



Sunlight, vitamin D and food allergy

Susan A. Rudders^a and Carlos A. Camargo Jr^b

Purpose of review

The role of vitamin D in the development of food allergy is unclear. We summarize recent data on the epidemiologic link between sunlight (UVB) and food allergy, and evidence for and against a specific role for vitamin D status.

Recent findings

Since 2007, most epidemiologic studies have supported low sunlight (as measured by season of birth and latitude) as a risk factor for food allergy. Investigators have also looked directly at vitamin D status (as measured by serum 25OHD level) and its potential role. Although conflicting, the vitamin D studies suggest a more complicated association than a linear dose response in all individuals, with some studies indicating different associations based on host characteristics (e.g. concomitant eczema, genetic polymorphisms, country of birth). Most studies have not fully examined the myriad effects of sunlight but have instead focused on a single maternal, neonatal or childhood 25OHD level.

Summary

Many studies have linked sunlight with the development of food allergy but whether this is directly related to vitamin D status or a myriad of other sunlight-derived, seasonal and/or geographic factors remains uncertain. More studies are needed to investigate the role of sunlight and vitamin D status in food allergy because of their potential for primary prevention and disease modification.

Keywords

epidemiology, food allergy, prevention, risk factors, sunshine, vitamin D

INTRODUCTION

In what has been called the ‘second wave of the allergy epidemic’ [1], recent national surveys show a rapid increase in childhood food allergy with food allergy now affecting 4–8% of U.S. children [2,3] and even higher percentages of children in other developed countries [1,4]. The reasons for this rise in food allergy prevalence, however, remain unclear. Hypotheses include changes in early infectious disease exposures, population-level dietary changes and potential environmental influences, including the effects of a modern lifestyle [5]. The potential role of low sunlight exposure, with consequent lowering of vitamin D status, has received growing attention in recent years, and has biological plausibility based on vitamin D’s numerous immunomodulatory effects [6]. In this article, we review recent data on the epidemiologic link between sunlight and food allergy, and evidence for and against a specific role for vitamin D status.

SUNLIGHT AND FOOD ALLERGY

The potential link between sunlight, vitamin D and anaphylaxis was introduced by Camargo *et al.* [7] in

2007 based on novel findings that EpiPen prescriptions in the United States followed a distinct latitudinal pattern (Fig. 1). Independently of several potential confounders (including demographic and healthcare provider characteristics), there were increased EpiPen prescriptions in northern vs. southern areas of the United States. These ecologic findings supported the hypothesized link between decreased UVB radiation and anaphylaxis, including food-induced anaphylaxis (FIA). This study was followed by Australian studies reporting similar findings for EpiPens [8] and hypoallergenic formula

^aDivision of Asthma and Allergy, Department of Pediatrics, Rhode Island Hospital, Alpert School of Medicine at Brown University, Providence, Rhode Island and ^bDepartment of Emergency Medicine, and Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Correspondence to Dr Susan A. Rudders, Rhode Island Hospital/Hasbro Children’s Hospital, 593 Eddy Street, Providence, RI 02906, USA.

Tel: +1 401 444 7528; fax: +1 401 444 2168;

e-mail: srudders@lifespan.org

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KEY POINTS

- Numerous epidemiologic studies have linked UVB exposure with food allergy but whether this is directly related to vitamin D status or a myriad of other sunlight-derived, seasonal and/or geographic factors remains uncertain.
- Studies looking directly at vitamin D (as measured by serum 25OHD level) are conflicting but may suggest a more complicated association than a uniform, linear dose response in all individuals.
- Further studies are urgently needed to better investigate the role of sunlight and vitamin D status in food allergy because of their potential for primary prevention and disease modification.

