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## Vitamin D Status and Asthma Flare-ups in Children: A Non-systematic Review

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### ABSTRACT

Several non-calcemic actions of vitamin D are well-documented in the literature. Its role in childhood asthma is now an area of on-going research. Studies indicate that the severity of childhood asthma is directly correlated with reduced serum vitamin D levels. This non-systematic review aims to discuss the association of vitamin D status with asthma flare-ups in children. We searched the PubMed database for articles that met the objective of this review. Vitamin D may play a vital role in lung health by inhibiting inflammation, partly by maintaining the regulatory T cells, and by direct induction of innate antimicrobial mechanisms. Vitamin D also inhibits adaptive immunity by delaying the proliferation of T-helper cells. For instance, the neutrophilic asthma phenotype is characterized by neutrophilic inflammation, whose induction is mediated by type 2 T-helper cells. Thus, vitamin D is related to the pathogenesis of asthma based on its ability to block the proliferation of T-helper cells. Predictably, hypovitaminosis D is associated with florid asthma symptoms, asthma flare-ups, decreased lung function, and increased drug usage, as well as severe disease. Several reports have shown a strong relationship between wheezing symptoms/asthma severity in children and low serum 25-hydroxyvitamin D levels. These findings support the use of vitamin D<sub>3</sub> supplementation as a potential strategy for reducing disease flare-ups in children.

**Keywords:** Adaptive immunity, asthma, child, regulatory T-lymphocytes, helper T-cells, vitamin D deficiency



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### INTRODUCTION

Asthma has assumed global prominence as the most common non-communicable respiratory disease in children.<sup>[1]</sup> Asthma is now regarded as a heterogeneous disease with several phenotypes and underlying endotypes.<sup>[2]</sup> Disease heterogeneity is seen in the variable clinical presentations and the nature/extent of airway inflammation and remodeling. Asthma phenotypes and endotypes appear to represent a multitude of the host (gene)-environment reciprocal influences that occur over different periods.<sup>[3]</sup>

Epidemiologic data now indicate that dietary factors, such as hypovitaminosis D, are associated with florid asthma symptoms, asthma flare-ups, decreased lung function and increased drug usage, as well as severe disease.<sup>[4]</sup> The non-calcemic actions of vitamin D are well-documented in the medical literature.<sup>[5–7]</sup> Precisely, role of vitamin D in childhood asthma is currently an area of on-going research. The research questions to be addressed should include as follows: First, whether vitamin D supplementation in infancy is protective against viral infections (which could act as triggers to asthma flare-ups).<sup>[8]</sup> Second, whether vitamin D supplementation could be administered together with inhalational steroid therapy to ameliorate disease flare-ups in school-age children.<sup>[8]</sup> And third, whether vitamin D supplementation is more effective in populations at risk for hypovitaminosis D.<sup>[8]</sup> Several studies have highlighted

that asthma severity in children directly correlates with low serum vitamin D levels.<sup>[9-12]</sup> More importantly, these findings bring to the fore the potential utility of vitamin D supplementation in reducing disease flare-ups in childhood, although some authors suggest that this practice cannot yet be made a general recommendation.<sup>[8]</sup> The present non-systematic review aims to discuss the association of vitamin D status with asthma flare-ups in children.

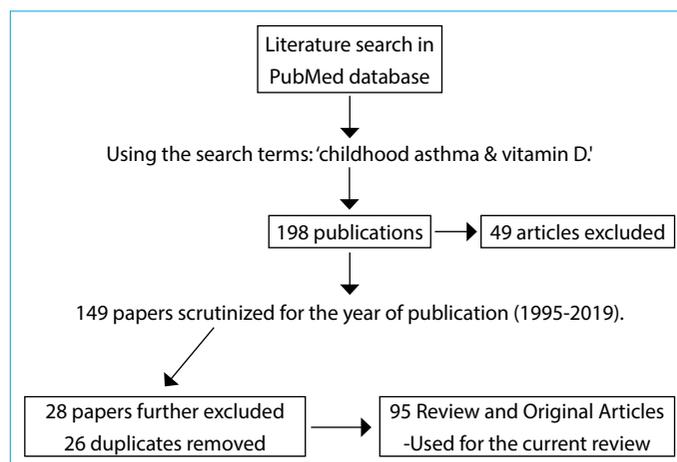
### Literature Search: Strategy and Outcome

