Review Article

Food allergy is linked to season of birth, sun exposure, and vitamin D deficiency

Teruaki Matsui [a, *], Kajiyo Tanaka [b], Hirotaka Yamashita [c, d], Ken-ichi Saneyasu [c], Hiroyuki Tanaka [c, d], Yoshihiro Takasato [a], Shiro Sugiura [a], Naoki Inagaki [c, d], Komei Ito [a]

[a] Department of Allergy, Aichi Children's Health and Medical Center, Aichi, Japan
[b] Department of Nutritional Sciences, Nagoya University of Arts and Sciences, Aichi, Japan
[c] Laboratory of Pharmacology, Department of Bioactive Molecules, Gifu Pharmaceutical University, Gifu, Japan
[d] United Graduate School of Drug Discovery and Medical Information Sciences, Gifu University, Gifu, Japan

ABSTRACT

The season of birth and ultraviolet B exposure have been related to the occurrence of food allergy. The levels of vitamin D produced from skin by ultraviolet B exposure might reflect this relationship. Vitamin D is known to induce antimicrobial peptides, protect intestinal flora, enhance the gut epithelial barrier, suppress mast cell activation and IgE synthesis from B cells, and increase the number of tolerogenic dendritic cells and IL-10-producing regulatory T cells. Vitamin D deficiency has been shown to exacerbate sensitization and allergic symptoms in a murine model of food allergy. However, in clinical situations, contradictory observations have been reported regarding the relationship between food allergy and vitamin D deficiency/supplementation. In this review, we have explored the links between food allergy and vitamin D levels. One explanation for the discrepant findings is confounding factors such as race, age, residency, skin color, and epigenetic changes that contribute to vitamin D levels. In addition, the season of birth influences the development of atopic dermatitis, which could lead to food sensitization. Finally, ultraviolet radiation could lead to regulatory T cell expansion and immunosuppression, irrespective of vitamin D status. Based on our current understanding, we believe that correction of vitamin D deficiency by supplementation, appropriate skin care, and sufficient ultraviolet radiation exposure could alter the prognosis of food allergy. To identify potential treatment strategies for food allergy, it is essential to gain a better understanding of the appropriate levels of vitamin D and ultraviolet radiation exposure.

Introduction

Food allergy (FA), the incidence of which has been increasing worldwide, is known to affect ~5% of the total population and ~8% of the pediatric population.[1] However, the definite causes and reasons for the increase in incidence of FA remain unclear. Coincident with the rise in FA, cases of vitamin D deficiency have also been increasing worldwide.[2] Further, numerous lines of evidence link vitamin D deficiency with FA. In this comprehensive review, we have focused on the relationships among the season of birth, ultraviolet B (UVB) exposure, vitamin D deficiency, and FA.

Risk factors associated with allergic sensitization and FA

Bjourksten et al., in 1976, were the first to report that reactions to pollen and animal epithelium allergy differed based on the season of birth.[3] Since then, several reports have shown that the rate of allergic sensitization varies according to the month of birth. Subsequently, Kimpen et al. found that cord blood IgE concentration showed a significant cyclic trend, with a peak near the end of April and a trough in late October.[4] Further, the risk of food sensitization was observed to peak among individuals born in winter, while it was the lowest among those born in spring.[5] In Japan, Kuzume et al. showed that total serum IgE levels and egg white-specific IgE levels at 3 months of age were different according to the season of birth—lower in patients born in spring and summer, and higher in those born in autumn and winter.[6] Furthermore, the cumulative solar UV exposure during the 3 months before and after birth was inversely correlated to IgE levels. Previously, we reported the relationship between the season of birth and food sensitization

* Corresponding author. Department of Allergy, Aichi Children's Health and Medical Center, 7-426 Morioka, Obu-city, Aichi 474-8710, Japan.
E-mail address: teruaki_matsui@mx.achmc.pref.aichi.jp (T. Matsui).
Peer review under responsibility of Japanese Society of Allergology.

and showed that cumulative UV exposure after birth was negatively correlated with food sensitization during infancy.[7] Similar findings showing correlations between food sensitization and the month and season of birth have been reported.[7–9]

