

## Review Article

# The Role of Vitamin D in Pediatric Asthma

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Submitted: 31 October 2014

Accepted: 10 January 2015

Published: 12 January 2015

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## Keywords

- Vitamin D
- Asthma
- Atopy
- Allergen immunotherapy
- Pediatrics

## Abstract

The detrimental effects of vitamin D deficiency in pediatrics have become increasingly apparent and extend beyond skeletal health. Unfortunately, vitamin D deficiency is highly prevalent in atopic pediatric patients, in whom it may disrupt the immune system and induce significant worsening of reactive airways. This review presents evidence that lung development and immune regulatory functions are vitamin D-dependent. We also review clinical studies that explore how vitamin D supplementation may prevent respiratory infections and help improve asthma control, and we elaborate how these effects may vary among populations. We reveal the strong need of screening measures for vitamin D deficiency in high risk pediatric populations, particularly African-Americans, Hispanic-Americans, and children with obesity. Finally, we emphasize that all children, especially those who are asthmatic, should be assessed to ensure adequate intake or supplementation with at least the minimum recommended doses of vitamin D. The simple intervention of vitamin D supplementation may provide significant clinical improvement in atopic disease, especially asthma.

## VITAMIN D AND ASTHMA IN CHILDREN

Vitamin D has long been established as necessary for bone metabolism. Vitamin D deficiency is generally defined as serum 25-hydroxyvitamin D [25(OH)D] levels < 20ng/mL, with 20-30 ng/mL considered insufficiency, although current endocrine guidelines recommend maintenance of circulating levels between 40ng/mL and 60ng/mL [1]. Current vitamin D intake recommendations for children are based upon bone health and the prevention of rickets. Recent studies have also found an important role of vitamin D in extra skeletal health, particularly in asthma and immune function, which is the subject of this review.

### Vitamin D has basic regulatory roles in immune cells

Almost all cells in the body possess vitamin D receptors, including cells of the immune system. This has fueled more research and hypotheses that vitamin D may be integral to immune system regulatory functions. Vitamin D deficiency can affect Th1 and Th2 cytokines, which may also contribute to the development of atopy [2,3]. Neonatal mice with vitamin D deficiency develop a Th2-skewed pulmonary immune phenotype and reduced IL-10-secreting T regulatory cells [4].

Studies also suggest an inhibitory effect of vitamin D on Th17 response [5,6]. Th17 cells are inflammatory cells and thought to have a role in asthma pathogenesis, including nonatopic asthma [7]. By culturing CD4+ T cells under Th17 polarizing conditions, one study found higher Th17 cell differentiation in young asthmatic patients than in healthy controls, and this was inhibited in both groups by the addition of 25(OH)D [5]. It has also been

shown that vitamin D can restore the capability of regulatory T (T reg) cells to secrete IL-10 in response to dexamethasone in steroid-resistant patients with asthma [8]. Downregulation of Foxp3, a transcription factor important in the development of regulatory T cells, is associated with allergic asthma [9]. In atopic asthmatic children undergoing allergen immunotherapy (IT) and receiving vitamin D supplementation, improvement of clinical symptoms was associated with higher induction of Foxp3+ cells and higher TGF- $\beta$  production during 12 months of IT, both of which correlated with serum 25(OH)D levels [10,11].

Vitamin D Receptor (VDR) activation inhibits IgE expression in B cells and enhances IL-10 expression, which studies show can protect against atopic conditions [12-14]. However, the absence of VDR resulted in failure to generate airway hyperreactivity in a mouse model, which was attributed to defective invariant natural killer T (iNKT) cells [15]. VDR knockout mice have significantly fewer iNKT cells and have Th2 cells that may produce less IL-13 and less IL-4, although this result was inconsistent [15]. Studies on mice in utero demonstrated that vitamin D deficiency resulted in a significant reduction of iNKT cells due to increased apoptosis of early iNKT cell precursors in the thymus [16]. Whether these impaired iNKT responses are responsible for protection against airway hyperreactivity cannot be deduced. Other negative effects have been found in VDR deficient mice, particularly in the development of autoimmunity. One study concluded that VDR mediates T cell homing to the gut, resulting in low levels of IL-10 in VDR knockout mice as well as an increased inflammatory response and greater propensity to inflammatory bowel disease in an experimental model [17]. The complete lack of VDR is an

extreme situation; and increased VDR activation may still be superior to insufficient VDR activation in protecting against atopy in routine circumstances.

