



Vitamin D: can the sun stop the atopic epidemic?

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Purpose of review

To review recent evidence on the capacity of vitamin D to prevent atopic disease, focussing on food allergy and asthma, and potential underlying mechanisms.

Recent findings

The incidence of allergic disease continues to increase worldwide. Vitamin D status is influenced by sun exposure and dietary intake. Vitamin D deficiency is linked to an increased incidence of allergic disease and asthma. These associations are generally strongest in early life. The capacity of vitamin D to enhance antimicrobial pathways, promote peripheral immunological tolerance and maintain mucosal barrier integrity may underlie these associations. Interventional studies have addressed the capacity of vitamin D supplementation *in utero* and early life to reduce the incidence of disease. Ancillary studies have provided insights into potential biological mechanisms linked to these effects.

Summary

Observational studies show an inverse association between vitamin D levels and development of food allergy and asthma. Secondary analyses of two recent interventional studies suggest that achieving vitamin D sufficiency throughout pregnancy reduces the incidence of asthma/recurrent wheeze at 3 years. Longitudinal studies of vitamin D requirements *in utero* and postnatally, better understanding of factors that influence bioavailability of vitamin D and mechanistic insights into vitamin D effects on neonatal-specific immune pathways are awaited.

Keywords

allergic disease, asthma, food allergy, prevention, treatment, vitamin D

INTRODUCTION

Vitamin D synthesis is initiated in the skin following UVB exposure, with lower levels obtained through diet (e.g. oily fish, offal) or supplementation. Vitamin D insufficiency and deficiency are commonly defined by measurement of circulating levels of the precursor 25-hydroxyvitamin D (25(OH)D) of less than 75 nmol/l (30 ng/ml) and less than 50 nmol/l (20 ng/ml), respectively. Vitamin D availability is influenced by latitude of residence, season, diet and cultural behaviours. The prevalence of vitamin D insufficiency and deficiency is increasing around the globe, in parallel with the observed increase in diseases with an immune component like allergy and asthma [1^{*,2*},3^{**}].

The prevalence of atopic diseases has increased over the past few decades. The rise in the prevalence of asthma has been followed by a more recent rise in food allergy, often referred to as the 'second wave of the allergy epidemic'. The increase in food allergy is best described for peanut allergy, with a five-fold increase reported between 1995 and 2006 with peanut allergy in the United Kingdom. Currently, 2% of school-age children are affected with

peanut allergy in the United Kingdom and United States [4–6]. Globally, food allergy affects about 7% of children [6,7] and 10% of adults [8] with the highest prevalence of food allergies being reported in Australia where approximately 10% of infants and 4.5% of school-age children from the general population have challenge-proven or clinic-defined food allergy [9,10]. Asthma affects around 10% of children globally. The prevalence of asthma at age 4 years is two times higher in children with challenge-proven food allergy at age 1 and three times higher in children with multiple food allergies, even if food allergies resolve [11].

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KEY POINTS

- The rise in food allergy and asthma has been accompanied by changes in lifestyle that are associated with low vitamin D status.
- Lower sun exposure and lower vitamin levels have been associated with higher risk and higher rates of allergic sensitization, food allergy and asthma.
- Vitamin D has been demonstrated in experimental studies to favour antimicrobial and tolerogenic immune responses.
- Longitudinal studies of vitamin D and its effect on the prevention and treatment of food allergy and asthma are needed to improve our understanding of impact of vitamin D in early life and its potential role in stopping the atopic epidemic.

Food allergy often presents in the first 12 months of life. Asthma, for which atopy and recurrent infectious wheeze in early life are well recognized risk factors, is often diagnosed by 5 years of age. The early presentation of these conditions highlights the influence of *in utero* and early life exposures on disease development. Environmental impact, particularly in early life, is supported by observational studies reporting that immigrants tend to adjust to the prevalence of food allergy of their adopted country [12]. Changes in lifestyle that have accompanied the increased prevalence of asthma and food allergy include: urbanization, with increased pollution, use of asphalt, cleaner water supplies and cleaner homes; a more sedentary lifestyle and time spent indoors; increased use of immunizations and antibiotics; changes in infant feeding and increased adoption of the Westernized diet. Considering some of these changes, low vitamin D levels emerge as a potential risk factor for the development of food allergies and asthma.

