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Vitamin D and the development of allergic disease: how important is it?

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Summary

Vitamin D has known effects on lung development and the immune system that may be important in the development, severity and course of allergic diseases (asthma, eczema and food allergy). Vitamin D deficiency is prevalent worldwide and may partly explain the increases in asthma and allergic diseases that have occurred over the last 50–60 years. In this review we explore past and current knowledge on the effect of vitamin D on lung development and immunomodulation and present the evidence of its role in allergic conditions. While there is growing observational and experimental evidence for the role of vitamin D, well-designed and well-powered clinical trials are needed to determine whether supplementation of vitamin D should be recommended in these disorders.

Keywords

Vitamin D; Immunomodulation; Development; Asthma and Allergy

Introduction

Allergic (atopic) diseases result from an interaction between individual genetic susceptibility and exposure to environmental factors. According to twin studies, the genetic contribution to allergic disease has been estimated to be about 50%, with heritability estimates ranging from 36–79% [1]. Since the beginning of the 20th century, allergic disease has shown a

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continuous upward trend in prevalence such that asthma, atopic dermatitis, and food allergies currently are common chronic conditions in westernized societies [2]. A multitude of environmental factors, have triggered the steep rise in this trend over the last five decades [3]. Accordingly, sensitization rates to one or more common allergens among school children and adults have globally increased and now approach 40%–50% [3]. As a result, allergic conditions are the sixth most costly chronic disease category in the United States [4]. Worldwide, health care costs have reached approximately US\$ 21, AU\$ 7.8 (US\$ 7.32), £1 (US\$ 1.7) billion annually in the US, Australia and UK, respectively [4–6]. In Europe, the costs of health care for asthma alone amounts to more than 25 (US\$ 34) billion [7]. The number of disability-adjusted life years (DALYs) lost due to asthma worldwide has been estimated to be about 15 million per year. Worldwide, asthma accounts for around 1% of all DALYs lost [8].

Along with a clear genetic basis in allergic disease, environmental factors, including early neonatal nutrition, may have an important influence on allergy development and, thus, present an opportunity to prevent or delay the onset of the disease [1, 9]. Vitamin D may be an important environmental factor. Evolutionarily, early humans evolved in sun-rich environments and the increased efficiency of vitamin D production in the skin is thought to be a major driving factor in human skin depigmentation as humans migrated away from the equatorial areas [10, 11]. 7-Dehydrocholesterol (7-DHC) in the skin is converted to previtamin D₃ after exposure to UVB rays, and is then transformed to vitamin D₃ (cholecalciferol) by a thermally induced isomerization. Vitamin D₃ can also come from the gut, via diet or supplements. Vitamin D₃ in circulation then undergoes hydroxylation in the liver to 25-hydroxyvitamin D₃ (25OHD), which then is hydroxylated further in the kidney to its biologically active form 1,25-dihydroxyvitamin D₃ (1,25[OH]₂D or calcitriol) [12, 13]. Henceforth in this review, the term “vitamin D” will refer to 1,25[OH]₂D, unless otherwise stated. Vitamin D mediates its biological effect through the vitamin D receptor (VDR) which was discovered to be present in a variety of tissues, suggesting the importance of the vitamin D system in various cellular and tissue functions [13–17]. Hence, over the past few years, researchers have paid a great deal of attention to the effect of vitamin D on immunologic mechanisms as one potentially modifiable environmental factor [18, 19]. This is mostly due to the advent of the ability to easily measure 25OHD levels and other vitamin D metabolites in serum or plasma and the growing recognition that vitamin D insufficiency (defined as 25OHD levels of less than 30 ng/ml) exists in most populations around the world [20]. In the US, there is evidence to show that vitamin D insufficiency has increased almost 2-fold over a span of about 10 years, from the late 1980s and early 1990s through the early 2000s [21]. Indeed, it has been proposed that vitamin D insufficiency has contributed to the rise of asthma and allergic disease, [22] and various biological mechanisms for how vitamin D may play a role in the development and treatment of asthma and allergies have been proposed [23]. Historically, Rappaport and colleagues [24, 25] investigated the modifying effect of vitamin D on allergic conditions as early as the 1930s and reported relief of symptoms in a majority of allergic patients treated with viosterol (a vitamin D preparation produced by the irradiation of ergosterol) compared to controls, a finding subsequently supported by several studies [23, 26–29]. These studies have also shown that the determinants of vitamin D status are multifactorial and a nonlinear relationship has been