In a murine model of allergic airway inflammation, coadministration of 25(OH)D with OVA-specific immunotherapy reduced allergic airway inflammation and responsiveness upon OVA challenge [18]. Reduced Th2 cytokine expression in murine lungs was also found when 25(OH)D was coadministered as compared to IT alone [18]. Furthermore, one murine model revealed that vitamin D deficiency in early life does not affect airway hyperreactivity but is associated with increased disease severity with greater eosinophilic inflammation and airway remodeling, both of which improved with vitamin D supplementation [4]. The systemic effects of VDR activation are not yet fully understood and the effects found in animal models cannot yet be extrapolated to humans. However, these studies are insightful in that vitamin D and VDR may have great involvement in early immune system regulation.

### Vitamin D promotes lung development

Recent data suggest that the physiologic hormone 1,25-dihydroxycholecalciferol, the active form of vitamin D, is a paracrine factor that modulates fetal lung maturation and airway smooth muscle cell proliferation and differentiation, although the mechanisms are unclear [19]. The effects of perinatal vitamin D deficiency on overall pulmonary function were explored in an animal model, using tracheal contraction as a functional marker of airway contractility [20]. An increase in airway resistance following methacholine challenge was found in those animals that lacked cholecalciferol (vitamin D3) supplementation in the animal diet, but not in those that were supplemented with low or high dose vitamin D3 [20]. High dose perinatal vitamin D3 supplementation appeared to effectively block the increase in tracheal contractility that developed in the deficient group [20]. Additionally, several human studies have found that deficient cord blood vitamin D levels are associated with increased risk of early wheezing or recurrent lung symptoms in young children, though not with asthma [21-23]. Asthma is frequently diagnosed later in childhood however, and one study found a negative association of maternal vitamin D intake and the presence of physician-diagnosed asthma in 10-year-olds [24].

### High Dose Vitamin D Supplementation May Yield Fewer Primary Care Visits for Acute Respiratory Infection

Vitamin D deficiency predisposes to infection in part due to effects on cathelicidin, an antimicrobial peptide. Cathelicidin is a chemoattractant for neutrophils and monocytes, and it enhances microbial killing in phagocytic vacuoles. Cathelicidin has a vitamin D-dependent mechanism [25]. Airway inflammation caused by viral infections, particularly respiratory syncytial virus (RSV), has been found in basic studies to be decreased by vitamin D replacement [26].

In one randomized, double-blind, placebo-controlled study in New Zealand, 260 women and their infants were assigned to placebo or low or high dose vitamin D from 27 weeks gestation to delivery and from birth to age six months, respectively. It was

found that children from the placebo group had a significantly higher proportion (99%) of doctor's visits for acute respiratory infections from birth to 18 months of age, compared to those children receiving high dose vitamin D (87%) [27]. Interestingly, this effect was mainly due to the significantly lower number of visits between ages 6-18 months [27]. At six months of age, an infant's maternal antibodies are continuing to wane and an infant is gradually increasing the development of his or her own antibodies. It is possible that the influence of vitamin D becomes more important in an infant's immune system at this time point, by unclear mechanisms. The clinical effect of fewer primary care visits was significant only in the group receiving the higher doses of vitamin D (2000IU/800IU versus 1000IU/400IU in mother and infant, respectively) [27]. A possible dose-dependent response to vitamin D is suggested, and it is possible that there is a threshold level of vitamin D required to induce measurable effects.

The high dose of vitamin D in this study is greater than the minimum dose recommended by the current guidelines of the American Academy of Pediatrics (AAP). The AAP recommends a minimum daily intake of 400IU of vitamin D for all children, beginning at birth and based on the prevention of rickets [28]. The U.S. Endocrine Society recommends 400-1000IU of vitamin D intake per day for infants, 600IU-1000IU daily for children ages 1 and older, and 1500-2000IU daily for those aged 19 years and older [27]. The minimum daily intake recommendations by age are summarized in Table 1 [1]. It is not yet known whether these minimum recommended amounts are enough to provide all of the potential nonskeletal health benefits associated with vitamin D. In order to raise serum 25(OH)D levels consistently above 30ng/mL, at least 1000IU per day in children and 1500-2000IU per day in adults may be required [1]. Recommendations do not distinguish between vitamin D2 and D3, although some studies suggest vitamin D3 may be more efficacious [30,31]. Of note, in many countries, as in the aforementioned New Zealand study, foods are not mandated to receive fortification of vitamin D as in the United States [27]. Whether residents of countries without routine fortification would require a greater dose of supplementation is unclear. Regardless, it is possible that the dose of vitamin D sufficient to prevent rickets is inadequate to yield beneficial immune effects in some patients. Analysis in the aforementioned study revealed the number needed to treat is 9 pregnant women and infant pairs with high dose vitamin

