

EFFECTS OF VITAMIN D IN NEONATES AND YOUNG INFANTS: AN UPDATED SYSTEMATIC REVIEW

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ABSTRACT

Background: Vitamin D is a fat-soluble vitamin essential for calcium metabolism, maintaining calcium homeostasis, and supporting skeletal mineralization. Low maternal levels of vitamin D during pregnancy are linked to various adverse neonatal outcomes. This study aims to systematically review the effects of Vitamin D in neonates and infants in literatures of the last 5 years.

Methods: The systematic review followed PRISMA 2020 standards and examined full-text English literature published between 2019 and 2024. This review excluded editorials, review papers from the same journal, and submissions without a DOI. Literature was sourced from online platforms such as PubMed, SagePub, SpringerLink, and Google Scholar.

Result: A total of 2,866 articles were retrieved from online databases (PubMed, SagePub, SpringerLink and Google Scholar). After three rounds of screening, four articles directly relevant to the systematic review were selected for full-text reading and analysis.

Conclusion: Vitamin D is essential for skeletal, immune, and neurodevelopmental health in children. Maternal supplementation during pregnancy is crucial for ensuring adequate levels in infants and neonates, along with promoting sunlight exposure and dietary intake, particularly in regions with high rates of maternal vitamin D deficiency.

Keyword: Vitamin D, neonates, infants

INTRODUCTION

Vitamin D is a fat-soluble vitamin essential for calcium metabolism, maintaining calcium homeostasis, and supporting skeletal mineralization. Recent research highlights its immunomodulatory and antimicrobial roles, showing that it contributes to the optimal functioning of the innate immune system. It does so by stimulating the production of antimicrobial peptides in epithelial cells, neutrophils, and macrophages.¹

Beyond its well-known role in bone health and calcium regulation, Vitamin D is crucial for cardiovascular health, glucose metabolism, cell differentiation, and immune function. Although observational studies suggest lower Vitamin D levels may be linked to a higher prevalence of diseases, there is no conclusive evidence of a causal relationship. Conflicting results from Vitamin D supplementation studies add to the complexity, with discrepancies attributed to various factors such as initial Vitamin D levels, dosage, adherence to the supplementation regimen, and inconsistent monitoring of levels during trials. There is also debate over the optimal levels of Vitamin D, with some experts suggesting higher thresholds than others for sufficiency and for achieving non-classical health benefits.²

Vitamin D deficiency is recognized worldwide as a significant public health issue, affecting people at all stages of life. The primary sources of Vitamin D are sun exposure and a few specific foods, but obtaining adequate amounts from these sources alone is challenging. Once in the body, Vitamin D binds to a specific protein and undergoes two hydroxylation processes, first in the liver and then in the kidney, to become its active form. This active Vitamin D is not only produced in the kidneys but also in other organs, indicating its wide-ranging impact on the body.²

Low maternal levels of vitamin D during pregnancy are linked to various adverse neonatal outcomes, including babies being small for gestational age, preterm births, negative effects on the development of bones and teeth, and a higher risk of infectious diseases. Studies indicate that maternal 25 OH D levels below 20 ng/ml significantly increase the likelihood of such outcomes. Additionally, there is a growing body of evidence suggesting a relationship between vitamin D levels and sepsis, with vitamin D supplementation being associated with a decreased incidence of sepsis. Furthermore, lower neonatal 25 OH D levels are connected to an elevated risk of early and late onset neonatal sepsis, sepsis in general, and a higher risk of lower respiratory infections in newborns.³

Inadequate maternal vitamin D supplementation and reduced maternal exposure to ultraviolet light during pregnancy are major factors contributing to neonatal hypovitaminosis D at birth.⁴ This study aims to systematically review the effects of Vitamin D in neonates and infants in literatures of the last 5 years.

METHODS

Protocol

The author carefully followed the rules laid out in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. This was done to make sure the study met all its standards. The selection of this methodological approach was specifically aimed at ensuring the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review examined the effects of Vitamin D in neonates and infants in literature over the past 5 years. This study meticulously analyzed data on literatures to provide insights and enhance patient treatment strategies. The primary objective of this paper is to highlight the collective significance of the identified key points.

Inclusion criteria for this study entail: 1) Papers must be in English, and 2) Papers must have been published between 2014 and 2024. Exclusion criteria comprise: 1) Editorials; 2) Submissions without a DOI; 3) Previously published review articles; and 4) Duplicate entries in journals.