shown between serum levels and biological effects [23, 30]. However, these studies need to be replicated using more rigorous and modern methods. There is controversy over what levels are optimal for overall health. However, the serum level of 25OHD 30–40 ng/mL (75–100 nmol/L) has been suggested as a lower threshold of an optimal serum level for the immune effects of vitamin D [12, 31, 32]. According to the lower defined threshold value for bone health [33, 34], more than one-third of the population worldwide may have low levels of vitamin D (25OHD < 20 ng/mL [50 nmol/L]) [35]. This fact highlights the potential for risk modification of low vitamin D on the worldwide increase in rates of allergic sensitization.

Vitamin D and immunomodulation related to allergy

Vitamin D has immunomodulatory effects on allergen-induced inflammatory pathways [19] by acting on VDR expressed on a variety of immune cells, including B cells, T cells, dendritic cells and macrophages [36, 37]. Many of these cells, such as activated macrophages and dendritic cells, are capable of synthesizing biologically active vitamin D from circulating 25OHD [38–40]. This mechanism, extrarenal expression of CP27B, enables immune cells to rapidly increase local levels of vitamin D, potentially needed to shape adaptive immune responses [39–41]. In this context, a clinical study involving mild allergic asthmatics who underwent segmental allergen challenge showed a significant increase in vitamin D receptor binding protein (VDBP) and 25OHD in bronchoalveolar lavage fluid (but not in their serum levels) 24hrs after allergen challenge, thus, suggesting a role for vitamin D mediated immune responses in the local asthmatic late-phase reaction [42].

Vitamin D has shown the ability to inhibit both T_h1- and T_h2-type responses by suppressing both the production of IL-12-generated IFN- γ as well as IL-4 and IL-4-induced expression of IL-13 [43]. This ability could be of importance since the balance of T_h1 and T_h2 affects the pattern of immune response. While asthma is thought to be a T_h2 dominant condition and is largely characterized by the production of cytokines such as IL-4, IL-5, IL10 and IL-13, and the production of IgE by B cells [44–46], some experimental and human studies do not support a unidirectional effect (either inhibition alone or enhancement alone) of vitamin D on adaptive T cell responses [23, 47–50]. For example, one study investigated the associations of circulating 1,25[OH]₂D on T_h1/T_h2 serum markers in patients with concomitant nasal polyps and allergic rhinitis. They found a negative correlation between plasma 1,25[OH]₂D with IgE and IL-4 levels, and a positive correlation between 1,25[OH]₂D with IFN- γ [51].

The differences in the observations on T_h1-T_h2 balance among allergic conditions has been attributed to variation in the baseline vitamin D status, timing of exposure to allergen, and chronicity of vitamin D administration relative to sensitization [23]. The type and concentration of allergen as well as the balance of immune responses (T_h1 cytokines/T_h2 cytokines) to different types of allergens are additional factors contributing to variability in response [52, 53]. How the absolute change in vitamin D levels from the baseline vitamin D status over a time period might affect the balance of T_h1/T_h2 cytokines in response to various allergens is a matter for further investigation. It has been proposed that in the absence of vitamin D signaling, the T cell compartment has a potentially stronger T_h1

phenotype and that at pharmacological levels, vitamin D suppresses both T_h1 and T_h2 immune responses [54, 55].

Vitamin D has potent antiproliferative effects on CD4⁺ T cells as well as the ability to inhibit T lymphocyte function, both directly, and via effects on antigen-presenting cells (APCs) [49, 56]. T_h1-cell responses are responsible for some of the pathogenic features in allergic patients particularly chronic features, including epithelial cell apoptosis, smooth-muscle-cell activation and may contribute to mucus secretion [45]. In addition to inhibiting T_h1-associated pro-inflammatory cytokines [37, 49, 56–58], vitamin D has been shown to act on T_h17 cells to suppress the production of IL-17 [22, 59]. Additionally, Rausch-Fan *et al.* has shown that vitamin D modulates cytokine production in human peripheral blood mononuclear cells and allergen-specific T_h cell clones; an effect which was time and concentration dependent [60].