VITAMIN D IN FOOD ALLERGY

Previous studies have linked low vitamin D status with the development of food allergies by showing differences in the prevalence of food allergy in geographical locations with different degree of sun exposure. For instance, countries located further from the equator tend to have higher rates of prescription of hypoallergenic milk formulas, adrenaline auto-injectors and emergency admissions for food allergy. Season of birth is also reported to influence rates of food allergy [3¹¹]. With food allergy developing early in life, the hypothesis that vitamin D levels in the ante-natal and peri-natal period and in the first few months of life may

influence the development of food allergy arose; however, the evidence from different studies is conflicting and several negative studies have been reported [3¹¹,13–15]. In the recent Irish BASELINE birth cohort report, circulating levels of 25(OH)D measured in maternal sera at 15 weeks of gestation and umbilical cord blood were not associated with food allergy and other atopic diseases in the offspring at 2 or 5 years of age [16]. Other earlier observational studies in this area were recently reviewed [3¹¹]. Limitations of some of these studies include estimation of vitamin D status by food frequency and/or sun exposure questionnaires, rather than direct assessment of circulating 25(OH)D levels; a single measurement of vitamin D status (in pregnancy, lactation or at/shortly after birth) rather than multiple longitudinal assessments, which is then linked to health outcomes months or years later; and reliance on parent-reported rather than clinician/oral food allergen challenge diagnosis of food allergy.

Direct evidence of the influence of vitamin D in the development of food allergy comes from the Healthnuts study, in which infants of Australian-born parents with vitamin D insufficiency were over 10-times more likely to have two or more challenge-proven food allergies and 11 and approximately 4 times more likely to develop peanut allergy and egg allergy respectively compared with those with adequate vitamin D levels, independently of eczema status [17]. Within the large National Health and Nutrition Examination Survey (NHANES) 2005–2006, vitamin D deficiency was associated with higher levels of IgE sensitization in children and adolescents aged between 1 and 21 years. Peanut was among the allergens with which the most prominent association between IgE sensitization and low vitamin D status was observed. The same association was not consistently observed in adults (>21 years) [18]. In a recent study from Iceland, where vitamin D is an important part of the diet and supplementation encouraged, IgE-sensitized children had a lower vitamin D intake compared to non-sensitized children and vitamin D supplementation decreased the odds of IgE sensitization at 12 months of age (odds ratio = 0.2; 95% confidence interval, 0.1–0.98) [19]. A comprehensive longitudinal study of a high-risk cohort in Australia repeated 25(OH)D measurements from birth until 10 years of age and demonstrated that persistent vitamin D deficiency was associated with increased risk of asthma, eczema and allergic sensitization, and overall that these associations were strongest in infancy [20].

A recent systematic review of vitamin D supplementation for primary allergy prevention identified one randomized controlled trial and four nonrandomized studies that were eligible and thus evidence