We searched the PubMed database for articles written in the English language between January and April 2019 using the combination of two terms: 'childhood asthma and vitamin D.' The search engine yielded 198 publications, out of which we excluded 49 articles which were unrelated to the review topic. We scrutinized the remaining 149 publications for articles published within the last 25 years (1995-2019). We further excluded 28 papers and removed 26 duplicates, leaving 95 review articles and original articles which formed the bulk of the information used for the current narrative review (Fig. 1).

### The Non-calcemic Actions of Calcitriol and Asthma Pathogenesis

Given the diverse distribution of vitamin D receptors in the human body, vitamin D has multiple non-calcemic actions. The significant non-calcemic effects of vitamin D comprise the control of hormone secretion (insulin and parathyroid hormone), immune function, as well as cellular proliferation and differentiation.<sup>[5]</sup> The active form of vitamin D (1, 25-hydroxyvitamin D, or calcitriol) exerts different effects on innate immunity and adaptive immunity. Vitamin D stimulates the former by inducing the expression of antimicrobial peptide (cathelicidin) in myeloid and epithelial cells,<sup>[13,14]</sup> whereas it inhibits the latter by suppressing B-cell proliferation and immunoglobulin production<sup>[15]</sup> and retarding the proliferation of T-helper cells (Th cells) or CD4+ cells.<sup>[16]</sup>

Vitamin D may play a vital role in lung health by inhibiting inflammation, partly through maintaining the regulatory T-cells (Treg cells), and by direct induction of innate antimicrobial mechanisms.<sup>[4,17]</sup> The primary actions of the Treg cells are immunosuppression as well as downregulation of induction and proliferation of effector T cells.<sup>[18]</sup> As a chronic inflammatory disease, the typical clinical features of asthma occur as a result of an inappropriate stimulation of the immune system, particularly by environmental air-borne allergens.<sup>[19]</sup> Reports show that inflammation and remodeling, especially of the respiratory epithelium and distal airways, are the distinctive features of the pathobiology of severe



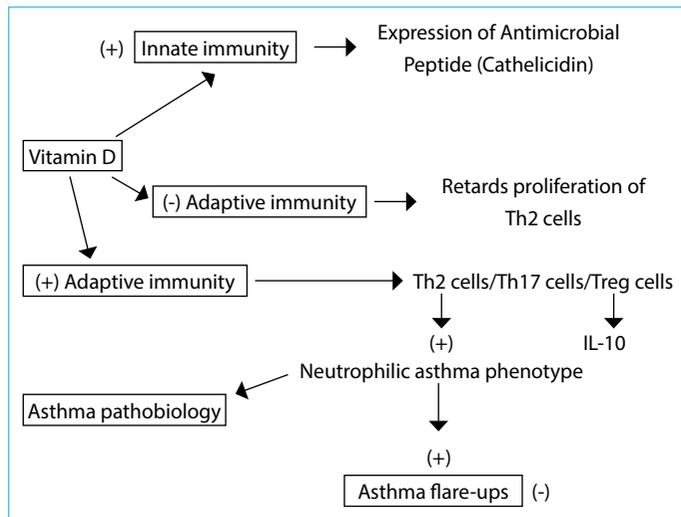
**Figure 1.** Literature search: strategy and outcome.