Regulatory T cells (Tregs), including naturally occurring and induced Tregs, play an important role in maintaining immune homeostasis in response to allergen exposure by suppressing T_h2 mediated inflammation such as airway eosinophilia, mucous hypersecretion, and airway hyper-responsiveness [53, 61, 62]. Tregs use multiple suppressive mechanisms, including IL-10 and TGF-beta as well as cytotoxic T lymphocyte antigen 4 and programmed death 1 as surface molecules to regulate downstream immune activation [63]. Vitamin D can induce antigen specific IL-10-producing Tregs, that express low levels of the CD4⁺CD25⁺ Treg-associated transcription factor FoxP3 [64, 65]. Consequently, secreted IL-10 inhibits inappropriate allergen specific T_h2-driven immune responses and regulates allergic sensitization [61, 66]. Similarly, allergen immunotherapy and glucocorticoid therapy for allergy and asthma have shown increased IL-10 synthesis by Tregs [66–68]. Vitamin D supplementation of cholecalciferol (140,000 IU) has been also associated with an increased Tregs frequency (%Tregs) in apparently healthy individuals with vitamin D insufficiency after 4 weeks [69]. However, Chi *et al.* demonstrated that cord blood 25OHD levels were inversely associated with the proportion of CD25⁺, CD25^{Bright}, and CD25⁺FoxP3 T-regulatory cells [46]. Thus, it is likely that the effect of vitamin D on Tregs is complex and depends on the contextual cellular milieu and factors such as the age of the individual, pregnancy, as well as health and disease status.

Vitamin D and its receptor (VDR) are both essential for development of Natural Killer (NK) cells and the expression of IL-4 and IFN- γ production [70]. NK cells contribute to the development of T-cell mediated allergic airway inflammation [71–73] and are capable of producing numerous pro-inflammatory cytokines such as IFN- γ , TNF- α , GM-CSF, and MIP-1a upon IgE stimulation and exhibit cytotoxicity against IgE-coated target cells through Fc γ RIII [74]. Natural killer T (NKT) cells are a distinct subset of T lymphocytes that can produce both T_h1 (IFN- γ) and T_h2 (IL-4) cytokines and have been investigated for their role in asthma and allergy [75–77]. Du *et al.* studied the interaction of low vitamin D levels on asthma exacerbations [78]. They identified three associated common variants in the class I MHC-restricted T cell-associated molecule gene (*CRTAM*), which is highly expressed in activated human CD8⁺ and NKT cells. Their findings implicate a mechanism by which vitamin D might prevent asthma exacerbations through CD8⁺ and NKT cells, particularly during viral infections.

Effect of vitamin D on development (fetal lung & immune system) and normal function

Vitamin D in pregnancy and fetal development

The Barker hypothesis first posited that environmental influences early in development and during intrauterine life, could increase the risk of chronic disease later in life [79]. Numerous epidemiological studies have shown strong associations between maternal diet and altered risk of chronic disease, particularly asthma [80–82]. Active vitamin D (1,25[OH]₂D) dramatically rises during pregnancy, with levels reaching up to 124% to 135% of normal values [83, 84]. As a result, the role of vitamin D during pregnancy has recently come to the forefront as studies have documented an increased risk to maternal and fetal health in relation to low serum levels of 25OHD [85].

In addition to the well-described skeletal effects of vitamin D, such as calcium homeostasis [86, 87] and bone development, it may promote proper fetal implantation and regulates placental development [88, 89]. Moreover, vitamin D regulates immune responsiveness by enhancing the activity of immunosuppressive Tregs and suppresses pro-inflammatory Interleukin-17 expressing T_H17 cells [64, 90]. In addition, vitamin D is well known for its role in regulating the expression of the neutrophil associated cathelicidin antimicrobial protein (*CAMP*) as well as numerous defensins molecules, particularly beta defensin 1 [91]. Collectively, these findings suggest that vitamin D has immunosuppressive effects in placental tissue and promotes enhanced protection of the mother and fetus against infection.