was limited [21]. This systematic review suggested that vitamin D supplementation during pregnancy, lactation and infancy may not decrease the risk of developing food allergy, asthma and/or wheezing. In the Vitamin D Antenatal Asthma Reduction Trial (VDAART), pregnant women were randomized to supplementation with 4400 IU/day versus 400 IU/day of vitamin D from the first trimester of pregnancy. A significant reduction in allergic sensitization at 3 years of age was seen in the offspring of higher dose supplemented women [22]. However, a recently published randomized-controlled trial of 975 infants taking vitamin D supplementation in low dose (400 IU) or high dose (1200 UI) from the age of 2 weeks reported that high-dose vitamin D supplementation did not prevent food sensitization at 12 months of age, compared to the low-dose regimen. Allergic diseases did not differ between groups, except for cow's milk allergy, which was more prevalent in infants in the high-dose arm of the study. Infants with high cord blood 25(OH)D (≥ 100 nmol/l) also had a higher risk of food sensitization compared with those with lower 25(OH)D levels (75–99.9 nmol/l) [23]. The levels of 25(OH)D are exceptionally high in this cohort with over half of the participants exhibiting in excess of 75 nmol/l. An early study by Hypponen *et al.* [24] may be pertinent in interpretation, where both low and excessive levels of circulating 25(OH)D were correlated with increased IgE in a nonlinear relationship.

Overall, the effect of vitamin D status on allergic sensitization and food allergy remains controversial. Factors contributing to the discrepancy of results reported in the literature are listed in Table 1. The heterogeneity between studies, possible confounding factors and limited longitudinal data highlight the need for further randomized-controlled trials of vitamin D supplementation in pregnancy and infancy to study its possible effect in the prevention of sensitization to food allergens and in the promotion of oral tolerance.

VITAMIN D IN ASTHMA

A large body of observational data link vitamin D insufficiency and deficiency with an increased incidence, and poor control of asthma [1[•]]. Interventional studies in adults and children demonstrate significant variations in study design with respect to dose and frequency of supplementation. A reduction in asthma exacerbations, commonly caused by acute respiratory tract infections, and improved asthma control, with modest steroid sparing effects, have been reported in several, but not all, studies [1[•]]. Additional challenges in the interpretation of these data include failure in some studies to record

Table 1. Various factors can influence the relationship between serum vitamin D levels and risk of developing atopic diseases, such as food allergy and asthma/recurrent wheezing, in research studies

Examples of factors influencing vitamin D levels and our understanding of their relationship with atopic diseases

Sun exposure
Country of residence
Migratory status
Skin colour
Ethnicity
Age
Diet
Vitamin D supplementation (timing, formulation and dose)
Genetic polymorphisms affecting vitamin D metabolism
Epigenetic changes that contribute to vitamin D levels
Vitamin D binding protein
Interaction with disease-associated genetic polymorphisms, e.g. ORMDL3
Definition of atopic diseases (e.g. in food allergy, self-reported, doctor-diagnosed, challenge-proven)
Study design (cross-sectional, longitudinal, RCT)
Cut-off to define vitamin D insufficiency/deficiency
Longitudinal versus single assessments of vitamin D status

RCT, randomized controlled trial.

baseline vitamin D status, or measuring status at a single time point which is then linked to clinical observations recorded months later [2^{••}] (Table 1). Importantly meta-analyses and systematic reviews indicate incremental benefits of vitamin D supplementation, particularly in individuals who demonstrate vitamin D deficiency at recruitment receiving frequent supplementation [25,26].

In the Childhood Asthma Study (CAS), a cohort of children at high-risk of developing asthma and allergy was followed up from birth until 10 years of age. An inverse association between 25(OH)D concentrations and the risk for allergic sensitization at 6 months and 2 and 3 years of age, and between risk for asthma/wheeze, eczema and sensitization at 10 years was reported. An inverse association between 25(OH)D levels was also observed with two other risk factors for asthma, namely early nasopharyngeal colonization with *Streptococcus* species and age of first febrile lower respiratory illness [20]. Overall, these findings support vitamin D deficiency as a risk factor for persistent asthma.

A role for vitamin D in the primary prevention of asthma and asthma-associated risk factors is of great current interest. Observational studies indicate that vitamin D insufficiency and deficiency in pregnancy is linked to asthma in the child [1[•],2^{••}]. Two

important and large clinical interventional studies of vitamin D supplementation in pregnancy, the Vitamin D Antenatal Asthma Reduction Trial (VDAART) and the Copenhagen Prospective Studies in Asthma in Childhood 2010 (COPSAC) in the USA and Denmark respectively, reported strong trends for improved clinical outcomes based on intention to treat [22,27]. Strikingly, in secondary analyses, maternal vitamin D sufficiency at recruitment in trimester 1 and allocation to the high-dose supplementation arm were linked to significant and sizeable reductions in childhood wheeze and asthma at 3 years of age [28,29], implying that longitudinal analyses of vitamin D status may be more informative. Furthermore, postnatal supplementation of black infants born preterm who received sustained supplementation with vitamin D, compared with diet-limited supplementation, resulted in a reduced risk of recurrent wheezing by 12 months' adjusted age [30].

FACTORS INFLUENCING VITAMIN D LEVELS

Changes in lifestyle occurring in recent decades are recognized to contribute to the high levels of vitamin D deficiency and insufficiency seen globally, including in pregnancy [2]. However, genetic factors also influence circulating 25(OH)D concentrations. A recent systematic literature review identified 35 gene variants to be associated with abnormal vitamin D levels, of which a third were directly linked to vitamin D metabolism [31]. For example, the vitamin D binding protein (DBP) is the major transporter of circulating vitamin D metabolites. Its gene is the most polymorphic gene known and controls vitamin D availability [32]. In the Healthnuts study, the association between 25(OH)D levels and food allergy at 1 and 2 years of age was examined by genotype of rs7041 (GG associated with high, GT/TT with low DBP levels). Low vitamin D levels at age 1 year and persistent vitamin D insufficiency were associated with food allergy, especially in infants with GG (but not GT/TT) genotype. Conversely, maternal antenatal vitamin D supplementation was associated with less food allergy, particularly in infants with GT/TT genotype. These findings support the role of persistent vitamin D deficiency and genetic polymorphisms linked to greater vitamin D bioavailability, in attenuating the association between low vitamin D and food allergy [33].

Genes outside the vitamin D metabolic pathway may also influence vitamin D responsiveness or act in concert with disease-associated genotypes. This includes, interleukin (IL)-4, IgE pathway genes and those influencing epithelial barrier integrity [15].

The chromosomal region 17q21 is a major childhood asthma-risk locus. Recently, the high-risk genotype, associated with early onset childhood asthma and recurrent wheeze, was linked to clinical outcomes following combined analyses of the COPSAC and VDAART trials. Protective effects of maternal vitamin D supplementation were observed in children with a protective [rs12936231 GG; hazard ratio (HR)=0.49], but not the high-risk allele (CC-genotype, HR = -1.08), which in turn is associated with increased ORMDL3 expression by bronchial epithelial cells. Within the VDAART trial, the low-risk GG genotype was associated with increased plasma levels of sphingolipids. These data support a new model whereby vitamin D supplementation increases sphingolipid metabolism that in turn reduces asthma risk [34]. The authors propose that increased ORMDL3 associated with the high-risk CC-genotype, inhibits sphingolipid metabolism. It is possible that these effects extend beyond airway epithelium. Schmiedel reported that increased ORMDL3 expression in 17q21 asthma-risk variants was greatest (three-fold) in CD4⁺ T lymphocytes and controls their IL-2 production [35]. This might plausibly influence T-regulatory function, which is highly dependent on IL-2 [36], but awaits further studies.

IMMUNE MODULATION BY VITAMIN D

The capacity of vitamin D to enhance antimicrobial and regulatory pathways that maintain peripheral tolerance and dampen allergic and airway inflammation may underpin the association of vitamin D sufficiency with respiratory health, and improved asthma control in adult and pediatric studies and potentially oral tolerance to food allergens [1,15](Fig. 1).

The innate immune response of the neonate is crucial for host-defence and protection against infection, required to meet distinct neonatal challenges and evolving over the first months and years of life [37]. Ancillary studies within a subset of babies within VDAART demonstrated that infants born to high-dose supplemented mothers demonstrated a greater inducible proinflammatory cytokine response to innate stimuli (mitogen, TLR-agonists), and higher levels of TLR gene expression. An additional finding was a four-fold higher, albeit still low, IL-17A response following TCR-ligation in cord blood cultures of babies from the high-dose supplementation study arm, likely to help the newborn fight infection, but contrasting with earlier observations in adults [1,38]. Using samples from participants in the Healthnuts study, Neeland *et al.* found that children with persistent egg allergy had higher rates of vitamin D deficiency than children with transient

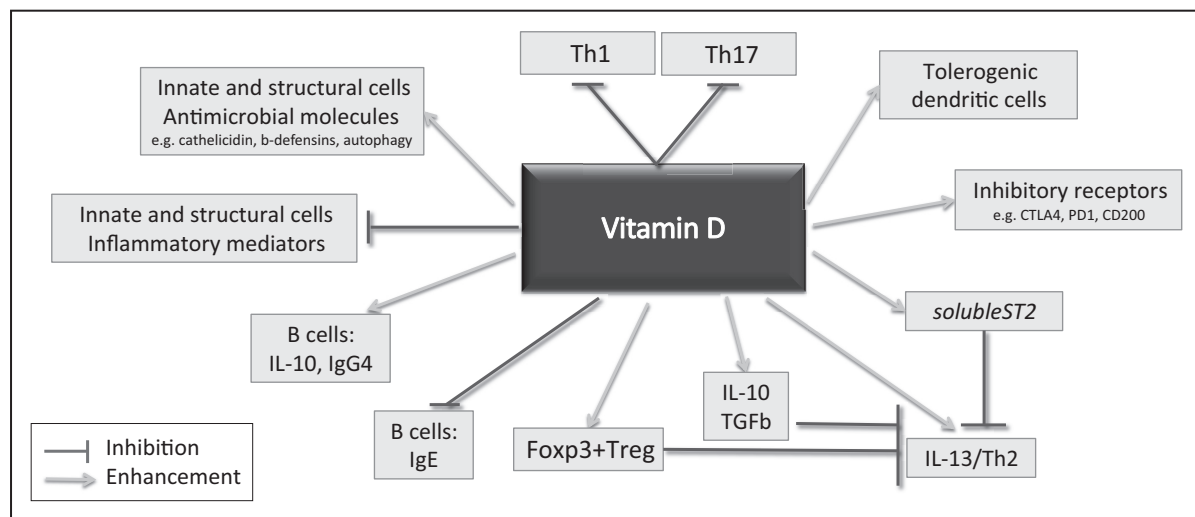


FIGURE 1. Actions of vitamin D ($1\alpha,25$ -dihydroxyvitamin D₃) proposed to contribute to respiratory health and the control of asthma and allergic disease. Many of these vitamin D regulated effects have been described in culture, correlates made in patients with vitamin D status or modulation seen post vitamin D supplementation. All these data derive from studies in pediatric and adult individuals. How these relate to unique aspects of foetal and infant immunity are of interest. For full referencing see [1[¶]].

egg allergy. Persistent egg allergy was linked to a unique innate immune signature with increased circulating monocytes and dendritic cells that produced more inflammatory cytokines compared to transient egg allergy. Increased serum vitamin D levels correlated with changes in innate changes associated with natural tolerance to egg [39[¶]].

Microbes colonize the neonatal gut immediately following birth, and likely influence immune development and health outcomes [37[¶]]. Vitamin D influences the composition of the gut microbiome [40]. Within the VDAART cohort, and elsewhere, an association between the intestinal microbiome in 3-month-old to 6-month-old infants who later develop food sensitization and food allergy was reported [41]. Understanding the relationship between vitamin D status, intestinal microbiome, immunity and long-term health remains of interest. Although not a focus of this review, vitamin D has a positive effect in maintaining epithelial barrier integrity in the gut, the skin and the lung [42] where vitamin D receptor deletion leads to the destruction of tight and adherens junctions. All these sites are linked to allergic sensitization and increased permeability that may lead to local inflammation and enhanced sensitization.

Vitamin D positively correlates with and enhances the frequency of T-regulatory cell frequency in children and adults. For example, the frequency of IL-10+ and Foxp3+ T regulatory cells is increased in culture with $1\alpha,25$ -dihydroxyvitamin D₃, and circulating 25(OH)D levels positively associates with

Foxp3+ Treg frequency and IL-10 levels in the periphery and in the airways [1[¶]]. These effects are likely mediated through modulation of T cell and dendritic cell function, and vitamin D enhances the expression of inhibitory surface receptors (e.g. CTLA4, PD1, CD73, CD200) involved in this interaction [1[¶]]. However, the relative importance of these pathways in underpinning clinical observations *in utero* and early life is less clear since the immune profile at birth is acknowledged to differ from that of adults to meet the very different constraints imposed in early life [37[¶]]. In vitamin D insufficient women suffering from recurrent pregnancy loss, 2-months of supplementation with 2000 IU/day vitamin D increased their circulating Foxp3+ T cells [43] and their Treg/Th17 increased, an effect that was not observed in nonsupplemented women. In VDAART ancillary studies, no difference in Foxp3+Treg frequency in cord blood of newborns between study arms was seen, however, inducible levels of anti-inflammatory IL-10 were significantly increased in the high-dose supplemented study arm [38[¶]], although these studies did not investigate infant immunity at later times. A recent report demonstrated that vitamin D upregulates the expression of the serine protease inhibitor, alpha-1-antitrypsin in human CD4⁺ T cells, an effect also seen in cord blood cultures (Hornsby and CH, unpublished). Alpha-1-antitrypsin was required for vitamin D-induced IL-10 synthesis in CD4⁺ T cells [44]. Early reports suggested impaired maternal alpha-1-antitrypsin levels are linked with poor

pregnancy outcomes [45], however any link with vitamin D in pregnancy remains speculative. In other recent reports, a relationship between increased vitamin D levels and IL-10-secreting Treg in children with cows' milk allergy (CMA) [46] with patients with CMA exhibiting greater vitamin D deficiency and lower numbers of CD4⁺CD25^{high}Foxp3⁺IL10⁺ Treg cells. In another milk allergy study, allergic children showing lower serum vitamin D levels than healthy children and increased Foxp3-mRNA expression predicted faster acquisition of tolerance in infants with CMA [47].

CONCLUSION

Observational studies have linked vitamin D status to risk of allergic sensitization, food allergy and asthma in the young. Interventional studies indicate that vitamin D sufficiency from early life and throughout pregnancy may reduce asthma incidence, but longitudinal data on food allergy are lacking. Experimental studies to date suggest an immunomodulatory role for vitamin D to increase antimicrobial protection and enhance regulatory responses and tolerance.

FUTURE PERSPECTIVES

Optimising vitamin D supplementation regimens that are initiated early in pregnancy or even pre-conception, and postnatally is highly desirable, as is a better understanding of the advantages of supplementation of the infant, breastfeeding mother or both. Factors that influence vitamin D bioavailability and responsiveness, including genotype, are not yet fully explored. Defining the impact of vitamin D supplementation on sensitization to food and aero-allergens, including longitudinal and interventional studies, is of interest. Evidence from animal models indicate that vitamin D status in utero impacts lung development and maturation; further human studies, whilst challenging, are desirable [48]. Simultaneous mechanistic studies will enhance our understanding of the immunomodulatory effects of vitamin D during pregnancy, lactation and infancy and identify how distinctive aspects of foetal and infant immunity are altered and thereby maximise potential for intervention. Combining vitamin D sufficiency with other successful approaches to promote allergen-specific tolerance induction in early-life, such as early introduction to allergenic foods [5,6], may offer added benefits.

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Conflicts of interest

There are no conflicts of interest.

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