asthma in children.<sup>[20]</sup> Severe asthma consists of multiple phenotypes, such as the inflammatory phenotypes which comprise severe allergic asthma, eosinophilic asthma, and neutrophilic asthma.<sup>[21]</sup> Neutrophilic inflammation is the hallmark of neutrophilic asthma: a phenotype that can occur with or without eosinophilic inflammation.<sup>[22]</sup> Induction of neutrophilic inflammation is mediated by type 2 T-helper (Th2) cells.<sup>[23]</sup> Furthermore, recruitment of neutrophils can be mediated by type 17 T-helper (Th17) cells, thought to be responsible for disease pathogenesis, especially in patients who do not respond to corticosteroid therapy, and show airway hyperresponsiveness and reduced improvement in airflow limitation or first second of forced expiration (FEV1) after the treatment.<sup>[24]</sup> Vitamin D influences the functions of epithelial cells, T- and Blymphocytes, and antigen-presenting cells. In addition, by inducing the Treg cells to produce interleukin-10, Vitamin D modulates inflammation in asthma and thus probably reduces disease severity.<sup>[25]</sup> The pathogenic link between vitamin D and asthma also involves the vitamin's suppressive action on the proliferation of Th cells.<sup>[16]</sup> Given the mediatory role of Th2 and Th17 cells in neutrophilic inflammation, deficiency of vitamin D may lead to accentuation of the inflammatory processes in asthma (Fig. 2). Also, attenuation of the innate antimicrobial mechanisms following hypovitaminosis D may lead to asthma flare-ups or wheezing-associated illnesses through the increased risk for respiratory tract infections.<sup>[26-29]</sup>

### Vitamin D Status and Asthma Flare-ups

#### Prenatal/Early-life Vitamin D Exposure and Respiratory Disorders

Prenatal vitamin D status has been studied by several investigators to establish a link with the subsequent development of asthma. Their study methods comprised third-trimester evaluation of mothers' dietary intake of vitamin D with validated questionnaires,<sup>[30-33]</sup> and estimation of maternal blood



**Figure 2.** Schematic diagram showing the non-calcemic actions of Vitamin D in asthma pathobiology.

(+) = stimulatory action/induction, (-) = inhibitory action, Th2 cells = type 2 T-helper cells, Th17 = type 17 T-helper cells, Treg cells = the regulatory T cells, IL-10 = interleukin-10.

or cord-blood vitamin D levels (Table 1).<sup>[28,29,34–37]</sup>

A prospective pre-birth cohort study of 1194 mother-child dyads by Camargo et al. in the United States aimed to investigate if higher prenatal maternal ingestion of vitamin D was associated with lower odds for repeated childhood wheezing in the third year of life.<sup>[30]</sup> The authors evaluated mothers' prenatal ingestion of the vitamin using a validated food-frequency questionnaire (FFQ). The primary outcome of their study was a positive asthma predictive index (API), which referred to two or more wheezing episodes with a personal diagnosis of eczema or a parental history of asthma. The authors' significant finding was the association of a lower risk of recurrent wheezing (positive API) with the highest quartile of daily prenatal vitamin D intake compared with the lowest quartile of daily consumption.<sup>[30]</sup> Better still, their findings suggest that prenatal ingestion of the vitamin by mothers probably protects young children from wheezy disorders. Although the large sample size was a strong point for the study, the confounders to prenatal maternal vitamin D intake (which included maternal exposure to other nutritional factors associated with asthma risk) was a study limitation. The authors adjusted for these potential confounding factors, which, however, did not alter the study results.<sup>[30]</sup>

Elsewhere in Scotland, Devereux et al. investigated whether a similar relationship exists between prenatal maternal vitamin D intake and reduced odds of wheezing in young children.<sup>[31]</sup> They conducted a prospective birth cohort study of 2000 healthy pregnant women whose ingestion of vitamin D was determined in the third trimester

from an FFQ. However, maternal FFQ data and respiratory parameters through the fifth year were obtained for 1212 children. The study outcomes included wheezing symptoms, spirometry, bronchodilator response, atopic sensitization and fraction of exhaled nitric oxide (FeNO) levels at five years. After adjustment for confounding variables, including the children's vitamin D consumption, the highest and lowest quartiles of total vitamin D ingestion by the mothers were associated with lower odds for wheeze in the fifth year of life. Also, lower total ingestion of vitamin D by mothers during pregnancy was related to a diminished response to bronchodilators. In contrast, we should note that the researchers failed to demonstrate an associations of maternal vitamin D consumption with FeNO levels and spirometry.