Studies in animals and humans have shown that circulating levels of maternal 25OHD crosses the placenta freely. Importantly, placental trophoblast cells express the VDR and CYP27B1 (1αOHase) and hence are capable of converting 25OHD into the active hormonal form [92, 93]. Several observational studies suggest that low 25OHD level promotes intra-uterine growth restriction and low birth weight and has modest effects on pre-term birth [94, 95]. Thus, mounting evidence indicates that vitamin D is necessary for normal fetal development and organ function, although the molecular mechanism by which fetal vitamin D levels influence the complex fetal development pathways remain unclear [96].

Association with lung development

In addition to immunomodulatory effects during fetal development, vitamin D also has known genomic effects and thus the ability to influence fetal lung development [85, 97]. Experimental evidence in rats show that fetal alveolar type II epithelial cells express *VDR*, suggesting that pulmonary maturation is responsive to vitamin D exposure [98–100]. In humans, Kho *et al.* recently examined gene expression profiles during human fetal lung development and identified a number of genes associated with the vitamin D pathway whose expression was developmentally regulated [97]. Although the exact role these vitamin D related genes play in fetal lung development remains to be fully explored, several genes (*LAMP3*, *PIP5K1B*, *SCRAB2* and *TXNIP*) were also found to be significantly overexpressed in cells derived from asthmatic children, thus, suggesting a link between vitamin D pathway genes, fetal development and asthma [97]. Studies in mice and human performed by Zosky *et al.* further support the notion that maternal vitamin D deficiency during fetal lung

development may impact early life lung structure and function and increase the risk of chronic lung disease later in life [101, 102].

Correlation of serum vitamin D of mother and newborn

Studies show a strong correlation between maternal 25OHD levels and cord blood 25OHD levels of neonates. In a recent study of 107 pregnant mother-infant pairs, cord blood levels of 25OHD were shown to be approximately $62 \pm 16\%$ of maternal levels and correlated positively with maternal 25OHD levels ($r=0.83$, $P<0.001$) [103]. The influence of vitamin D on early childhood health and growth has emerged as an area of great interest [104]. In this context, infections, including respiratory infections, are an important cause of neonatal childhood morbidity and mortality and, in this regard, several studies have documented a correlation between deficiencies in 25OHD levels in early life with increased rates of respiratory infections [105]. This is of particular interest, as respiratory infections in the first years of life have been associated with an increased risk of allergic asthma in young children [106].

Asthma and allergy

The prenatal and early life period have been identified as “windows of opportunity” during which immune responses can be permanently programmed. The role of vitamin D during this period in the prevention of asthma and allergies in children remains controversial. Positive and negative results of several epidemiologic studies have been published [23]. Reasons for these differing results are numerous, and can be gleaned from patterns of the results that have emerged. Firstly, all the published studies to date that have reported a protective effect of vitamin D have all assessed vitamin D intake in pregnancy from food frequency questionnaires [107–110], which are known to be an indicator of long-term diet pattern [111, 112], hence long-term intakes of vitamin D. Next, studies that have assessed either 2nd and 3rd trimester maternal vitamin D status (via 25OHD levels) [110, 113–116] or cord blood 25OHD levels [117–122] have not shown a consistently protective effect on asthma and allergies. Since 25OHD is known to fluctuate by season [123–125] and the intraclass correlation coefficient over several years of 25OHD levels is only on the order of 0.3 [126], it is likely that a one-time assessment of vitamin D status is not sufficient for the question of whether vitamin D can prevent asthma or allergies. Additionally, the ineffective trial of vitamin D supplementation in the 3rd trimester in showing effect modification of clinical characteristics of asthma and allergies, underscoring the fact that intervening in the 3rd trimester may be too late for these outcomes. The only observational study that showed that maternal vitamin D status was protective for asthma measured 25OHD levels in the first trimester [102]. The studies that used Food Frequency Questionnaires (FFQs) are consistent with this notion since these are markers of long-term intakes encompassing the first trimester. Thus, vitamin D supplementation trials that begin earlier in pregnancy are needed. One such trial, The Vitamin D Antenatal Asthma Reduction Trial (VDAART): a randomized controlled trial of vitamin D supplementation in pregnancy for the primary prevention of asthma and allergies in children, is currently underway (ClinicalTrials.gov: NCT00920621).

Role of vitamin D in prevention and modification of asthma and allergy

After pregnancy and during early life

I. Asthma—Vitamin D may potentially decrease the severity of asthma and allergies through a variety of mechanisms (figure 1) including effects on immune cells, improved handling or prevention of predisposing infections [19, 127–129], decreased inflammatory responses, improved lung function [130–132], effects on airway smooth muscle function and mass, reduced airway remodeling [19, 133] and reversal of steroid resistance (by IL-10 production and modifying ligand-induced down-regulation of glucocorticoid receptors [66]). Several studies have investigated the relationship between vitamin D deficiency and asthma exacerbations. A low level of vitamin D at age 6 was associated with increased allergies and asthma at age 14 in one study from Australia and serum 25OHD levels in children of both ages were negatively associated with concurrent allergic phenotypes in males [134]. In 616 Costa Rican children with asthma aged 6–14 years, Brehm *et al.* found that 28% of the children had insufficient 25OHD levels. On a log scale, 25OHD level was associated with reduced risks of any hospitalization for asthma in the previous year (odds ratio [OR], 0.05) and any use of anti-inflammatory medications in the previous year (OR, 0.18). In addition, 25OHD levels were significantly and inversely associated with total IgE and eosinophil count [135]. Brehm *et al.*, using collected data in 1024 participants of the Childhood Asthma Management Program (CAMP), a placebo-controlled randomized trial of inhaled budesonide vs. nedocromil, showed that vitamin D insufficiency (25OHD <30 ng/ml) was associated with higher risks for severe asthma exacerbations leading to ED visits or hospitalizations [136]. There was a greater effect among children who were randomized to the inhaled budesonide arm, suggesting an interaction between vitamin D and corticosteroid use. Searing *et al.* [137] in a cross-sectional study of 100 asthmatic children, showed that 25OHD levels were inversely associated with serum IgE, number of skin prick tests to perennial aeroallergens, lung function, and use of inhaled or oral corticosteroids. *In-vitro* studies using peripheral blood mononuclear cells showed that vitamin D amplified glucocorticoid induction of mitogen-activated protein kinase phosphatase (MPK)-1 and IL10, which are critical for anti-inflammatory and immunosuppressive effects. In a study of 54 adult asthmatics, subjects with vitamin D insufficiency had lower lung function and increased airway hyperresponsiveness [138]. In addition, 25OHD levels in this study were inversely correlated with tumor necrosis factor (TNF)- α expression and positively correlated with dexamethasone-induced MPK-1 expression. Other studies have also found that lower 25OHD levels are associated with poor asthma control [139], lower lung function and the presence of exercise-induced bronchoconstriction [140] in asthmatic children, and the severity of atopic dermatitis [141].

Bosse *et al.* [142] have shown *in vitro* that vitamin D increases glucocorticoid bioavailability in bronchial smooth muscle cells suggesting a further beneficial role for vitamin D in the prevention and treatment of asthma. This interaction between vitamin D and corticosteroids was investigated in a recent clinical trial. In “Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma (VIDA)”, Castro *et al.* investigated if taking vitamin D in addition to a standard asthma medication would prevent the worsening of asthma symptoms or attacks [143]. In their study, adult asthmatics were randomly