**Table 1: Recommended Minimum Daily Intake of Vitamin D.**  
Established by the The U.S. Endocrine Society for bone health [1].

Age	Vitamin D2 or D3 dose per day
< 1 year	400IU
1 - 19 years	600IU
19-70 years	600IU
70+ years	800IU

#### Common Terms

25(OH)D = major circulating form of vitamin D and best indicator of vitamin D status

Cholecalciferol = vitamin D3

Ergocalciferol = vitamin D2

Vitamin D sufficiency:  $\geq 30$  ng/mL

Vitamin D insufficiency: 20-29 ng/mL

Vitamin D deficiency: < 20 ng/mL

D supplementation in order to prevent one acute respiratory infection visit, which compares favorably with other preventive health strategies [27].

### **African-American children should be screened for vitamin d deficiency**

It has long been established that African-American children and children with obesity are at greater risk for vitamin D deficiency [32]. Adipose tissue takes up vitamin D, which is a fat-soluble vitamin. Unfortunately, obesity is also associated with greater prevalence of asthma and risk of asthma exacerbations [33-35]. African-American children are also disproportionately affected with asthma, and this disparity increased from 2001-2010, after which black children were reportedly twice as likely as white children to have asthma [36,37]. African-American children also experience greater clinical severity of asthma. Black asthmatic children are four times as likely as white asthmatic children to be hospitalized [38]. In preschool children with severe intermittent wheezing treated with inhaled corticosteroid therapy, vitamin D deficiency was associated with a higher rate of exacerbations that required oral steroids, and this was statistically significant only in nonwhite children [39].

Cutaneous vitamin D synthesis can be limited by darker skin pigmentation due to increased melanin, as well as by seasonal and atmospheric factors that limit the availability of UV light. Black adults incur changes in serum 25(OH)D only with extreme frequency of outdoor exposure [40]. The racial disparity was so large that black adults who engaged in daily outdoor activity still had lower vitamin D levels than inactive white adults [40]. Baseline levels of 25(OH)D in urban African-American children were not higher in those who spent greater time outdoors, and there was no seasonal variation found [41]. Therefore, increased outdoor exposure is unlikely to correct the high rates of vitamin D insufficiency in black urban children [41]. Furthermore, vitamin D insufficiency has been reported to have high prevalence even in equatorial populations. Outdoor exposure did not provide sufficient vitamin D to children in one Costa Rican study [42]. As children with dark skin pigmentation are even more likely to have inadequate dermal vitamin D production, other sources, namely diet and supplementation, are frequently necessary. Current guidelines state that all at-risk children, including African-American and Hispanic-American children as well as children with obesity should have screening 25(OH)D levels performed [1].

### **Optimal vitamin D level may vary with genotype**

While vitamin D supplementation generally will increase serum 25(OH)D over time, 25(OH)D levels can be influenced by many unidentified factors including genetic predisposition. Several candidate genes are possibly influential on circulating 25(OH)D including VDR which encodes the vitamin D receptor, CYP2R1 which encodes the microsomal 25-hydroxylase, and GC which encodes the vitamin D binding protein [43-45]. One meta-analysis of eight case-control studies found that VDR polymorphisms, specifically TaqI and BsmI, contribute to asthma susceptibility overall. They found that FokI VDR polymorphisms were also significantly associated with increased asthma risk in certain populations [46]. One report found no association

between VDR polymorphisms and asthma prevalence but did find that the VDR ApaI genotype was positively associated with well-controlled asthma and fewer daily activity limitations [45]. The ET/ET genotype of vitamin D binding protein was reported to confer protection against the development of asthma (OR 0.63 v. 1.0,  $p < 0.05$ ) compared with the wild type genotype DT/DT in a young Hispanic population [44]. Finally, an association of the genotype of CYP27B1, a vitamin D activation enzyme, was demonstrated with 25(OH)D concentration. The correlation only occurred in summer/autumn but not winter/spring [47]. The study also revealed a nonlinear association between 25(OH)D and IgE levels, with IgE elevated at both high and low vitamin D levels [47]. There may be increased risk of disease outcomes at both high and low concentrations of 25(OH)D because the optimal concentration of 25(OH)D varies according to genotype [43]. Furthermore, expressions of genes may vary by season, suggesting differing affinities to vitamin D from diet and sunlight throughout the year [47].