In a related study of 1669 mother-child dyads by Erkkola et al. in Finland,<sup>[32]</sup> the investigators monitored the children from birth for asthma, allergic rhinitis and atopic eczema, which were assessed with a validated questionnaire at five years of age. They also evaluated maternal diet using a validated FFQ. Interestingly, the consumption of diet-derived vitamin D by mothers was indirectly correlated with the risk of respiratory atopy in children after adjustment for possible confounding variables.<sup>[32]</sup> In contrast, mothers' intake of only supplemental vitamin D was not associated with similar results. Again, the study results did not change after the authors adjusted for maternal intake of other dietary factors.<sup>[32]</sup>

The studies which ascertained maternal vitamin D status through estimation of blood or cord blood levels of 25-hydroxyvitamin D were conducted in Canada,<sup>[34]</sup> the United Kingdom,<sup>[35]</sup> Spain<sup>[36]</sup> and the United States.<sup>[37]</sup> In a cross-sectional study of 344 mother-child dyads by Carroll et al.,<sup>[34]</sup> there was an observed 50% reduction in the odds of maternal asthma with every 35 nmol/L elevation in 25-hydroxy vitamin D levels. However, the authors failed to document any association with the development of wheezing in infants of these mothers. Gale et al. noted that mothers' serum vitamin D levels of >75 nmol/L were associated with an increased risk of atopic dermatitis and asthma in their children at the ninth month and ninth year of life respectively.<sup>[35]</sup> The authors conducted a prospective cohort study of 466 mothers and 178 children in which they determined mothers' vitamin D status by measuring their serum vitamin D concentrations. The prospective cohort study by Morales et al. examined 1724 children at 12 months and 4–6 months. Maternal vitamin D status was assessed by determining the plasma 25-hydroxy vitamin D levels.<sup>[36]</sup>

Interestingly, the investigators did not establish associations of maternal plasma vitamin D levels with childhood

**Table 1.** Some studies showing the effect of prenatal vitamin D status on the risk of respiratory disorders in childhood

Authors/year	Country	Study design	Study population	Age of subjects at assessment	Determination of vitamin D status	Major findings
Camargo et al., 2007	United States	A prospective pre-birth cohort study	1194 mother-child dyads	3 years	Maternal FFQ	The highest quartile of prenatal maternal vitamin D intake associated with a lower risk of recurrent wheezing <sup>†</sup>
Devereux et al., 2007	Scotland	A prospective cohort study	2000 pregnant women & 1212 children	5 years	Maternal FFQ	The highest and lowest quartiles of maternal vitamin D were associated with lower risks of wheezing <sup>†</sup> Lower maternal vitamin D intake was associated with a reduced bronchodilator response
Erkkola et al., 2009	Finland	A prospective cohort study	1669 mother-child dyads	5 years	Maternal FFQ	Higher maternal dietary vitamin D intake was associated with a lower risk of asthma and allergic rhinitis <sup>†</sup>
Carroll et al., 2011	Canada	A cross-sectional study	340 mother-infant dyads	5-29 weeks	Maternal whole blood 25 (OH) D	Maternal 25 (OH) D was inversely related to asthma odds in mothers No relationship with wheezing in infancy
Gale et al., 2008	United Kingdom	A prospective cohort study	466 mothers & 178 children	9 months & 9 years	Maternal serum 25 (OH) D	Maternal 25 (OH) D levels >75 nmol/L were associated with increased risk of asthma and atopic eczema
Morales et al., 2012	Spain	A prospective cohort study	1724 children	12 months & 4-6 years	Maternal plasma 25 (OH) D	An inverse relationship between maternal 25 (OH) D level and the risk of lower RTI
Rothers et al., 2011	United States	A prospective cohort study	219 children	Birth-5 years	Cord blood 25 (OH) D	Low and high cord blood 25 (OH) D associated with increased air-allergen sensitization

FFQ=food-frequency questionnaire; RTI= respiratory tract infections; 25 (OH) D= 25-hydroxy vitamin D; <sup>†</sup> After an adjustment was made for potential confounders.

asthma and wheezing but observed that mothers' vitamin D status was indirectly correlated with their infants' susceptibility to lower respiratory tract infections. Finally, Rothers et al., in a prospective cohort study of 219 children, evaluated cord-blood 25-hydroxy vitamin D levels of neonates at birth.<sup>[37]</sup> They reported that cord blood levels less than 20 ng/ml were associated with raised IgE levels and air-allergen sensitization. In contrast, there was no observed relationship between cord-blood 25-hydroxyvitamin D levels and subsequent asthma at the fifth year of life.

### Vitamin D Status of Children and Asthma Morbidity

The association of childhood vitamin D status with asthma

morbidity has been documented in several reports; some of these reports were observational studies,<sup>[38-43]</sup> while other reports were clinical trials (Table 2).<sup>[12, 44-46]</sup>

The cross-sectional study by Brehm et al. in Costa Rica assessed 616 pediatric asthmatic patients using biomarkers of asthma severity and allergy as outcome measures.<sup>[38]</sup> The authors found elevated total IgE and eosinophilia in patients with low serum vitamin D levels. Also, elevated serum vitamin D levels resulted in reduced hospitalizations, use of steroids and airway hyperresponsiveness. In a related study of 560 children with asthma (n=287) and without asthma (n=273) in Puerto Rico, Brehm et al. used outcome measures, such as severe asthma flare-ups, pul-

**Table 2.** Vitamin D status in children and asthma morbidity

Authors/year	Country	Study design	Study population	Outcome measures	Major findings
Brehm et al., 2009	Costa Rica	Cross-sectional study	616 children with asthma aged 6-14 years	Markers of asthma severity and allergy	An inverse relationship between vitamin D levels and total IgE & eosinophil count.
Brehm et al., 2012	Puerto Rico	Cross-sectional study	560 children with asthma (n=287) and without asthma (n=273) aged 6-14 years	Severe asthma flare-ups, pulmonary function <sup>‡</sup> , and atopy	Increased vitamin D levels were associated with reduced hospitalization, use of anti-inflammatory drugs and airway hyperresponsiveness. Vitamin D insufficiency <sup>†</sup> was associated with severe asthma flare-ups, atopy and lower FEV1/FVC.
Chinellato et al., 2011	Italy	Cross-sectional study	75 children with asthma aged 5-11 years	Pulmonary function <sup>‡</sup> Asthma control	Serum 25-hydroxyvitamin D levels positively correlated with FEV1 & FVC Higher serum 25-hydroxyvitamin D levels associated with better asthma control.
Chinellato et al., 2011	Italy	Cross-sectional study	45 children with intermittent asthma	Exercise-induced bronchoconstriction Pulmonary function <sup>‡</sup>	Serum 25-hydroxyvitamin D levels positively correlated with FEV1 & FVC Lower serum 25-hydroxy vitamin D levels were associated with a positive response to an exercise challenge.
Freishtat et al., 2010	United States	Cross-sectional case-control study	92 children with asthma and 21 without asthma, aged 6-20 years	Physician-diagnosed asthma	Vitamin D insufficiency and vitamin D deficiency <sup>*</sup> were significantly higher in asthma cases than in controls.
Searing et al., 2010	United States	Cross-sectional study	100 children with moderate-to-severe persistent asthma	Corticosteroid use and airflow limitation	Corticosteroid use and worsening airflow limitation associated with lower 25-hydroxy vitamin D levels in the asthmatic children.
Urashima et al., 2010	Japan	A randomized double-blind, clinical trial	217 school children	Asthma flare-ups	Reduced risk of asthma flare-ups in children with asthma after vitamin D3 supplementation.
Majak et al., 2011	Poland	A randomized, double-blind, parallel-arm clinical trial	48 children with newly diagnosed asthma aged 5-18 years	Asthma flare-ups	Fewer asthma flare-ups in children who received vitamin D3 supplementation as an adjunct to inhaled corticosteroid.
Yadav & Mittal, 2014	India	A randomized, double-blind, placebo-controlled trial	100 children with asthma	Asthma flare-ups Emergency visits PEFR Steroid dosage	Vitamin D3 supplementation reduced the number of flare-ups and emergency visits, increased PEFR, and reduced the requirement of steroids.
Tachimoto et al., 2016	Japan	A randomized, double-blind, placebo-controlled trial	89 school children with asthma aged 6-15 years	GINA asthma control CACT scores	Vitamin D3 supplementation improved GINA asthma control and CACT scores.

<sup>†</sup>Serum 25-hydroxy vitamin D levels <30 ng/ml; <sup>\*</sup>Serum 25-hydroxyvitamin D levels <20 ng/ml; <sup>‡</sup> Determined by spirometry; FEV1= forced expiratory volume in the first second, FVC = forced vital capacity; PEFR=peak expiratory flow rate; GINA=Global initiative for asthma, CACT=childhood asthma control test.

monary function, and atopy, to assess the relationship between their vitamin D status and asthma morbidity.<sup>[39]</sup> Vitamin D insufficiency (serum levels <30 ng/ml) was related to disease flare-ups, atopy and lower FEV1/FVC on spirometry. In an Italian study, Chinellato et al. investigated 75 children with asthma (using lung function and asthma control as outcome measures),<sup>[40]</sup> and 45 children with intermittent asthma (using lung function and exercise-induced bronchoconstriction as outcome measures).<sup>[41]</sup> They reported a direct association of serum vitamin D levels with FEV1 and FVC, as well as with better asthma control.<sup>[40]</sup> Similarly, elevated serum vitamin D levels were associated with high FEV1 and FVC values, whereas low serum vitamin D levels were associated with a positive response to an exercise challenge.<sup>[41]</sup> Using physician-diagnosed asthma as the outcome measure, Freishtat et al. in the United States estimated the vitamin D status of 92 children with asthma and 21 children without asthma.<sup>[42]</sup> They observed that both vitamin D insufficiency and the deficiency (serum level <20 ng/ml) were significantly more elevated in asthmatic children than in their non-asthmatic counterparts. In the same country, Searing et al. evaluated the relationship between serum vitamin D levels in 100 children and asthma severity using corticosteroid use and airflow limitation as to the outcome measures.<sup>[43]</sup> The significant findings of their cross-sectional study were the associations of steroid therapy and deteriorating airflow limitation with lower serum D levels in childhood asthma.

In clinical trials involving supplemental vitamin D3 (calcitriol) in childhood asthma,<sup>[12, 44, 45]</sup> interesting results were also reported. For instance, two trials were conducted in Japan: a randomized, double-blind, clinical trial involving 217 children<sup>[44]</sup> and a randomized, double-blind, placebo-controlled trial on 89 school children with asthma.<sup>[45]</sup> In the former study, asthma flare-ups were used as the outcome measures. The investigators reported a reduced risk of asthma flare-ups after vitamin D3 supplementation in their subjects.<sup>[44]</sup> In the latter study, the outcome measures consisted of Global Initiative for Asthma asthma control and Childhood Asthma Control Test (CACT) scores. Notably, vitamin D3 supplements improved these outcome measures in the study population.<sup>[45]</sup> Elsewhere in Poland, Majak et al. conducted a randomized, double-blind, parallel-arm clinical trial on 48 children with newly-diagnosed asthma.<sup>[10]</sup> Using asthma flare-ups as the outcome measures for the patients who received vitamin D3 supplements as an adjunct to inhaled corticosteroid, they reported fewer flare-ups in these children when compared to the patients on inhaled corticosteroid alone. Finally, Yadav and Mittal in India evaluated the effects of supplemental calcitriol on 100 children with asthma in a randomized, double-blind,

placebo-controlled trial.<sup>[12]</sup> The outcome measures were asthma flare-ups, emergency visits, peak expiratory flow rate (PEFR) and steroid dosage. The major findings were the significant decrease in the frequency of flare-ups and emergency visits, PEFR elevation and decrease in steroid requirements.

## CONCLUSION

There is no consensus yet on the association of maternal vitamin D status with subsequent asthma/wheezing in young children. Although a preponderance of the reports suggests a positive association, a few of them suggest otherwise. Most of the observational studies have, however, shown the efficacy of vitamin D3 (calcitriol) supplementation in reducing asthma morbidity: especially disease flare-ups. Furthermore, this beneficial effect of the vitamin has been corroborated by clinical trials although their sample sizes were small. Trials with larger sample sizes should be able to provide more reliable data on this causal relationship between vitamin D status and childhood asthma. Molecular mechanisms underpinning this relationship need further exploration.

## Disclosures

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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