received an initial dose of 100,000 IU of oral cholecalciferol followed by 4000 IU/day for 28 weeks or placebo (n = 201 vs. 207) while using inhaled ciclesonide (Alvesco). After a 12-week inhaled corticosteroids stability phase with 320 µg/d of ciclesonide, the dose of ciclesonide was reduced to 160 µg/day for 8 weeks, followed by maintenance dose of 80 µg/day for another 8 weeks. Although they found that vitamin D supplementation had no significant effect on the overall rate of first treatment failure or exacerbation in patients with asthma and low vitamin D levels, at 28 weeks, there was a significant difference in cumulative ciclesonide dosing between the vitamin D and placebo groups (111.3 vs. 126.2 µg/day; $P = .02$). In addition, there was significant reduction in the overall asthma treatment failure and the exacerbations in subjects that achieved a normal vitamin D level. This trial was likely underpowered for the primary outcomes of first treatment failure, as the authors acknowledged that there was a lower than expected event rate in the control group. Furthermore, several observational studies have already established that the interaction between corticosteroids and vitamin D in asthma is much stronger in children than in adults with asthma [144–146], thus well-designed and well-powered trials in children are needed.

II. Atopic dermatitis, allergic rhinitis and food allergy—Several clinical, genetic and experimental studies suggest that prior history of atopic dermatitis (AD) and its severity are a major risk factors for the development of allergic rhinitis, asthma and specific sensitization, highlighting the importance of the epidermal barrier in the pathogenesis of these allergic disorders [147]. Low levels of vitamin D appear to be inversely correlated with AD severity, and vitamin D deficiency at birth is associated with higher risk of developing AD. Also, a pilot randomized trial of vitamin D supplementation in children demonstrated a favorable effect on AD symptoms during winter months [148]. It is possible that this effect was mediated by the induction of endogenous antimicrobial peptides in the skin in AD by oral vitamin D supplementation [149].

Few studies have investigated vitamin D status in allergic rhinitis and food allergy. Allergic rhinitis has been shown to be a risk factor for developing asthma [150–152]. Ciprandi *et al.* [152] showed that nasal symptoms, airflow, and markers of inflammation directly correlate with lower airway markers including forced expiratory volume in 1 second (FEV₁). Leynaert *et al.* [153] found that approximately 75% of asthmatics report rhinitis; patients with rhinitis have increased risk for asthma and lower airway reactivity compared to patients without rhinitis; and the risk for asthma increases from 2.0% in subjects without rhinitis to 18.8% in subjects with allergic rhinitis when exposed to either pollen or animal dander. Mai *et al.* [154] also investigated the relationship between serum 25OHD and the incidence of allergic rhinitis in adults. The study included a random sample (N=1351) from an adult population who participated in Nord-Trøndelag Health Study (HUNT). In the 11-year follow-up of the subjects, they showed that 9% of men and 15% of women developed allergic rhinitis. Among men, serum 25OHD level <50 nmol/L at baseline was associated with an increased risk of allergic rhinitis (adjusted OR 2.55, $p=0.001$); each 25 nmol/L reduction in 25OHD level was associated with an adjusted OR of 1.84. However, women had lower risk of allergic rhinitis with adjusted OR of 0.83 ($p>0.05$) for each 25 nmol/L reduction in serum 25OHD level.

It has been suggested vitamin D deficiency might impair epithelial barrier integrity, that in turn leads to increased and inappropriate mucosal exposure to food antigens and also a pro-sensitization immune imbalance that compromises immunological tolerance [155].

Consequently, early correction of vitamin D deficiency might promote mucosal defense, maintain healthy microbial ecology and allergen tolerance, and decrease risk of food allergies in children [149, 156]. Food allergy is a known provoking cause of AD and the prevalence of IgE-mediated food allergy is about 35% in children affected with AD [38]. Kull *et al.* showed vitamin D in water-soluble form increased the risk of allergic disease in children of less than 4 years old compared with supplementation of vitamin D given in peanut oil [157]. This study justifiably raised questions about the varying results of vitamin D supplementation on risk modification of food allergy and other allergic diseases [158]. However, the study did not measure baseline nor follow-up vitamin D levels. Sharief *et al.* [159] showed that higher levels of IgE sensitization were associated with vitamin D deficiency in children and adolescents. Accordingly, 25(OH)D levels of less than 15 ng/mL were associated with evidence of sensitization to various allergens. For example the odds ratios of allergy for peanut, ragweed, and oak were 2.39, 1.83 and 4.75, respectively [159]. Similarly, mean 25(OH)D serum levels have been lower in moderate and severe atopic dermatitis (AD) children, suggesting potential benefit of serum level correction using vitamin D supplementation in AD [141]. Allen *et al.* [160] demonstrated that infants of Australian-born parents with vitamin D insufficiency (25OHD < 50 nmol/L) had higher risk of peanut (OR, 11.51) and/or egg (OR, 3.79) allergy than those with adequate vitamin D levels. They were also more likely to have multiple food allergies (> 2) rather than a single food allergy (OR, 10.48 vs. OR, 1.82) [160]. Moreover, Mullins *et al.* [161], similar to Vassallo *et al.* [162], reported significantly higher rates of food allergy in children born in the autumn/winter, suggesting a relationship between relative food allergy rates and monthly sun exposure.