Adrenaline auto-injector prescriptions to treat anaphylaxis mainly caused by foods were higher in northern regions than in southern regions of the United States.[10] Similarly, in 5-year-old or younger patients who suffered from FA, food-induced anaphylaxis was more common in those born in autumn or winter than in those born in spring or summer.[11,12] Following these reports, similar findings have been described from all over the world.[13–16]

All these studies indicate that the season of birth, geographical location, and UVB exposure are risk factors associated with allergic sensitization and FA. However, contrasting results were also reported in a study, wherein no association was found between FA in the first year of life and season of birth, ambient UVB levels at birth, or maternal vitamin D supplementation.[17] However, this same study did find a correlation between vitamin D deficiency and FA.[17]

The potential link between vitamin D deficiency and FA

Solar UVB penetrates the skin and converts 7-dehydrocholesterol to previtamin D3, which is then rapidly converted to vitamin D3. In the liver, vitamin D is metabolized to 25-hydroxyvitamin D (25(OH)D), which is the most abundant metabolite of vitamin D and commonly used to determine a patient's vitamin D status. The 25(OH)D is then metabolized to 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] by the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1).[18] Extra-renal synthesis of 1,25(OH)$_2$D occurs in many tissues and cells, including keratinocytes and immune cells such as T cells and dendritic cells (DCs).[19] Humans can also obtain vitamin D from their diet.[18] However, the main source of vitamin D is sun exposure, contributing to 80–90% of an individual's serum 25-hydroxyvitamin D levels.[20] The solar exposure time required for vitamin D synthesis from sun exposure is longer in winter than in summer, with serum 25(OH)D levels reported to change cyclically with the season.[20]

Vitamin D deficiency has been identified as a major public health problem, which is continuously increasing across the globe.[2,21] Although there is no consensus on the optimal levels of 25(OH)D, vitamin D deficiency is often defined as a level less than 50 nmol/L.[18] Surprisingly, 25(OH)D concentration <50 nmol/L was reported to be present in 54% of pregnant women and 75% of newborns globally.[2] Correlation was seen between maternal and cord blood 25(OH)D levels, both showing a seasonal distribution.[22] Thus, a newborn's vitamin D status mostly depends on the maternal vitamin D status. During the first year of life, exclusive breastfeeding without adequate sun exposure is an important risk factor for vitamin D deficiency.[20] Additionally, an individual's exposure to sunlight has been limited by changes in lifestyle, such as the use of sunscreens, wearing of clothing that covers the skin, and increasing time spent indoors with closed windows that block UVB, all of which have been linked to an increased risk of vitamin D deficiency.[2,21]

Thus, similar to FA, vitamin D deficiency is also affected by seasons and other factors such as maternal vitamin D status. Therefore, we further explored the relationship between vitamin D deficiency and FA.

Season of birth and immune cells

Thysen et al. have shown a birth season-related fluctuation in neonatal immune cell subsets by phenotyping 26 different immune cells and identifying 20 cytokines and chemokines in cord blood. Specifically, summer newborns presented the lowest levels of all cell types and mediators; fall newborns displayed high levels of activated T cells and IL-13; and while winter newborns had the highest levels of innate immune cells, IL-5, and activated T cells.[23]

Mast cells

Yip et al. have reported that mouse and human mast cells can convert 25(OH)D to 1,25(OH)$_2$D via CYP27B1 activity.[24] Further, they showed that both metabolites could suppress IgE-mediated pro-inflammatory and vasodilatory mediator production from human mast cells in a vitamin D receptor (VDR)-dependent manner. Furthermore, these metabolites significantly reduced IgE-mediated passive cutaneous anaphylaxis reaction.[24]

Regulatory T cells

Almerighi et al. have reported that 1,25(OH)$_2$D inhibits CD40L-induced pro-inflammation and co-stimulation of CD4$^+$ T lymphocytes and enhances IL-10 production by CD4$^+$ T cells.[25] It has also been shown that 1,25(OH)$_2$D promotes the development of regulatory T cells (Tregs) expressing cytotoxic T-lymphocyte-associated protein 4 as well as forkhead box P3.[26]

B cells

B cells can generate 1,25(OH)$_2$D, which enhances IL-10 expression of activated B cells by recruiting VDR to the promoter of Il10.[27] Naïve T cells co-cultured with 1,25(OH)$_2$D-primed B cells showed reduced expansion, likely triggered by the expression of CD86 on B cells.[28] Wittke et al. have reported that IgE serum levels are increased in VDR-knockout (KO) mice.[29] Consistently, 1,25(OH)$_2$D was found to strongly suppress IgE production by human B cells,[30] and the IgE response in a type 1 allergy mouse model could be impaired by a VDR agonist.[30] Subsequently, this inhibition of IgE production by 1,25(OH)$_2$D was found to be mediated by its trans-repressive activity through the VDR-corepressor complex, which affects chromatin compacting around the Iϵ region.[31]

Dendritic cells

Szeles et al. have reported that an abundance of 25(OH)D causes dendritic cells (DCs) to turn on 1,25(OH)$_2$D sensitive genes, and activation of VDR by 1,25(OH)$_2$D reprograms the DCs to become tolerogenic.[32] When monocytes were treated with vitamin D3, DCs became semi-mature, expressing intermediate levels of co-stimulatory and major histocompatibility complex (MHC) class II molecules and could convert CD4$^+$ T cells to IL-10-secreting Tregs.[33] While vitamin D has insignificant effects on DC maturation and only weakly primes DCs to induce suppressive T cells, 25(OH)D not only exerts an inhibitory effect on DC maturation but also primes the DCs to promote Tregs to produce suppressive IL-10.[34]

Intestinal mucosal immunity

Toll-like receptor activation of human macrophages up-regulates expression of VDR and vitamin D-1-hydroxylase genes, leading to induction of the antimicrobial peptide cathelicidin.[35] Kong et al. have reported that 1,25(OH)$_2$D enhances tight junctions by increasing the levels of tight junction proteins and trans-epithelial electric resistance.[36] The expression of E-cadherin on gut epithelial and tolerogenic DCs was suppressed in CYP27B1-KO and VDR-KO mice compared to that in the wild type, leading to dysbiosis of the gut microbiota.[37]

When mice were fed a vitamin D-deficient diet, genes encoding the antimicrobial angiogenin-4 protein were down-regulated and

levels of bacteria in the colonic tissue were elevated 50-fold compared with that in controls.[38] Assa *et al.* have also shown that vitamin D deficiency altered the composition of the fecal microbiota and reduced transepithelial electrical resistance and permeability of the intestine.[39]

Thus, vitamin D deficiency could cause inadequate production of antimicrobial peptides, dysbiosis of the gut microbiota, and impairment of the mucosal barrier.

Animal studies of vitamin D deficiency and allergies

Heine *et al.* have reported that 25(OH)D deficiency promotes the development of type I sensitization and that correction of its serum concentrations enhances the benefit of specific immunotherapy in a murine model of allergic airway inflammation.[40] We showed that vitamin D deficiency exacerbated sensitization and allergic diarrhea in a murine FA model; the model was sensitized by both intraperitoneal and oral OVA administration and symptoms were induced by oral administration of OVA. We also confirmed that IL-4 expression in mesenteric lymph nodes was significantly elevated in vitamin D-deficient mice compared with that in control mice, which might be related to the mechanism underlying the exacerbation of sensitization and FA symptoms.[41] Maternal and early-life vitamin D deficiency also notably influenced the susceptibility to FA in another murine model.[42] Additionally, vitamin D deficiency also decreases the expression of the tight junction protein between adjacent epithelial cells and the percentages of $CD4^+CD25^+Foxp3^+$ Tregs in the spleen and mesenteric lymph nodes.[42]

Thus, there are a large number of studies providing clear evidence that vitamin D has several immunomodulatory effects that could be linked to FA. Vitamin D deficiency exacerbated allergic sensitization and FA symptoms in the murine model. In addition, as elaborated below, there have been clinical studies showing a direct relationship between vitamin D and FA.

Vitamin D deficiency and sensitization in clinical situations

Using data from a national health and nutritional survey, it was found that in children and adolescents, allergic sensitization to 11 of 17 allergens, including foods, was more common in those with 25(OH)D deficiency. However, no consistent associations were seen between 25(OH)D levels and allergic sensitization in adults.[43] Beak *et al.* also found that low levels of 25(OH)D could be related to polysensitization of food allergens.[44] Low 25(OH)D levels in cord blood and maternal blood before delivery have been associated with a higher risk of food sensitization throughout childhood in Taiwan.[45,46] In contrast, Xin *et al.* reported that there was no association between low vitamin D levels in cord blood and food sensitization, but that persistence of a low vitamin D status at birth and early childhood could increase the risk of sensitization.[47]

Vitamin D deficiency and FA in clinical cases

The antenatal and cord blood 25(OH)D levels are positively associated with risk of FA in children within the first 2 years of life, based on a birth cohort study of 378 mother–child pairs.[22] The same study also found that 25(OH)D levels were negatively correlated with Treg cell numbers. A higher incidence of food-induced anaphylaxis was seen in regions with lower annual mean solar radiation and lower vitamin D levels in South Korea.[48] Neeland *et al.* reported that children with persistent egg allergy demonstrated higher rates of vitamin D deficiency than children with transient egg allergy. Moreover, serum vitamin D levels were inversely correlated with proportions of myeloid DCs and classical monocytes.[49] Lower vitamin D levels were found in infants with

cow's milk allergy who were exclusively or predominantly breast-fed than in the control group.[50] On the other hand, Molloy *et al.* reported that there was no evidence that vitamin D deficiency during the first 6 months of infancy is a risk factor for FA at 1 year of age.[51]

Vitamin D supplementation and FA

Maternal intake of vitamin D has been inversely associated with sensitization to food allergens at 5 years of age.[52] On the other hand, in a double-blinded placebo-controlled trial, maternal vitamin D supplementation for 6 weeks during lactation increased the risk of FA in the offspring up to 2 years of age.[53] Tuokkola *et al.* have reported conflicting data that vitamin D supplementation during pregnancy is associated with an increased risk of FA in their offspring by 3 years of age, whereas vitamin D intake from foods during pregnancy is associated with a decreased risk of FA.[54] During a follow-up phase of an interventional trial of high-dose vitamin D given during pregnancy, it was found that food sensitization and FA were not correlated with vitamin D supplementation.[55] Thus, the relationship between vitamin D supplementation and FA remains controversial.

Possible factors explaining the discrepancy in the relationship between vitamin D deficiency and FA

As shown above, in clinical situations, conflicting data exist regarding the relationship between vitamin D deficiency and FA. Especially, it is not clear whether vitamin D supplementation can alter the prognosis of FA. Below, we have considered possible explanations for these conflicting data.

The definition of vitamin D deficiency

Willits *et al.* conducted a systematic review and meta-analysis of vitamin D and FA in children and reported no significant association between 25(OH)D status and risk of FA. Owing to the lack of an established threshold of vitamin D deficiency, they conducted subgroup analysis by stratifying the threshold of vitamin D deficiency. Interestingly, they did not find any significant relationship between FA and vitamin D deficiency when <20 ng/mL of 25(OH)D was considered as deficiency, while they did find an increased relevance of FA when < 30 ng/mL of 25(OH)D was considered as deficiency. Therefore, they reported that the study was limited by insufficient knowledge regarding the optimal vitamin D status.[56] Considering the increasing health problems associated with vitamin D deficiency, it is critical that we establish universally accepted normal serum 25(OH)D levels.[2,20]

Excessive vitamin D

Not only deficient but also excessive 25(OH)D levels have been related to high IgE concentrations.[57,58] Cairncross *et al.* reported that vitamin D deficiency was not associated with allergic diseases. In contrast, high 25(OH)D concentrations were associated with a two-fold increased risk of FA in preschool children in New Zealand.[59] Thus, both deficient and excessive amounts of vitamin D are potential risk factors associated with FA.

Race

Keet *et al.* reported that the risk of FA is the greatest among Caucasians, who are most sensitively produce vitamin D from skin via exposure to UVB.[14] In fact, darker skin rich in melanin decreases the synthesis of vitamin D in skin.[20] In a birth cohort study, it was

found that infants of Australian-born parents, but not of parents born overseas, with vitamin D insufficiency were more likely to show positive results in oral food challenge tests for peanut and egg at 1 year of age.[17,60] Thus, skin color and race could affect the susceptibility of the vitamin D status.

Epigenetics

Vitamin D activation enzyme CYP27B1 genotype ($-1260C > A$) was reported to be associated with increased IgE concentrations.[57] Vitamin D deficiency detected by cord blood was not associated with food sensitization; however, when examined jointly with single nucleotide polymorphisms (SNPs), vitamin D deficiency increased the risk of food sensitization among those carrying CC/CT genotypes of *IL4* (rs2243250).[47,61] Koplin et al. examined the relationship between genetic polymorphism of vitamin D binding protein (DBP) levels and FA.[62] They reported that low serum 25(OH)D level at 1 year was associated with FA, particularly among infants with the GG genotype but not in those with GT/TT genotypes.[62] Moreover, maternal antenatal vitamin D supplementation was associated with less FA, particularly in infants with GT/TT genotypes, and persistent vitamin D insufficiency increased the likelihood of persistent FA, particularly in those with the GG genotype.[62] Junge et al. have reported that cord blood 25(OH)D level was positively associated with physician-diagnosed FA and atopic dermatitis (AD), and negatively associated with the methylation level of the TSLP enhancer region in the LINA cohort study.[63] Interestingly, the methylation level was stable from birth until 3 years of age. Lockett et al. have reported that autumn birth increased the risk of repeated eczema, and methylation of 92 CpGs showed an association with season of birth in the epigenome-wide association study of a subset of an 18-year-old participants of a birth cohort study.[64] Thus, the epigenetic background affects the susceptibility to vitamin D deficiency.

Season of birth and AD

Infantile eczema and AD and exposure to food allergens through these sites are considered to be the leading causes of FA.[65,66] In the case of AD, Aoki et al. reported that more patients aged <1 year were born in autumn than in spring[67]; subsequent studies also reported similar seasonal differences.[6,68,69]

Although conflicting data exist, Kim et al. reported that vitamin D levels were lower in AD patients and that vitamin D supplementation could be a therapeutic option for AD.[70] Some reports showed that fall birth is common among FA subjects, but these observations were no longer significant when infantile eczema was included.[14,15] On the other hand, we showed that the frequency of autumn and winter birth in FA patients was significantly higher than that in the control population, irrespective of the presence of infantile eczema.[16]

Vitamin D is dispensable for UVB-induced immunosuppression

Yamazaki et al. have reported that exposure to UVB induced the expansion of Treg cells up to 50−60% of the CD4$^+$ T cells in the irradiated skin, which lasted for 2 weeks after exposure.[71] When antigen-loaded DCs, differentiated from the bone marrow of UV-irradiated mice, were adoptively transferred into naïve mice or mice pre-sensitized with antigen, the recipients exhibited a reduced immune response following antigen challenge when compared to that in mice without DC transfer.[72] Further, UV radiation is reported to inhibit the induction of contact hypersensitivity and induce Tregs, similar to the topical application of 1,25(OH)$_2$D. When Langerin$^+$ DCs were depleted, the induction of Tregs was abrogated by both ultraviolet radiation (UVR) and topical application of 1,25(OH)$_2$D. However, VDR-KO mice were equally susceptible to UVR-induced immunosuppression when compared to wild-type controls. Taken together, these observations suggest that 1,25(OH)$_2$D exerts immunosuppressive effects similar to UVR and is dispensable for local UVR-induced immunosuppression.[73]

Discussion and conclusion

In summary, there are numerous data that supports the link between FA and season of birth. The possible mechanisms might
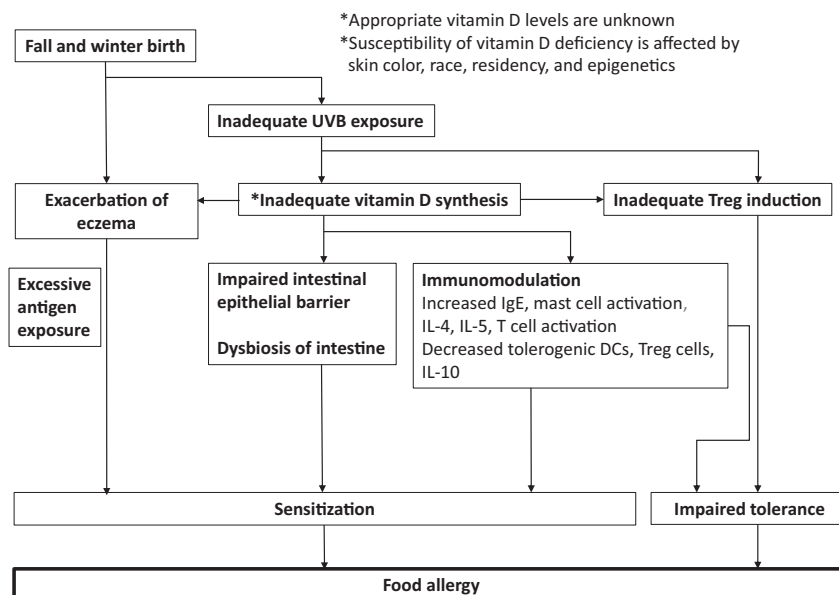
Fig. 1. A hypothesis of the link between the season of birth and food allergy (FA). First, fall or winter birth could exacerbate eczema, leading to excessive food antigen exposure and sensitization. Second, inadequate ultraviolet B (UVB) exposure can cause inadequate expansion of regulatory T cells (Tregs), possibly leading to impaired food tolerance. Third, vitamin D deficiency could impair the intestinal epithelial barrier, cause dysbiosis of the intestine, and modulate immune responses related to sensitization. Thus, vitamin D deficiency caused by inadequate UVB exposure shows a strong correlation with FA.

include vitamin D deficiency due to a shortage of UVR exposure. In fact, several in vitro and in vivo experiments suggested that vitamin D deficiency leads to FA. Nonetheless, there are some conflicting data regarding the relationship between vitamin D and FA based on clinical observations.

As to the relationship between season of birth and FA, we propose a hypothesis, as shown in Figure 1. Fall and winter birth could exacerbate eczema, possibly leading to excessive food antigen exposure and sensitization. Eczema and AD were shown to be strongly related to food sensitization and FA.[65,66,74] Some studies have successfully shown that skin care early in life could reduce the risk of AD.[75–77] Therefore, aggressive skin care for fall and winter-born children might reduce the risk of FA.

In addition, a shortage of UVR exposure can cause inadequate Treg expansion, possibly leading to impaired food tolerance irrespective of vitamin D deficiency. Thus appropriate UVR exposure might be necessary to reduce the risk of FA. However, sun protection is emphasized because UVR exposure is known as a risk factor for skin cancer.[78,79] On the other hand, inadequate UVR exposure is reported to be a risk factor for other diseases such as colorectal cancer, breast cancer, non-Hodgkin lymphoma, multiple sclerosis, cardiovascular disease, metabolic syndrome, and Alzheimer's disease.[80,81] Therefore, future studies are needed that determine the adequate amount of UVR exposure, balancing the risks and benefits with consideration of differences in skin color, season, and latitude.

Finally, vitamin D deficiency caused by inadequate vitamin D synthesis from skin could impair the intestinal epithelial barrier and antimicrobial peptides, possibly leading to dysbiosis of the intestine. Further, such deficiency could modulate immune responses including mast cells, DCs, B cells, and T cells, leading to sensitization and impaired food tolerance. Thus, vitamin D deficiency caused by inadequate UVB exposure shows a strong correlation with FA. Correcting vitamin D deficiency might improve the prognosis of FA. A precise definition of vitamin D deficiency and more clinical studies correcting for co-factors such as existing eczema, skin color, race, residency, skin color, sex, and age are warranted.

References

1. Sampson HA. Food allergy: past, present and future. *Allergol Int* 2016;**65**: 363–9.
2. Saraf R, Morton SM, Camargo Jr CA, Grant CC. Global summary of maternal and newborn vitamin D status - a systematic review. *Matern Child Nutr* 2016;**12**: 647–68.
3. Björkstén F, Suoniemi I. Dependence of immediate hypersensitivity on the month of birth. *Clin Allergy* 1976;**6**:165–71.
4. Specker B, Tsang R. Cyclical serum 25-hydroxyvitamin D concentrations paralleling sunshine exposure in exclusively breast-fed infants. *J Pediatr* 1987;**110**: 744–7.
5. Aalberse R, Nieuwenhuys E, Hey M, Stapel S. 'Horoscope effect' not only for seasonal but also for non-seasonal allergens. *Clin Exp Allergy* 1992;**22**:1003–6.
6. Kuzume K, Kusu M. Before-birth climatologic data may play a role in the development of allergies in infants. *Pediatr Allergy Immunol* 2007;**18**:281–7.
7. Matsui T, Tanaka K, Nakagawa T, Sasaki K, Nakata J, Sugiura S, et al. Sun exposure inversely related to food sensitization during infancy. *Pediatr Allergy Immunol* 2015;**26**:628–33.
8. Nilsson L, Kjellman NI. Atopy and season of birth. *Allergy* 1996;**51**:138–9.
9. Nilsson L, Björkstén B, Hattevig G, Kjellman B, Sigurs N, Kjellman NI. Season of birth as predictor of atopic manifestations. *Arch Dis Child* 1997;**76**:341–4.
10. Camargo Jr CA, Clark S, Kaplan MS, Lieberman P, Wood RA. Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. *J Allergy Clin Immunol* 2007;**120**:131–6.
11. Vassallo MF, Banerji A, Rudders SA, Clark S, Mullins RJ, Camargo Jr CA. Season of birth and food allergy in children. *Ann Allergy Asthma Immunol* 2010;**104**: 307–13.
12. Vassallo MF, Banerji A, Rudders SA, Clark S, Camargo Jr CA. Season of birth and food-induced anaphylaxis in Boston. *Allergy* 2010;**65**:1492–3.
13. Kim J, Chang E, Han Y, Ahn K, Lee SI. The incidence and risk factors of immediate type food allergy during the first year of life in Korean infants: a birth cohort study. *Pediatr Allergy Immunol* 2011;**22**:715–9.
14. Keet CA, Matsui EC, Savage JH, Neuman-Sunshine DL, Skripak J, Peng RD, et al. Potential mechanisms for the association between fall birth and food allergy. *Allergy* 2012;**67**:775–82.
15. Kusunoki T, Morimoto T, Sakuma M, Mukaida K, Yasumi T, Nishikomori R, et al. Effect of eczema on the association between season of birth and food allergy in Japanese children. *Pediatr Int* 2013;**55**:7–10.
16. Tanaka K, Matsui T, Sato A, Sasaki K, Nakata J, Nakagawa T, et al. The relationship between the season of birth and early-onset food allergies in children. *Pediatr Allergy Immunol* 2015;**26**:607–13.
17. Allen KJ, Koplin JJ, Ponsonby AL, Gurrin LC, Wake M, Vuillermin P, et al. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. *J Allergy Clin Immunol* 2013;**131**:1109–16. e1–6.
18. Holick M. Vitamin D deficiency. *N Engl J Med* 2007;**357**:266–81.
19. Suaini NH, Zhang Y, Vuillermin PJ, Allen KJ, Harrison LC. Immune modulation by vitamin D and its relevance to food allergy. *Nutrients* 2015;**7**:6088–108.
20. Antonucci R, Locci C, Clemente MG, Chicconi E, Antonucci L. Vitamin D deficiency in childhood: old lessons and current challenges. *J Pediatr Endocrinol Metab* 2018;**31**:247–60.
21. Elsori DH, Hammoud MS. Vitamin D deficiency in mothers, neonates and children. *J Steroid Biochem Mol Biol* 2018;**175**:195–9.
22. Weisse K, Winkler S, Hirche F, Herberth G, Hinz D, Bauer M, et al. Maternal and newborn vitamin D status and its impact on food allergy development in the German LINA cohort study. *Allergy* 2013;**68**:220–8.
23. Thysen AH, Rasmussen MA, Kreiner-Møller E, Larsen JM, Følsgaard NV, Bønnelykke K, et al. Season of birth shapes neonatal immune function. *J Allergy Clin Immunol* 2016;**137**:1238–46. e13.
24. Yip KH, Kolesnikoff N, Yu C, Hauschild N, Taing H, Biggs L, et al. Mechanisms of vitamin D(3) metabolite repression of IgE-dependent mast cell activation. *J Allergy Clin Immunol* 2014;**133**:1356–64. e1–14.
25. Almerighi C, Sinistro A, Cavazza A, Ciaprini C, Rocchi G, Bergamini A. 1Alpha,25-dihydroxyvitamin D3 inhibits CD40L-induced pro-inflammatory and immunomodulatory activity in human monocytes. *Cytokine* 2009;**45**: 190–7.
26. Jeffery LE, