of interest.

Data sharing statement

This systematic review is based exclusively on data extracted from published studies. No individual-level or unpublished patient data were collected. The datasets generated and/or analyzed during the current research—including extraction sheets and summary tables—are available from the corresponding author on reasonable request.

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