Future Directions

There remains a great deal of controversy as to the role of vitamin D in overall health and what represents adequate levels of vitamin D in the blood for human health generally [163] and specifically for each of the reviewed allergic conditions. However, there is sufficient suggestion of a benefit of raising vitamin D levels to encourage more studies in this field. Future interventional and longitudinal cohort studies are needed to establish whether changes in maternal nutrient intake during pregnancy can be used as a healthy low-cost public health measure to reduce the incidence of childhood asthma and atopy [164]. Such studies will be very important in shedding light on the role of vitamin D in fetal development. More studies in established asthma are also necessary. Clinical trials investigating the role of vitamin D in modifying the severity of asthma and allergies and in controlling exacerbations need to be adequately powered, use the appropriate dose, and need to be of sufficient duration. Furthermore, a focus on children with persistent disease also seems to be appropriate. These trials should perform additional analyses that attempt to identify the appropriate vitamin D level that provides the maximal beneficial effects.

Vitamin D may regulate epigenetic events [165] that promote allergic conditions [166]. Hence, studies on molecular genetic and epigenetic mechanisms of vitamin D in allergic

diseases and disease severity (immunoinflammatory responses, steroid resistance, host defense) particularly in response to high and low vitamin D supplementation would provide mechanistic insights in the management and prevention of allergic diseases. As an example, a study in healthy adults who received either 400 or 2000 IU/d of vitamin D₃ for 3 months in winter demonstrated the up or down-regulation of 291 genes by vitamin D intake. That these genes effected as many as 80 different metabolic pathways, including immune modulation and enhanced antioxidant activity, emphasizes the potential importance of vitamin D status on transcriptional regulation [19, 167]. Thus, these clinical trials will also need to collect the appropriate specimens and consent to perform these genomic studies. These clinical and genomic studies will help to clarify the potential role of vitamin D on both the development and modulation of asthma and allergies.

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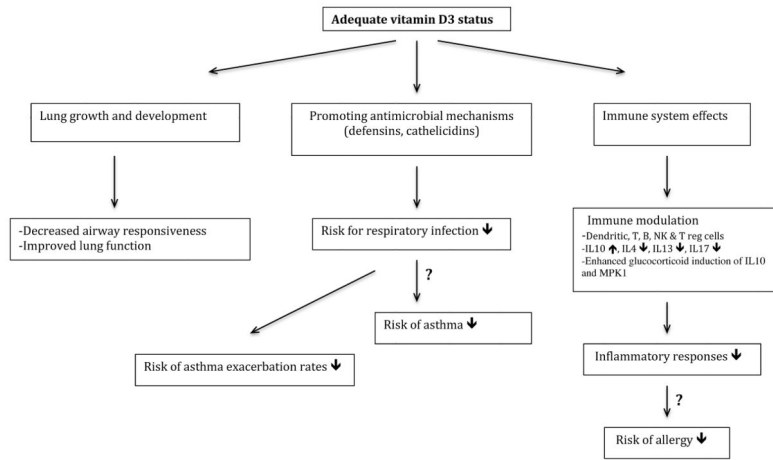


Figure 1. Potential effects of vitamin D in asthma and allergy development or modification. Several studies support the modification role of vitamin D in asthma and allergy. However, preventive effects of vitamin D in risk reduction of asthma and allergy development during pregnancy and early life requires more well designed longitudinal studies.