[9]. Although the authors argued that food allergy is the primary driver of prescriptions for epinephrine autoinjectors and hypoallergenic formula in children, criticism stemmed from the use of these food allergy proxies. Accordingly, recent U.S. studies have examined emergency department visits [10] and hospitalizations [11,12[•]] for food allergy in children and reported that both outcomes were more frequent in northern vs. southern regions. Specifically, we recently reported that the rate of U.S. pediatric hospitalizations for FIA between 2000 and 2009 increased dramatically nationwide but was more than twice as high in the north-east compared with the south [12[•]]. Outside the United States, similar patterns have also been described in FIA hospitalization rates both in Chile [13] and in Italy [14]. It should, however, be recognized that not all studies have been equally supportive. For example, a telephone survey relying on parent-report of food allergy status reported the opposite relationship (food allergy in U.S. south > north) [15] and a large

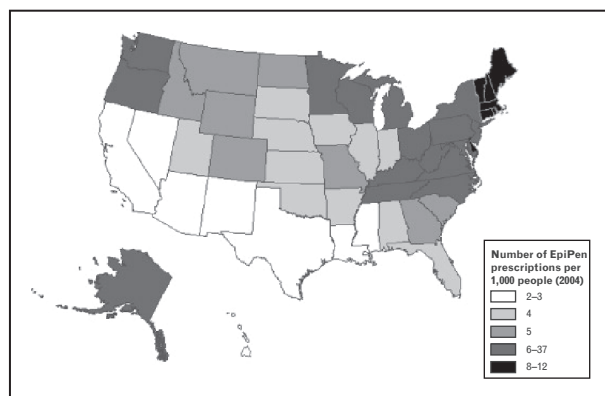


FIGURE 1. Regional differences in EpiPen prescriptions in the United States per 1000 persons. Reproduced with permission [7].

database study [16[•]] found no geographic difference in FIA fatalities, which may reflect management differences.

Further support for a role of sunlight comes from epidemiologic observations dating back to the 1990s that reported a possible link between season of birth and allergy [17,18]. Specifically, in 1997, Nilsson *et al.* [18] reported that in a cohort of children followed from 0 to 15 years, birth in September to February was associated with an increased incidence of atopic disease, including an increase in allergic sensitization to food. A specific link to clinical food allergy (using our current conception) was not reported but more recently, several investigators have explored the potential link between season of birth and food allergy per se. In 2010, Vassallo *et al.* [19] reported, from a cohort of over 1000 food allergy patients in Boston, that children less than 5 years old born in fall or winter had more than 50% higher odds of food allergy compared with controls. In another U.S. study, Keet *et al.* [20] investigated food allergy patients at a single specialty clinic and also participants in a national database and confirmed that fall birth was more common among food allergy patients. Interestingly, in this same study, the authors reported that the greatest risk occurred among white children and those with eczema and suggested, based on these findings, that both vitamin D and skin barrier function may be implicated in food allergy development. Most recently, Bird *et al.* [21[•]] reported that in a U.S. inner city asthma cohort ($n = 427$) there was increased sensitization to several foods (egg, peanut, soy) among black children born in the winter (Fig. 2). Similar findings connecting season of birth and food allergy have been reported from several other countries including cohorts in Australia [22] and Japan [23] (although the Japanese study reported differences in their results based on eczema status). Taken together, these data raise the possibility that there could be a crucial time in which sunlight affects immunologic development that is somehow reflected in season of birth. Whether the impact is during a specific point in pregnancy (e.g. first trimester) or during early infancy (e.g. during introduction to solid foods) is not yet known.

IS VITAMIN D THE KEY PLAYER?

Vitamin D physiology

Coincidentally with the rise in food allergy has been a growing awareness of the prevalence of vitamin D deficiency (VDD), a condition that is strongly linked to low levels of sunlight exposure. D3, the most effective vitamin D isoform [24], can be produced in the human epidermis by solar/thermal