Vitamin D insufficiency is common in a predominantly African-American and urban pediatric population. However, the levels of 25(OH)D did not differ significantly in such children presenting with no respiratory illness versus those presenting with varying degrees of respiratory illness, though the majority had insufficient 25(OH)D levels [48]. Similarly, a high prevalence of vitamin D insufficiency and deficiency was found in a different study of 125 children, and there was no relationship between serum level and asthma control [49]. It is possible that any influence of vitamin D was not revealed in just one point in time, especially when a wide spectrum of disease severity was being examined. It is also possible that the threshold needed for these extraskeletal vitamin D benefits was not reached in these particular populations. Young children ages 1-3 diagnosed with wheeze were found to have significantly lower 25(OH)D levels compared to age-matched controls [50]. Another study found no association of self-reported asthma and 25(OH)D levels in 10-year-olds but did not evaluate asthma symptoms further [51]. A retrospective, case-control study also found no difference in 25(OH)D levels between asthmatic children and controls, although there was a significant negative relationship with obesity [52]. While many studies have conflicting results, it is difficult to assess possible reasons for this when comparing studies with differing methodology. It is especially challenging because numerous pediatric studies on vitamin D and asthma have different inclusion criteria, outcome measures, and frequently major methodological shortcomings that limit confidence in the findings [53].

One study did find that children with both low and high 25(OH)D levels had increased risk of current wheeze, again suggesting a possible U-shaped association between vitamin D levels and respiratory health [43,54]. A population based study found low serum 25(OH)D levels were remarkably common in a Taiwanese pediatric population, with 90.3% of children insufficient, including 51% which were deficient, but no association with asthma was found [55]. Vitamin D insufficiency may be less detrimental toward the development of asthma in certain populations. If different populations have varying thresholds, there may be varying degrees at which vitamin D deficiency becomes influential on clinical outcomes. This study endorses the view that different genotypes are affected by

vitamin D differently. More research is needed to ascertain which populations would benefit most from vitamin D supplementation.

### **Vitamin D deficiency correlates with asthma severity in a wide age range**

Many clinical studies signify that vitamin D has an important role in the development of childhood asthma [50,56,57]. A study examining children with persistent asthma treated with inhaled steroids found a greater improvement of lung function over one year in children with vitamin D sufficiency versus deficiency [56]. Another study examined vitamin D levels in asthmatics ages 3-8 years old and a nonasthmatic control group [57]. Vitamin D deficiency was common in both groups, with no difference in 25(OH)D levels between the two groups. However, the total number of exacerbations, asthma severity, and systemic glucocorticoid need in the previous year were significantly greater in those with vitamin D deficiency [57]. This study supports the idea that the influence of vitamin D may be subtle or more likely to be revealed over a greater timeframe. Levels of 25(OH)D do not always correlate with the presence of asthma alone [51,57]. However, vitamin D levels have frequently been shown to significantly correlate with clinical severity of asthma, as in the aforementioned study [57]. Additionally, children with severe therapy-resistant asthma have been shown to have significantly lower vitamin D levels than children with moderate asthma [58]. Vitamin D supplementation has been shown to increase steroid responsiveness in steroid-resistant patients [8,59,60].

Children ages 3-24 months with wheezing due to RSV infection, a significant risk factor for the development of asthma, were found to have significantly lower vitamin D levels at presentation to an emergency department (ED) compared to controls [61]. Additionally, it was found that those children who suffered more respiratory tract infections and severe wheezing attacks in the previous year had lower vitamin D levels, and they also had greater frequency of ED visits, ICU admissions and longer hospital stays [61]. Another study evaluating 25(OH)D levels in 1315 children ages 5-18 found a beneficial effect of vitamin D on asthma, as those with insufficient vitamin D levels had significantly lower FVC and lower FEV1 on pulmonary function tests when compared to those with sufficient levels, by a mean difference of 81.9mL and 55.2mL, respectively [62]. An association of vitamin D insufficiency and exercise-induced airway reactivity has also been found [63].

The first prospective study showing that control of newly diagnosed asthma in children can be facilitated by vitamin D supplementation examined 48 school-aged, dust mite-allergic children with newly diagnosed asthma that had not yet been treated with inhaled steroids [64]. A significant positive correlation of 25(OH)D levels with baseline Asthma Therapy Assessment Questionnaire score and negative correlation with severe clinical manifestations of asthma was found. After 6 months of inhaled budesonide, those children who were also supplemented with 500IU of vitamin D3 had significantly fewer asthma exacerbations (46% v. 17%) [64]. When patients with high baseline 25(OH)D levels were examined separately, there was no significant clinical benefit found, suggesting that the protection of vitamin D supplementation is most apparent in those with more deficient levels [64]. Positive effects of vitamin

D on reduction of asthma symptoms and steroid use was also supported by the findings in 100 asthmatic children that indicated a significant positive correlation of vitamin D levels with FEV1 and FEV1/FVC ratio and significant inverse correlation of 25(OH)D levels with inhaled steroid use, oral steroids, and total steroid dose [65].

Clinical and immunologic efficacy of allergen IT has been correlated with 25(OH)D serum concentration in young asthmatics [10,11]. Children with higher serum levels of 25(OH)D experienced a more significant reduction in asthma symptoms score and a greater corticosteroid-sparing effect of IT [11]. While concomitant systemic corticosteroid use suppressed early clinical and immunologic effects of IT, it was discovered that supplementing patients with vitamin D prevented this adverse effect [11].

The protective effect of vitamin D seems to extend from infancy through adulthood, as studies have demonstrated beneficial effects of vitamin D supplementation on airway function in adults. Vitamin D supplementation along with inhaled controller medications in an asthmatic group ages 10-50 was found to be associated with FEV1 improvement that was significantly better than that in asthmatics taking inhaled controllers alone [66]. Another large adult study found vitamin D deficiency was associated with 25% greater odds of having an asthma exacerbation [67]. Vitamin D may benefit all ages, as one study found vitamin D supplementation is beneficial in an elderly population as well [68]. Vitamin D levels in adults over 65 were lower in those with uncontrolled asthma, and after 12 weeks of vitamin D supplementation, their Asthma Control Test scores improved [68].

### **CONCLUSION**

The simple intervention of vitamin D supplementation appears promising in helping to alleviate disease burden from asthma, the most common chronic condition in children of developed countries. Laboratory studies demonstrate that Vitamin D affects inflammatory cells and is important in lung development as well as the prevention of infection. However, there is not yet conclusive evidence for guidelines on vitamin D supplementation for asthma and immune purposes. Some studies fail to demonstrate positive effects of vitamin D on asthma, but there are many complicating factors to consider including varying populations with different genetic predispositions and environmental influences, limited sample sizes, and different disease severities and outcome measures assessed. Various studies so far suggest that vitamin D would likely have a positive effect on asthmatic children in many populations, but further investigation is needed in large scale supplementation studies over long time periods. After review of the literature, we conclude that vitamin D supplementation is likely helpful in the prevention of acute respiratory illnesses and in optimizing asthma management. There are known vitamin D-dependent immune mechanisms, and several studies reviewed have shown positive clinical associations with vitamin D sufficiency in asthmatics. Therefore, we emphasize current endocrine guidelines and recommend vitamin D supplementation or dietary intake of at least 600IU-1000IU daily for all children between 1-19 years old. We also emphasize the necessity of screening vitamin D levels in all high risk pediatric populations

where vitamin D deficiency is rampant, particularly in African-American, Hispanic-American, and obese children [29]. We especially reinforce the importance of vitamin D supplementation in children with vitamin D insufficiency and asthma, as they are likely to receive both skeletal and extraskeletal benefits that may be long lasting.

## ACKNOWLEDGMENT

This work was supported by National Institutes of Health Grants T32AI007174 (to S.B.), Dr. Zheng is CO-PI on this grant, AI07502 (to T.Z.), HL079349 (to Z.Z.), and HL107151 (to Z.Z.).

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**Cite this article**

Bantz SK, Zhu Z, Zheng T (2015) The Role of Vitamin D in Pediatric Asthma. *Ann Pediatr Child Health* 3(1): 1032.