

Vitamin D and asthma

Sheena D. Brown,¹ H. Hardie Calvert¹ and Anne M. Fitzpatrick^{1,2,*}

¹Department of Pediatrics; Emory University; Atlanta, GA USA; ²Children's Healthcare of Atlanta Center for Developmental Lung Biology; Atlanta, GA USA

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Asthma, one of the most prevalent diseases affecting people worldwide, is a chronic respiratory disease characterized by heightened airway inflammation, airway hyperresponsiveness and airflow obstruction in response to specific triggers. While the specific mechanisms responsible for asthma are not well understood, changing environmental factors associated with urban lifestyles may underlie the increased prevalence of the disorder. Vitamin D is of particular interest in asthma since vitamin D concentrations decrease with increased time spent indoors, decreased exposure to sunlight, less exercise, obesity, and inadequate calcium intake. Additionally, a growing body of literature suggests that there is a relationship between vitamin D status and respiratory symptoms, presumably through immunomodulatory effects of vitamin D. This review discusses vitamin D as it relates to asthma across the age spectrum, with a focus on human studies.

Introduction

Asthma, one of the most prevalent diseases affecting people worldwide, is a chronic respiratory disease characterized by heightened airway inflammation, airway hyperresponsiveness and airflow obstruction in response to specific triggers (Fig. 1). Common symptoms include chest tightness, wheezing, cough and difficulty breathing, which are commonly treated with two different classes of medications: inhaled corticosteroids, used as a daily controller medication, and β -adrenergic agonists, which are used to induce bronchodilation.¹ While the specific mechanisms responsible for asthma are poorly understood, in part due to the marked heterogeneity of the disorder in both adults² and children,³ numerous aberrant immune responses are clearly associated with the disorder.⁴ For example, T-helper cell type-2 (T_H2) cytokines, such as interleukin (IL)-4, IL-5, and IL-13, are upregulated in the asthmatic airway and are associated with increased eosinophilia,^{5,6} mast cell degranulation⁷ and increased levels of immunoglobulin E (IgE).^{6,7} Impairment of immunogenic tolerance, along with complex interactions between cells and inflammatory mediators, ultimately promotes airway injury in a process commonly referred to as airway “remodeling.”⁸ This

process involves smooth muscle hypertrophy, epithelial goblet-cell hyperplasia and permanent deposition of airway extracellular matrix proteins which may ultimately increase airflow obstruction and the respiratory symptom burden of the disorder.⁹

Within industrialized Westernized countries, the prevalence of asthma has steadily increased by 25% to 75% per decade since 1960, causing it to become a major public health concern.¹⁰⁻¹² The increased prevalence of asthma may be influenced by changing environmental factors associated with urban lifestyles. Indeed, numerous dietary hypotheses have been proposed.¹³⁻¹⁵ Among the nutrients and antioxidants included in this hypothesis, vitamin D is of particular interest since vitamin D concentrations decrease with increased time spent indoors, decreased exposure to sunlight, less exercise, obesity, and inadequate calcium intake.¹⁶ Additionally, a growing body of literature suggests that there is a relationship between vitamin D status and asthma-related respiratory symptoms,¹⁷⁻²² presumably through the immunomodulatory effects of vitamin D.^{23,24} This brief review discusses vitamin D as it relates to asthma across the age spectrum, with a focus on emerging human studies over the past decade. A literature review was performed for relevant publications spanning from 2002 to present. Publications were limited to those indexed on PubMed and written in English. Searches were made for “vitamin D” and “asthma,” excluding in vitro and animal studies. Relevant articles identified from this search are discussed below.

Vitamin D Overview

Vitamin D, a fat-soluble nutrient, is a secosteroid hormone which is widely recognized as a modulator of calcium absorption and bone health and further regulates neuromuscular function, cellular differentiation, insulin secretion, and blood pressure.^{25,26} Vitamin D also plays an important role in immune regulation through interactions between 1,25-dihydroxyvitamin D and vitamin D receptors (VDRs). VDRs are expressed on a variety of airway immune cells, where they function as classic nuclear steroid hormone receptors and ultimately regulate the transcription of numerous genes associated with inflammation and immunomodulation.²⁷ Vitamin D also plays an important role in respiratory infection by facilitating Toll-like receptor signaling through increased synthesis of human cathelicidin antimicrobial peptide,²⁸⁻³⁰ which is cleaved to generate the active cationic peptide, LL-37.^{31,32} Vitamin D also exerts direct effects on target

*Correspondence to: Anne M. Fitzpatrick; Email: anne.fitzpatrick@emory.edu
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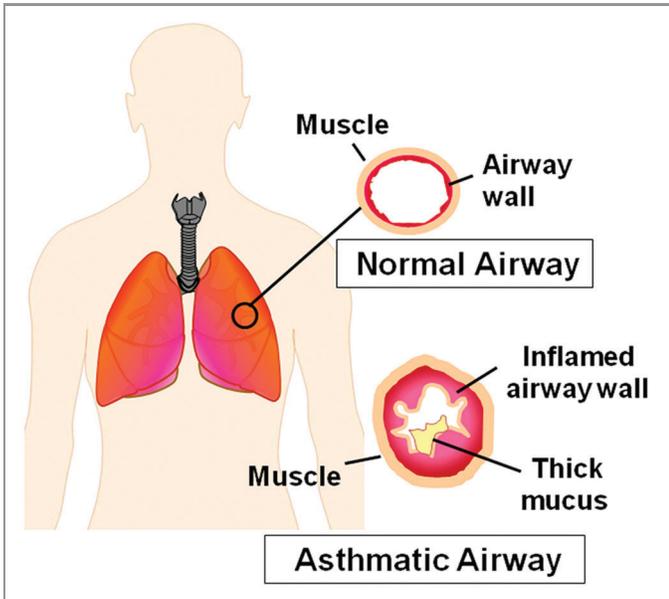


Figure 1. Airway inflammation associated with asthma.

cells independent of gene transcription³³ and may therefore be of relevance to airway inflammatory disorders.³⁴ While vitamin D can suppress IL-17³⁵ and IL-4-mediated expression of IL-13,^{35,36} it can also shift the Th1/Th2 balance toward Th2 dominance.³⁷ These contradictory actions may be due to the direct actions of vitamin D on CD4⁺ T cells to promote an IL-10-secreting T-regulatory population.³⁸

Biosynthesis of vitamin D. Biosynthesis of vitamin D begins primarily with absorption of solar ultraviolet-B (UVB) radiation and secondarily via consumption of vitamin D-rich and fortified foods, such as oily fish, fortified grains and dairy products.²⁶ Following exposure to UVB radiation, 7-dehydrocholesterol within the skin is converted to previtamin D₃ (Fig. 2), and eventually to the prohormone vitamin D₃, which is also referred to as cholecalciferol. Vitamin D₃ is then hydroxylated within the liver by 25-hydroxylase to 25-hydroxy-vitamin D₃ (25(OH)D), the major circulating metabolite of vitamin D. Under parathyroid control, 25(OH)D is hydroxylated by 1- α -hydroxylase in the kidney to its final and biologically active form, 1,25-dihydroxyvitamin D (1,25(OH)₂D₃), a key regulator of calcium and phosphate homeostasis. 1,25(OH)₂D₃, also referred to as calcitriol, is then transported throughout the body via the blood to various cells types that express VDRs, where gene expression is induced.^{24,39} Because the majority of vitamin D metabolism occurs in this skin, several factors are thought to influence vitamin D skin metabolism, including age, body fat, the level of skin melanin, and other variables such as latitude, the amount and degree of sun exposure, and use of sunscreen products with UV protection.⁴⁰ These factors have been

previously associated with vitamin D deficiency in epidemiologic studies.⁴¹⁻⁴³

Vitamin D thresholds. Serum concentrations of 25(OH)D are considered to be a biomarker and indicator of vitamin D status.^{44,45} Although vitamin D insufficiency has traditionally been defined as a serum 25(OH)D concentration of 20 to 29 ng/mL,⁴⁶ a panel of experts from the Institute of Medicine recently suggested that vitamin D insufficiency be redefined as a serum 25(OH)D concentration less than 20 ng/mL.⁴⁷ This recommendation was based on inconclusive evidence for the threshold of 29 ng/mL and evidence for adverse skeletal effects at thresholds less than 20 ng/mL.⁴⁷ However, this revised definition of vitamin D insufficiency has generated significant controversy^{48,49} and thus there is presently no universally accepted definition for “optimal” 25(OH)D concentrations independent of musculoskeletal health.

Maternal/Infant Vitamin D Exposure and Childhood Respiratory Symptoms

The rapid increase in asthma prevalence within Westernized countries is unlikely solely due to genetics. Instead, a number of environmental exposures may also alter the rate of asthma development.⁵⁰⁻⁵⁴ Of these modifiable environmental exposures, the role of diet in asthma is of particular interest^{13,55} since recent studies suggest that the development of asthma in children may be due to in utero exposure to nutrients from the mother’s diet.⁵⁶ Given the role of vitamin D in inflammation and immunomodulation, several studies have focused on in utero vitamin D exposure and subsequent asthma in children. While some studies quantified maternal dietary intake of vitamin D during the final trimester of pregnancy, others measured vitamin D levels within

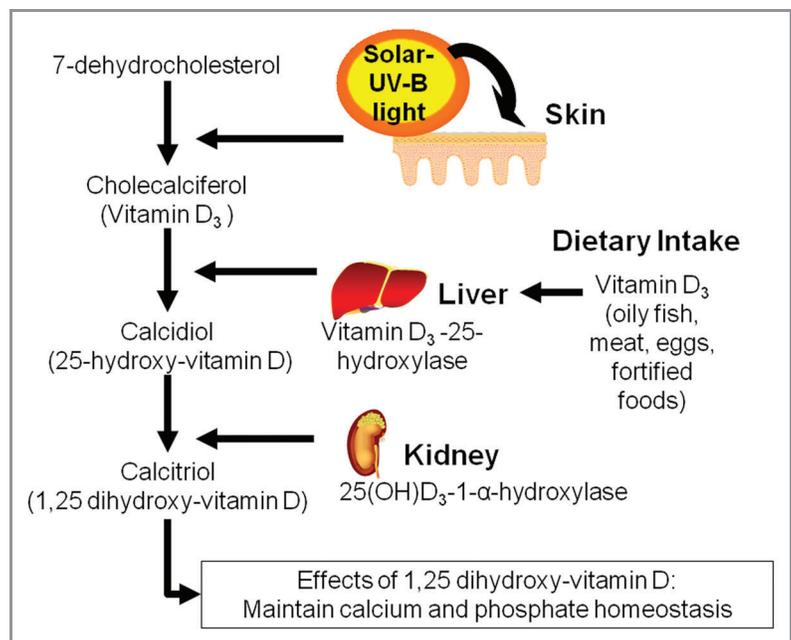


Figure 2. Biosynthesis of vitamin D.

Table 1. Studies of vitamin D exposure in early life and respiratory outcomes

Author	Year	Country	Study Design	Sample Size	Age of children at assessment	Determination of Vitamin D status	Association between vitamin D and respiratory outcomes
Belderbos ⁵⁷	2011	Netherlands	Prospective cohort	156 neonates	Birth to 1 y	Maternal food-frequency questionnaire and cord blood 25(OH)D	Lower 25(OH)D concentrations associated with an increased risk of respiratory syncytial virus infection
Camargo ⁵⁸	2007	United States	Prospective cohort	1194 mother-child dyads	3 y	Maternal food-frequency questionnaire	Highest quartile of vitamin D intake during pregnancy associated with a lower risk of recurrent wheezing
Camargo ⁵⁹	2011	New Zealand	Prospective cohort	922 newborns	Birth to 5 y	Cord blood 25(OH)D	Higher 25(OH)D associated with a decreased risk of respiratory infection and wheezing but no associations with childhood asthma noted
Carroll ⁶⁰	2011	Canada	Cross-sectional	340 mother-infant dyads	5–29 weeks	Maternal whole blood 25(OH)D	Increasing maternal 25(OH)D associated with decreased odds of asthma in mothers but no associations with infantile wheezing noted
Devereux ⁶¹	2007	Scotland	Prospective cohort	2000 pregnant women, 1212 children	5 y	Maternal food-frequency questionnaire	Highest and lowest maternal vitamin D intakes associated with lower risk of wheezing
Erkkola ⁶²	2009	Finland	Prospective cohort	1669 mother-child dyads	5 y	Maternal food-frequency questionnaire	Higher maternal vitamin D intake associated with lower risk of asthma and allergic rhinitis
Gale ⁶³	2008	UK	Prospective cohort	466 mothers and 178 children	9 mo and 9 y	Maternal serum 25(OH)D	Maternal vitamin D levels > 75 nmol/L associated with increased risk of atopic dermatitis and asthma
Miyake ⁶⁴	2010	Japan	Prospective cohort	763 mother-child dyads	16–24 mo	Maternal food-frequency questionnaire	Higher maternal vitamin D intake associated with a decreased risk of wheeze and atopic dermatitis
Morales ⁶⁵	2012	Spain	Prospective cohort	1724 children	12 mo, 4–6 y	Maternal plasma 25(OH)D	Increased maternal 25(OH)D associated with a decreased risk of lower respiratory infections but not wheezing or asthma
Rothers ⁶⁶	2011	United States	Prospective cohort	219 children	Birth to 5 y	Cord blood 25(OH)D	Both low and high cord blood 25(OH)D associated with increased aeroallergen sensitization but not with allergic rhinitis or asthma

the plasma and whole blood of pregnant women (Table 1). Several of these studies noted an inverse relationship between maternal vitamin D intake and the risk of subsequent wheezing in young infants and preschool children.^{58,61,62,64} However, vitamin D intakes varied considerably between geographic locations, from 548 IU/day in the United States⁵⁸ and 260 IU/day in Finland⁶² to 248 and 137 IU/day in Japan⁶⁴ and Scotland,⁶¹ respectively. It is also important to note that associations between prenatal vitamin D exposure, wheezing and subsequent asthma have not been consistent across studies. Whereas Devereux et al.⁶¹ did observe a negative association between vitamin D intake and wheezing in preschool children, no associations between vitamin D intake and asthma were noted in children 5 y of age. Similarly, in a Finnish birth cohort, infants supplemented with vitamin D during the first year of life were not more likely to have asthma in early adulthood.⁶⁷ Rather, in that study⁶⁷ and another,⁶⁸ the prevalence of allergic sensitization was greater at age 6 and age 31 y in those subjects who received regular vitamin D supplementation during infancy.

In other birth cohort studies where 25(OH)D concentrations were measured in the plasma and whole blood of pregnant

women, median 25(OH)D concentrations ranged from approximately 20 to 29.5 ng/mL.^{60,63,65} A 50% decrease in the odds of maternal asthma was further observed with every 35 nmol/L increase in 25(OH)D levels, suggesting a possible link between vitamin D status and asthma during pregnancy.⁶⁰ However, similar to the studies of maternal vitamin D intake, no consistent relationships between 25(OH)D concentrations and respiratory symptoms during childhood have been observed. For example, while Carroll et al.⁶⁰ failed to find an association between maternal 25(OH)D concentrations and the development of respiratory infections in their offspring, Morales et al.⁶⁵ found that circulating maternal 25(OH)D concentrations were associated with a lower risk of lower respiratory tract infections during infancy. However, again, no associations between maternal 25(OH)D and wheezing and asthma in childhood were noted.⁶⁵

To further delineate the role of vitamin D and childhood allergic disease, several studies have also examined concentrations of 25(OH)D in cord blood from newborn infants. In a recent cohort study based in the United States, cord blood 25(OH)D concentrations below 20 ng/ml were associated with increased IgE levels and aeroallergen sensitization.⁶⁶ Two similar birth

cohorts in New Zealand⁵⁹ and the Netherlands⁵⁷ also found that children with lower concentrations of cord-blood 25(OH)D had an increased risk of respiratory viral infection and wheezing during infancy. However, in these studies, there were no associations between cord-blood 25(OH)D concentrations and subsequent asthma at 5 y of age.^{59,66}

Collectively, these studies suggest that the benefits of vitamin D during early life may be limited to its effects on respiratory infections and viral-induced wheezing and not asthma *per se*.¹⁷ However, although vitamin D may have important roles in immune regulation during early life, excessive vitamin D exposure may also be associated with adverse health outcomes. For example, Rothers et al.⁶⁶ found that both low (< 20 ng/mL) and high (> 40 ng/mL) cord blood 25(OH)D concentrations were associated with increased IgE levels and aeroallergen sensitization. This finding is similar to other studies where an increased risk of allergic sensitization was noted in infants who received vitamin D supplementation.^{67,68} Likewise, Gale et al.⁶³ noted that maternal 25(OH)D concentrations greater than 75 nmol/L (30 ng/mL) were associated with 5-fold increased odds of asthma at 9 y of age in the exposed children. However, it is important to note that a large percentage of children were lost to follow-up, and thus the resulting sample of mothers had higher concentrations of 25(OH)D and were older, less likely to smoke during pregnancy, and more educated.⁶³ Therefore while there may be therapeutic window for vitamin D supplementation

in early life, further studies are needed to more clearly understand the risks of high vitamin D intake and bioavailability during the early childhood years.

Vitamin D in School-Aged Children with Asthma

Several recent studies have shown associations between vitamin D status and asthma outcomes in school-age children (Table 2), although there is considerable variation between the study populations. Of particular interest is the finding of racial disparities in vitamin D status. Due to higher levels of melanin, African Americans have the highest prevalence of vitamin D deficiency, with the highest prevalence in those living in urban environments.^{43,76} At the same time, asthma is also more prevalent in African American children.^{10,11} Only one study to date has focused on vitamin D status in school-aged African American asthmatic children. In this cross-sectional case-control study, Freishtat et al.⁷² demonstrated that 25(OH)D concentrations were ~54% lower in African American children with asthma when compared with African American children without asthma (23.1 vs. 40 ng/mL, respectively). However, 25(OH)D concentrations in the non-asthmatic group were significantly higher than previously-reported average values in African American children.²¹ The Childhood Asthma Management Program study, which consisted of a racially diverse population, also found that 24% of vitamin D deficient subjects were African American, compared

Table 2. Studies of vitamin D status in school-age children with asthma

Author	Year	n (% male)	Age (years)	Study Design	Sample	Outcome Measures	Findings
Brehm ⁴¹	2009	616 (60)	8.7	Cross-sectional	Mild-to-severe persistent asthma	Asthma exacerbations	Increased 25(OH)D associated with reduced hospitalization, reduced anti-inflammatory medication use and reduced airway hyperresponsiveness
Brehm ⁶⁹	2010	1024 (60)	8.9	Prospective cohort	Mild-to-moderate persistent asthma	Hospitalization or emergency department visit	Baseline 25(OH)D levels < 30 ng/mL associated with higher odds of hospitalization or emergency department over 4 y
Chinellato ⁷⁰	2011	75 (60)	9.6	Cross-sectional	Well-controlled and poorly controlled asthma	Spirometry, asthma control	Positive correlations noted between 25(OH)D and asthma control
Chinellato ⁷¹	2011	45 (60)	10	Cross-sectional	Intermittent asthma	Lung function and airway hyperresponsiveness	Lower serum 25(OH)D associated with decreased lung function and increased airway hyperresponsiveness with exercise
Freishtat ⁷²	2010	92 (63)	11.1	Cross-sectional	African Americans with and without asthma	Physician-diagnosed asthma	Decreased 25(OH)D in asthmatics vs. controls
Majak ⁷³	2011	48 (67)	11.5	Randomized, double-blind, parallel arm clinical trial	Newly diagnosed asthma	Asthma exacerbations	Fewer exacerbations in children with vitamin D ₃ supplementation added to inhaled budesonide
Searing ⁷⁴	2010	100 (64)	7	Cross-sectional	Moderate to severe persistent asthma	Corticosteroid use and airflow limitation	Decreased 25(OH)D associated with lower lung function and higher corticosteroid requirements
Urashima ⁷⁵	2010	217 (57)	10.0	Randomized, double-blind clinical trial	Schoolchildren (allcomers), subgroup with physician-diagnosed asthma	Asthma exacerbations	Reduced risk of asthma exacerbations in the subgroup with asthma after vitamin D ₃ supplementation

with only 7% in the vitamin D sufficient group.⁶⁹ The factors responsible for the racial disparity in vitamin D status are unclear and warrant further study.

Other cross-sectional studies of vitamin D status have also examined the associations between 25(OH)D concentrations and asthma control in school-age children. In both North American and Costa Rican populations, Brehm et al.^{41,69} found that 25(OH)D insufficiency was associated with increased total IgE concentrations, eosinophil counts, airway hyperresponsiveness, and increased symptoms and exacerbations. Similarly, in Italian studies, asthma control, lung function, and airway hyperresponsiveness were positively correlated with serum levels of 25(OH)D.^{70,71} Searing et al.⁷⁴ also noted lower lung function, increased corticosteroid requirements, and increased aeroallergen sensitization in children as a function of decreased 25(OH)D concentrations. While these studies show intriguing associations between vitamin D insufficiency (or deficiency) and asthma control, the cross-sectional nature of the 25(OH)D measurement and outcome assessment prevents causal interpretation. For example, reverse causation may be responsible for the findings, in that children with more poorly controlled asthma may be less likely to go outdoors and therefore may have lower 25(OH)D concentrations as a result of their illness.

Given the limitations associated with these epidemiologic studies, randomized controlled trials of vitamin D are needed in children to better understand the causal relationship between vitamin D status and respiratory outcomes such as asthma control in this population. However, few such trials have been performed. In one recent randomized, double-blind, placebo-controlled trial, Urashima et al.⁷⁵ compared 1,200 IU/day of vitamin D₃ vs. placebo administered to Japanese schoolchildren (all comers) age 6–15 y during the winter months. Although the primary outcome was the incidence of influenza infection, sub-analyses within the group of children with existing asthma were also performed with asthma exacerbations as a secondary outcome. In these sub-analyses, vitamin D₃ supplementation was associated with a decreased risk of exacerbations compared with placebo, with a

relative risk of 0.17.⁷⁵ Similarly, in a more recent randomized, double-blind 6-mo trial where 800 µg of inhaled budesonide was administered daily to a small group of 48 children with asthma in the presence or absence of 500 IU/day of vitamin D₃, children receiving supplemental vitamin D did not have a reduction in 25(OH)D during the winter months and also had a reduced risk of asthma exacerbations triggered by acute respiratory viral infections.⁷³ These initial findings suggest that vitamin D supplementation may have therapeutic benefit children with asthma, although additional randomized, double-blind, placebo-controlled studies are needed.

Vitamin D in Adults with Asthma

In adults, the recommended dietary intake for vitamin D ranges from 600 to 800 IU daily.⁴⁷ However, despite the large variety of foods supplemented with vitamin D, a large proportion of the adult population remains vitamin D deficient,^{77,78} perhaps due in part to inadequate sun exposure and the rising prevalence of obesity which can lead to decreased vitamin D bioavailability.⁷⁹ Similar to the studies in school age children, a number of cross-sectional studies in adults have also demonstrated associations between vitamin D status and asthma control (Table 3). Using data from the National Health and Nutrition Examination Survey, Keet et al.⁸¹ found that serum 25(OH)D concentrations were inversely related to current wheezing and asthma in subjects 6 y and older across the lifespan, such that a 10 ng/mL decline in 25(OH)D was associated with 20% increased odds of wheezing and 8% increased odds of asthma. Furthermore, in those subjects with current asthma, lower 25(OH)D concentrations were associated with increased odds of asthma exacerbations and healthcare utilization in the preceding year.⁸¹ Other studies have also noted associations between decreased serum 25(OH)D concentrations and decreased lung function, increased airway hyperresponsiveness to methacholine, and blunted glucocorticoid responsiveness.^{80,82,84} However, in a recent case-control study of obese subjects with and without asthma, no associations between

Table 3. Studies of vitamin D status in adults with asthma

Author	Year	n (% male)	Age (years)	Study Design	Sample	Outcome Measures	Findings
Black ⁸⁰	2005	14,091 (55)	> 20 y	Cross-sectional	General US population	Lung function	Higher serum 25(OH)D associated with increased lung function
Keet ⁸¹	2011	6857 (49)	23.6	Cross-sectional	General US population	Wheeze, history of asthma, and asthma exacerbation	Higher serum 25(OH)D associated with decreased odds of current wheezing and asthma as well as emergency visits for asthma and asthma exacerbations
Li ⁸²	2011	435 (38)	48.57	Cross-sectional	Newly diagnosed asthmatics	Lung function, total serum IgE	Higher 25(OH)D associated with greater lung function with no associations noted for IgE
Oren ⁸³	2008	290 (26)	43	Cross-sectional	Obese patients	Asthma and allergic rhinitis	25(OH)D deficiency (< 25 ng/mL) associated with increased odds of atopic dermatitis but no associations with asthma
Sutherland ⁸⁴	2010	54 (43)	38.3	Cross-sectional	Persistent asthma	Lung function, airway hyper-responsiveness, glucocorticoid responsiveness	Decreased 25(OH)D associated with decreased lung function, increased airway hyperresponsiveness, and reduced glucocorticoid responses

Table 4. Genetic studies of vitamin D and asthma

Author	Year	n	Location/ Population	Outcome Measures	Findings
Bossé ⁸⁶	2009	1,064	Québec, Canada/ French-Canadian families	Genotype of genes involved in the vitamin D pathway	SNPs in IL10, CYP24A1, CYP2R1, IL1RL1 and CD86 were associated with asthma and atopy
Poon ⁸⁷	2004	1,139	Quebec	VDR genetic variants in family-based cohorts	Six allelic variants were associated with asthma, while four variants were associated with atopy
Raby ⁸⁸	2004	582	United States/ Multi-center	Twenty-eight loci in 7 positional candidates were genotyped	VDR polymorphism demonstrated significant transmission distortion
Saadi ⁸⁹	2009	1,090	Jinan China/ Han population	SNPs in the VDR	Only one marker showed a significant association with asthma. Haplotype analysis of the VDR polymorphisms showed a significant association with asthma
Vollmert ⁹⁰	2004	32	Munich, Germany/ German	SNPs in the VDR and integrin β7	None of the SNPs were associated with asthma
Wjst ⁹¹	2005	951	Munich, Germany/ Germany and Sweden	13 SNPs in the VDR	In unaffected siblings, allele in the 5' region was undertransmitted while two other alleles in the 3' terminal region were overtransmitted
Wjst ⁹²	2006	947	Munich, Germany/ Germany and Sweden	Serum levels of vitamin D and genotyping of DNA single base variants	At least one positive SNP with a transmission disequilibrium of for asthma or total IgE and vitamin D was found in several genes

vitamin D status and asthma prevalence were noted.⁸³ The cross-sectional nature of these studies should again be emphasized since causation cannot be determined due to potential confounding of the study results. Ultimately, randomized controlled trials of vitamin D are needed in adults with asthma to determine the causal associations between vitamin D and asthma and to develop an evidence base for treatment. In the first known clinical trial focused on the role of vitamin D in allergic disease, Rappaport et al.⁸⁵ found that supplementation with 60,000 to 30,000 IU of vitamin D₂ per day resulted in significant relief of asthma and hay fever symptoms in more than 96% of patients suffering from asthma and seasonal allergies. Thus, vitamin D may have therapeutic effectiveness in adults with asthma, but more studies are clearly needed.

Genetics of Vitamin D and Asthma

Some studies have focused on genetic associations between vitamin D and asthma in larger populations. Of these, five studies have explored the relationship between VDR polymorphisms and asthma (Table 4).⁸⁷⁻⁹¹ While three of the studies found associations between several VDR polymorphisms and asthma,⁸⁷⁻⁸⁹ others found no such association.^{90,91} However, in the study by Vollmert et al.,⁹⁰ only one single SNP was examined as opposed to multiple variables. Additionally, all of the studies except Saadi et al.⁸⁹ included family-based cohorts.

Only a handful of studies have evaluated the link between asthma and polymorphisms in other genes involved in vitamin D synthesis, bioavailability and metabolism. In one study, modest associations were noted between several genes in the vitamin D pathway and asthma and allergic sensitization in populations enriched for subjects with current asthma.⁸⁶ A separate study of asthmatics also found haplotype associations for *CYP24A1*, the

primary enzyme associated with calcidiol metabolism, where a 5-point haplotype was associated with asthma, allergic sensitization, and vitamin D metabolites in asthmatic subjects.⁹² While these preliminary results suggest that genetic components may account for vitamin D status in subjects with asthma, other studies are needed to determine tease out the genetic vs. environmental underpinnings of vitamin D status in this population.

Conclusion

There is a growing interest in the role of vitamin D in asthma and respiratory disorders across the lifespan. While several observational studies and a handful of small clinical trials suggest that vitamin D may be beneficial in asthma and wheezing disorders resulting from respiratory viral infections, findings are not consistent. These studies also differ significantly in terms of the populations studied, the timing of the vitamin D intake assessments and the 25(OH)D sampling, the 25(OH)D thresholds used for determining insufficiency, and the respiratory outcomes of interest. Because of the limitations of observational studies which include confounding by indication, definitive recommendations for vitamin D in subjects with asthma across the lifespan cannot be made. Ultimately, randomized, double-blind, placebo-controlled studies are needed in asthma populations to sort out causal relationships between vitamin D status and outcomes and to develop recommendations for treatment. Further mechanistic studies are also needed to understand the mechanisms by which vitamin D exerts its effects both in healthy individuals and subjects with chronic inflammatory disorders such as asthma.

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