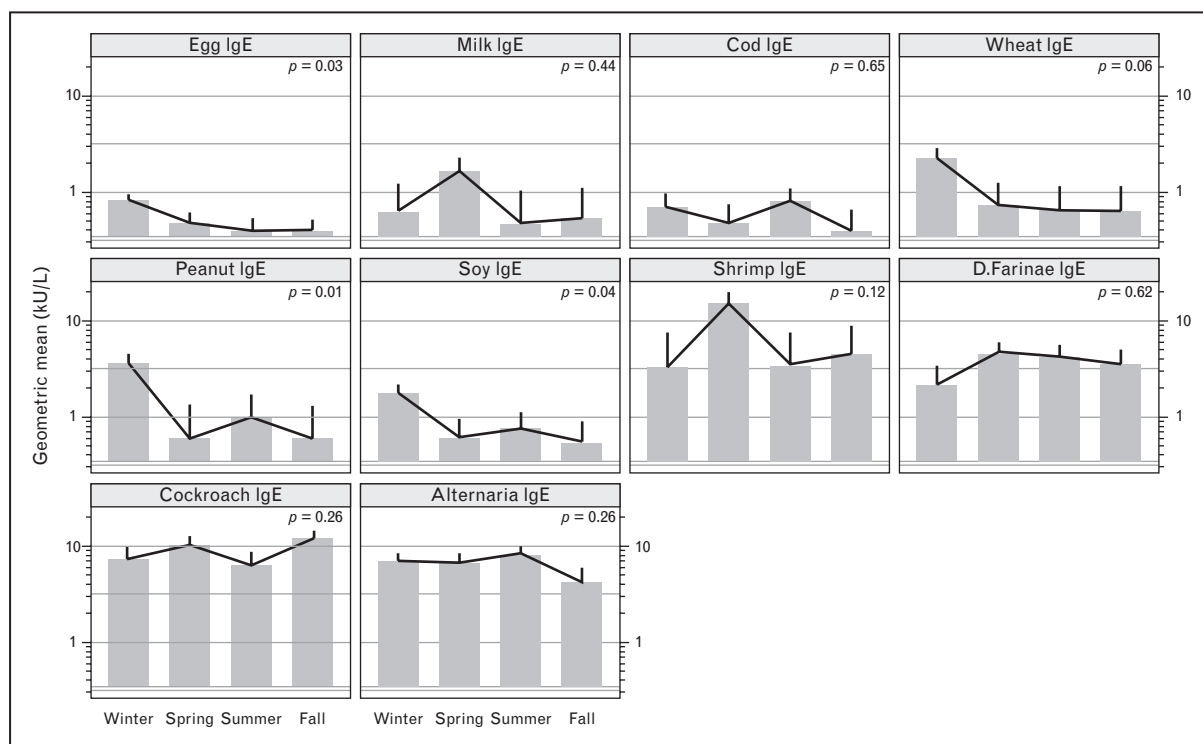


FIGURE 2. Association between specific IgE values and season of birth for black participants in a cohort of inner city asthmatic children. Reproduced with permission [21[■]].

conversion. Vitamin D is then converted in the liver into 25-hydroxyvitamin D (25OHD) and finally, in the kidney (and target tissues) into the active 'hormone' form, 1,25-dihydroxyvitamin D. Vitamin D levels are conventionally determined by 25OHD levels, which is the major circulating form and reflective of vitamin D intake from all sources (sunlight, dietary intake and supplementation). As little vitamin D is present naturally in most foods, vitamin D status is closely related to sunlight exposure. Ultraviolet radiation is estimated to provide more than 90% of vitamin D in humans [25]. As such, risk factors for VDD include many factors related to the individual's ability to synthesize sunlight-derived vitamin D, including geographic locations with less UVB radiation and 'dark' seasons (i.e. UVB intensity at more than 35° latitude is insufficient to synthesize vitamin D during late fall and winter). Furthermore, dark-colored skin, sunscreen use, skin coverage with clothing and increased time spent indoors have all been linked to an increased risk of VDD. Other nonsunlight-related risk factors include obesity (due to sequestration of vitamin D in adipose tissue) and gastrointestinal disorders (due to malabsorption of vitamin D precursors).

The precise 25OHD threshold that defines VDD is vigorously debated and may differ for children/adolescents vs. adults. Furthermore, it is newly

appreciated that different polymorphisms in vitamin D binding protein may result in similar levels of bioavailable vitamin D despite differences in 25OHD levels [26]. Regardless of the precise thresholds used, VDD has been found to be common worldwide. In the United States, data from the National Health and Nutrition Examination Survey (NHANES) 2005 to 2006 demonstrated that 42% of adults (≥ 20 years) had 25OHD levels less than 50 nmol/l [27]. Using the same national database, approximately 18% of U.S. children were deficient (< 50 nmol/l) [28]. Finally, even when compliant with routine prenatal supplementation, VDD has also been found to be common in pregnant women [29].

Vitamin D and the immune system

Since early in the last century, sufficient intake of vitamin D has been recognized as important for calcium homeostasis and bone health. Vitamin D receptors are, however, present in the vast majority of cells in the body and the conversion of vitamin D to its active form can occur outside the kidney, including in numerous immune cells. Accordingly, recent evidence suggests that vitamin D also has numerous important roles as an immune regulator within both the realms of innate and adaptive immunity [30].

Innate immunity includes the elements of our immune system that are 'hard-wired' to provide immediate defense against pathogens. Within the innate immune system, vitamin D appears, in general, to improve antimicrobial defenses. Specifically, cathelicidin, an antimicrobial peptide that provides an important innate barrier function against infections, has been shown to be vitamin D-dependent with enhanced production and improved antimicrobial response when stimulated by vitamin D [31]. Similarly, vitamin D has been shown to have important effects on the differentiation and function of several cellular components of innate immunity including monocytes/macrophages [30,32] and natural killer cells [33,34].

The adaptive immune system is characterized by the ability to recognize specific known threats and adapt to new pathogens. Almost all cells of the adaptive immune system express the vitamin D receptor, making them also capable of being vitamin D responsive [35]. When specifically considering a potential role for vitamin D in food allergy, vitamin D has been shown to affect several mechanisms that promote immunologic tolerance, including T regulatory cell function [36] and the induction of tolerogenic dendritic cells [37,38]. Recently, investigators reported that VDD in pregnant women impairs T regulatory cell function, which could have important implications for allergy predisposition/development in neonates [39]. The actions of vitamin D on T cells are more complex but also could link vitamin D with enhanced tolerogenic mechanisms. Vitamin D decreases proinflammatory cytokine release, upregulates regulatory cytokines (e.g. interleukin-10) and may have important effects on the TH1 and TH2 balance [40[¶]]. In terms of humoral immunity, vitamin D decreases B cell proliferation, plasma cell differentiation and immunoglobulin production [41]. Of particular relevance to food allergy pathogenesis, vitamin D inhibits the production of IgE [40[¶]] and vitamin D receptor agonists can suppress allergen-specific IgE synthesis both *in vitro* and *in vivo* [42,43]. Finally, it now appears that mast cells can actively metabolize 25OHD3 to dampen IgE-mediated mast cell activation [44]. Taken together, this information could have direct implications potentially on both primary prevention and treatment of food allergy.

Evidence for a role of vitamin D in food allergy

The growing body of knowledge on the immunomodulatory effects of vitamin D yields several hypotheses as to how VDD could be a risk factor for food allergy development. Vassallo and Camargo [6]

proposed several hypotheses, including that an altered gut microbiome could lead to increased sensitization. More recently, Keet *et al.* [20] focused on the role of a deficient skin barrier. The role of vitamin D on multiple allergic diseases, including asthma/wheeze, eczema, chronic urticaria and food allergy, has been investigated to varying extents and remains unclear. Existing evidence on the role of vitamin D specifically in food allergy comes from several sources, including: 1) cross-sectional studies, 2) cohort studies assessing vitamin D dietary intake during pregnancy, 3) cohort studies measuring maternal, cord blood, neonatal or childhood vitamin D status, and 4) a small number of interventional studies.

Several studies have investigated vitamin D levels and allergic diseases using cross-sectional designs. In 2011, Sharief *et al.* [45] reported from the NHANES database of over 3000 children and adolescents that VDD was associated with allergic sensitization to selected foods. A smaller Korean study [46] also suggested that VDD was associated with increased risk of food allergen sensitization. Meanwhile, Allen *et al.* reported from the Health-Nuts Study, a large prospective cohort of Australian infants, that children with 25OHD <50 nmol/l at 12 months were more likely to have challenge-proven food allergy but only among infants of Australian-born parents (suggesting a gene-environmental interaction) [47,48[¶]]. However, conflicting data exist. In a population of inner city children with asthma, in which season of birth correlated with allergy, there was no relationship between current vitamin D status and food allergen sensitization [21[¶]]. Furthermore, Wawro *et al.* [49] recently reported on >2000 children in two German cohort studies that those in the highest category of 25OHD level were more likely to have specific IgE positivity for food allergens. Finally, although some of these studies are supportive of the vitamin D-food allergy hypothesis, they are all unable to demonstrate causality due to their cross-sectional design and most are limited by their focus on food allergen-specific IgE, rather than clinical food allergy.

Current data from cohort studies [50–52,53[¶], 54–59] are even less uniform (Table 1). In 2010, Nwaru *et al.* [50] reported in a prospective cohort study that maternal intake of vitamin D during pregnancy was inversely associated with food sensitization; however, maternal diet history imperfectly assesses vitamin D status because diet makes only a small contribution to most people's vitamin D status [25]. Other studies have sought to assess vitamin D status directly via maternal, neonatal or childhood levels. The first study to assess neonatal 25OHD levels for this purpose was a study by Mullins *et al.* [51] which found a nonlinear (potentially U-shaped)

Table 1. Cohort studies that have evaluated the association between vitamin D status and food allergy-related outcomes

Study (year)	Patients (n)	Vitamin D assessment	Outcome	Main results	Reference
Nwaru <i>et al.</i> (2010)	Finnish type 1 Diabetes Prediction and Prevention Nutrition Study (n = 931 mother-child pairs)	Questionnaire data on maternal diet during pregnancy	Food-specific IgE at age 5	Maternal intake of vitamin D was inversely associated with food sensitization (OR = 0.56, 95% CI 0.35, 0.91)	[50]
Liu <i>et al.</i> (2011)	Boston Birth Cohort (n = 649 children)	Cord blood 25OHD	Food-specific IgE in early childhood	Decreased 25OHD in cord blood was not associated with food sensitization in the total population but did increase the risk among individuals with certain genotypes	[54]
Jones <i>et al.</i> (2012)	High risk infants from an Australian prospective birth cohort (n = 231 children)	Cord blood 25OHD	Positive skin prick test to food (egg, cow's milk, peanut), IgE-mediated food allergy (as defined by history of clinical reaction + positive skin prick test)	No association between cord blood 25OHD and allergen sensitization or food allergy	[58]
Mullins <i>et al.</i> (2012)	Peanut allergic children <72 months from an Australian specialty clinic (n = 115)	Neonatal 25OHD from dried blood samples	Peanut allergy (as defined by history of clinical reaction + positive skin prick test)	Nonlinear relationship between neonatal 25OHD and childhood peanut allergy (higher levels associated with lower risk)	[51]
Liu <i>et al.</i> (2013)	Boston Birth Cohort (n = 460 children)	25OHD in cord blood and at 2-3 years	Food-specific IgE in early childhood	The persistence of low vitamin D status at birth and in early childhood increased the risk of food sensitization (OR = 2.03, 95% CI 1.02, 4.04) Stronger association in children with interleukin-4 gene polymorphism	[55]
Weisse <i>et al.</i> (2013)	LINA German Cohort study (n = 378 mother-child pairs)	Maternal 25OHD at 34 weeks of pregnancy and cord blood 25OHD	Questionnaire data on doctor diagnosis of a food allergy	Maternal and cord blood 25OHD were positively associated with the children's risk of food allergy within first 2 years	[59]
Chawes <i>et al.</i> (2014)	Copenhagen Prospective Studies on Asthma in Childhood (n = 257 children)	Cord blood 25OHD	Food-specific IgE measured at 0.5, 1.5, 4 and 6 years	No association between cord blood 25OHD and food allergen sensitization [0-6 years]	[56]
Chiu <i>et al.</i> (2014)	Prediction of Allergies in Taiwanese Children (PATCH) study (n = 186 children)	Cord blood 25OHD	Food allergen sensitization at 0.5, 1, 1.5, 2, 3 and 4 years	Low 25OHD cord blood levels were associated increased risk of milk sensitization at age 2	[52]
Jones <i>et al.</i> (2015)	Subset of infants in randomized control trial (n = 225)	Cord blood 25OHD	Allergic cytokine responses at 6 months	Infants with higher 25OHD levels at birth (cord blood >75 nmol/l compared with <50) had lower allergic cytokine responses (interleukin-5, interleukin-13) at 6 months	[53]
Stelmach <i>et al.</i> (2015)	Polish Mother and Child Cohort Study (n = 190 children)	Cord blood 25OHD	Questionnaire data on doctor diagnosis of a food allergy	No association between cord blood 25OHD and food allergy	[57]

95% CI, 95% confidence interval; IgE, immunoglobulin E; 25OHD, 25-hydroxyvitamin D; OR, odds ratio.

association between neonatal 25(OH)D level and childhood peanut allergy. More recently, in a small Taiwanese birth cohort, cord blood 25OHD levels were associated with increased milk sensitization at 2 years [52] and in an Australian cohort, infants with higher 25OHD levels at birth (cord blood >75 nmol/l compared with <50) had lower allergic cytokine responses (interleukin-5, interleukin-13) at 6 months [53[¶]]. Although these studies support the potential for an association between vitamin D status and food allergy, when taken as a whole, the current body of cohort studies appears discordant. Data from a Boston birth cohort support an association only in distinct subpopulations [54,55]. Specifically, the authors reported cord blood VDD was not associated with food sensitization in the total population but did increase the risk among individuals with certain genotypes: interleukin-4 (rs2243250), MS4A2 (rs512555), FCER1G (rs2070901) and CYP24A1 (rs2762934) [54]. Interestingly, this same group later reported that persistently low levels throughout infancy/childhood did appear to increase risk of food sensitization overall [55]. Finally, to further complicate interpretation, some cohort studies [56–58] with direct measurement of 25OHD in cord blood have shown no association or even in the case of one study [59], report a positive association between 25OHD and risk for food allergy within the first 2 years. Criticism for the latter study, and some others showing no association, has included their reliance on parent or self-report for food allergy outcome measurement and significant loss to follow up.

Interventional studies (e.g. with random assignment of vitamin D supplement vs. placebo) would offer the best method to address causality; however, few exist to date. In 2013, Goldring *et al.* [60] reported data on a small randomized control trial in which 180 pregnant women at 27 weeks' gestation received either no vitamin D, 800 IU ergocalciferol (D2) daily until delivery or a single oral bolus of 200 000 IU cholecalciferol (D3). There was no significant difference in atopy (including food-specific IgE or 'doctor-diagnosed food allergy'), but the authors acknowledge that supplementation improved but did not optimize vitamin D status. In another recent publication, breastfeeding mothers ($n = 164$) of 1-month-old infants with facial eczema were randomly assigned to receive vitamin D3 supplements (800 IU/day) or placebo for 6 weeks [61]. The authors reported that there was no significant effect on eczema severity but surprisingly, doctor-diagnosed food allergy was more common in the vitamin D group. The authors acknowledged a large loss to follow up that may have resulted in significant bias but they did not

address the likely poor delivery of vitamin D via breastmilk at this supplement dose [62]. Nevertheless, both interventional studies raise questions regarding the importance of dose, mode of administration and timing. With regard to timing, if vitamin D has a role, when would it have its optimum effect: prenatally, neonatally or during infancy? Or is it optimal to receive vitamin D supplementation throughout this entire period? This could be addressed in future observational studies by measuring multiple levels at distinct time points or in interventional studies using different durations of supplementation.

CONCLUSION

Epidemiologic evidence supports low sunlight (UVB) exposure as a risk factor for food allergy, based on associations with season of birth and latitude. Data specifically on vitamin D status are conflicting but suggest that the relationship is nonlinear and requires consideration of numerous factors related to both the exposure and inherent characteristics of the host (e.g. concomitant eczema, genetic polymorphisms, country of origin). Most studies have not fully examined the myriad effects of sunlight but have instead focused on a single maternal, neonatal or childhood 25OHD level. In order to more clearly define this potential relationship, further studies are urgently needed to better investigate the role of sunlight and vitamin D status in food allergy because of their potential for primary prevention and disease modification.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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