Search Strategy

The keywords used for this research are “vitamin D”, “neonates”, and “infants”. The Boolean MeSH keywords inputted on databases for this research are: (*"vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields]*) AND (*"infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonatal"[All Fields] OR "neonate"[All Fields] OR "neonates"[All Fields] OR "neonatality"[All Fields] OR "neonatal s"[All Fields] OR "neonate s"[All Fields]*) AND (*"infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields]*)

Data retrieval

The authors assessed the studies by reviewing their abstracts and titles to determine their eligibility, selecting relevant ones based on their adherence to the inclusion criteria, which aligned with the article's objectives. A consistent trend

observed across multiple studies led to a conclusive result. The chosen submissions had to meet the eligibility criteria of being in English and a full-text.

This systematic review exclusively incorporated literature that met all predefined inclusion criteria and directly pertained to the investigated topic. Studies failing to meet these criteria were systematically excluded, and their findings were not considered. Subsequent analysis examined various details uncovered during the research process, including titles, authors, publication dates, locations, study methodologies, and parameters.

Quality Assessment and Data Synthesis

Each author independently evaluated the research presented in the title and abstract of the publication to determine which ones merited further exploration. The subsequent stage involved assessing all articles that met the predefined criteria for inclusion in the review. Decisions on including articles in the review were based on the findings uncovered during this evaluation process. This criterion aimed to streamline the paper selection process for further assessment, facilitating a comprehensive discussion of previous investigations and the factors that made them suitable for inclusion in the review.

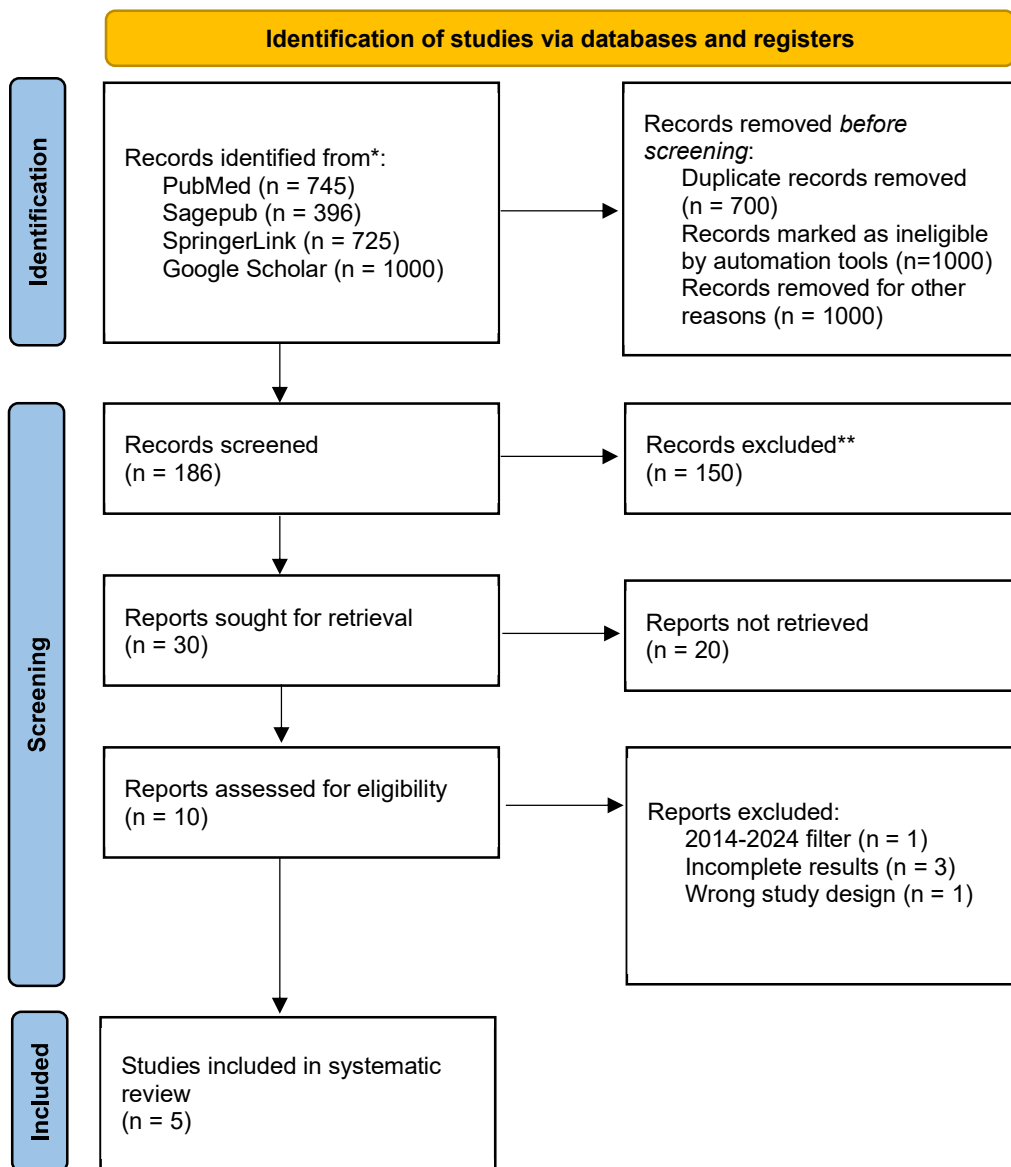


Figure 1. Article search flowchart

RESULT

The initial number of articles retrieved from online databases (PubMed, SagePub, SpringerLink, and Google Scholar) is 2,866 articles. After conducting three levels of screening, five articles that directly relate to the current systematic review

have been chosen for further assessment through full-text reading and analysis. Table 1 presents the selected literature included in this analysis.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Aly, et al. ⁵ (2019)	Cairo, Egypt	Randomized controlled trial	40 preterm infants	A double-blind randomized controlled trial investigated preterm infants receiving either 400 or 800 IU/day of vitamin D3. Treg cell count increase was significantly lower in the low-dose group after 1 week (1.9 ± 5.5 vs 60 ± 5.6 , $P = 0.0005$) and after 4 weeks (1.8 ± 5.7 vs 73.7 ± 5.6 , $P = 0.0028$). There were no significant differences in other outcomes, except for a longer hospital stay in the low-dose group (24.9 ± 5.14 vs 22 ± 3.49 , $P = 0.04$)
Rodgers, et al ⁶ (2023)	USA	Post hoc data analysis	156 children	The study investigated the association between circulating vitamin D levels and neurodevelopmental outcomes in 3–5-year-old children. Pregnant women were assigned different doses of vitamin D3, and their children underwent neurodevelopmental assessments. Higher vitamin D levels during testing were linked to better overall neurodevelopmental performance. Children born to mothers receiving 2000 IU/day scored higher in language skills compared to those receiving the standard dose. Certain genetic variations in the vitamin D binding protein were associated with differences in academic and language performance on the assessments.
Karras, et al. ⁴ (2020)	Greece	Cohort study	129 mother-neonate pairs	The study found that neonates deficient in

				<p>vitamin D exhibited higher levels of parathyroid hormone and lower corrected calcium concentrations compared to neonates with insufficient vitamin D levels. Mothers of deficient and insufficient neonates had lower levels of total 25(OH)D and 25(OH)D3 compared to mothers of vitamin D-sufficient neonates. Maternal alcohol use during pregnancy was associated with a significantly higher risk of neonatal vitamin D deficiency. Neonates with vitamin D deficiency were also more likely to have been born to mothers with vitamin D deficiency.</p>
<p>Behera, et al.¹ (2020)</p>	<p>Odisha, Eastern India</p>	<p>Prospective cohort study</p>	<p>40 neonates</p>	<p>The study found that neonates with vitamin D deficiency or insufficiency had significantly lower levels of 25 OH vitamin D compared to the control group. These deficient or insufficient neonates were at a much higher risk of developing culture positive sepsis, with an odds ratio of 273. Additionally, mothers of septic neonates had lower vitamin D levels compared to mothers of healthy neonates in the control group, and babies born to mothers with vitamin D deficiency or insufficiency were at an increased risk of sepsis, with an odds ratio of 4.71.</p>
<p>Chacham, et al.⁷ (2020)</p>	<p>India</p>	<p>Prospective observational study</p>	<p>200 infants and 200 mothers</p>	<p>The study included 200 infants and 200 mothers, with 80% of the infants being neonates and the remaining 20% being beyond the neonatal period. Vitamin D deficiency was found in</p>

				74% of the infants and 85.5% of the mothers, with nearly half of both groups having severe deficiency. Logistic regression analysis revealed a positive correlation between maternal and infant vitamin D levels, as well as with neonatal age group and low socioeconomic status. The main biochemical manifestations observed were hyperphosphatemia and hypocalcemia.
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Aly, et al.⁵ (2019) conducted oral vitamin D supplementation on premature born infants. T regulatory cell count is influenced by vitamin D supplementation in preterm babies. A higher Regulatory T cells (Treg) count is achieved at 1 and 4 weeks of 800 IU of vitamin D as compared to 400 IU.

Rodgers, et al.⁶ (2023) showed that elevated 25(OH)D levels in early life and increased doses of maternal vitamin D supplementation during pregnancy may positively impact neurodevelopmental outcomes. Additionally, the study suggests that variations in the vitamin D binding protein genotype are linked to neurodevelopment and may influence different aspects of neurodevelopmental functioning.

Karras, et al.⁴ (2020) concluded that neonatal vitamin D deficiency appears to be linked to maternal 25(OH)D concentrations at birth and maternal alcohol use. Neonates with vitamin D deficiency were also more likely to have been born to mothers with vitamin D deficiency.

Behera, et al.¹ (2020) suggested that neonates with insufficient vitamin D levels are more susceptible to sepsis, and lower vitamin D levels in mothers are associated with an increased risk of sepsis in their newborns.

Chacham, et al.⁷ (2020) concluded that neonatal age group, lower socioeconomic status, and maternal vitamin D deficiency were significant factors influencing vitamin D deficiency in infants.

DISCUSSION

Vitamin D levels are regulated by dietary intake and sunlight exposure. Short periods of sunlight exposure can sustain adequate vitamin D levels in infants, preventing severe deficiency. Neonatal vitamin D deficiency poses significant risks for acute and chronic metabolic complications, including neonatal rickets, hypocalcemia, and suboptimal skeletal development. Recent studies emphasize the critical role of maternal vitamin D levels in determining neonatal vitamin D status.¹

According to the American Academy of Pediatrics (AAP, 2008) and the Institute of Medicine, vitamin D deficiency is characterized by serum 25(OH) vitamin D levels below 15 ng/mL. Sufficiency is considered when levels range between 21-100 ng/mL, excess at 101-149 ng/mL, and intoxication at levels exceeding 150 ng/mL. However, the ideal vitamin D supplementation dose for preterm infants is uncertain. The American Academy of Pediatrics recommends 400 IU/day, while the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition previously suggested 800 IU/day. These doses aim to prevent metabolic bone diseases of prematurity, but the broader benefits of vitamin D supplementation in preterm infants, including immune function, are not well-understood.^{3,7}

Recent studies have provided increasing support for the antimicrobial effects of vitamin D. Vitamin D boosts innate immunity while suppressing the acquired immune response. It helps maintain the integrity of epithelial cells, the body's first line of defense against infection. Vitamin D activates key innate immune cells like monocytes, macrophages, and neutrophils, enhancing their ability to fight pathogens and produce antimicrobial peptides such as cathelicidin. It also prompts the production of antimicrobial proteins directly within immune cells. Furthermore, vitamin D inhibits the growth of various bacteria and prevents their invasion by enhancing clearance mechanisms.¹

Additionally, vitamin D modulates inflammatory responses, enhances neutrophil activity, and regulates the differentiation of T cells. T regulatory cell count is influenced by vitamin D supplementation in preterm babies. A higher Regulatory T cells (Treg) count is achieved at 1 and 4 weeks of 800 IU of vitamin D as compared to 400 IU. Infants administered with high doses of vitamin D were discharged nearly two days earlier compared to those who received lower doses.⁵

Previous study also indicate a correlation between vitamin D levels and neurodevelopment in children, suggesting that higher maternal vitamin D intake during pregnancy may benefit child neurodevelopment, particularly in the language domain. Additionally, the study suggests that the vitamin D binding protein (VDBP) genotype may influence child neurodevelopment independently of vitamin D status. Specifically, certain VDBP genotypes were found to impact different neurodevelopmental domains in varying ways.⁶

The American Academy of Pediatrics advises against direct sunlight exposure for infants under six months, which may contribute to vitamin D deficiency. Despite this, infants have a greater ability to produce vitamin D from sunlight due to their higher surface area to volume ratio. Preventive measures primarily focus on ensuring sufficient maternal vitamin D levels during pregnancy through supplementation or adequate sunlight exposure.³

However, in Mediterranean countries, there is a high prevalence of maternal hypovitaminosis D during pregnancy. This phenomenon is attributed to racial, social, and cultural factors, along with a lack of preventive strategies such as food fortification policies and sun exposure practices. Specifically, dark skin, clothing choices, and avoidance of sunlight, particularly in hot summer months, contribute to the increased prevalence of maternal hypovitaminosis D during pregnancy in this region. Asian children may need more sunlight exposure than white children due to darker skin.^{4,7}

CONCLUSION

In conclusion, vitamin D plays a crucial role in various aspects of health, including skeletal development, immune function, and neurodevelopment. Maternal supplementation during pregnancy is essential for ensuring optimal levels in infants and neonates. Adequate sunlight exposure and dietary intake are key preventive measures, especially in regions with high prevalence of maternal hypovitaminosis D.

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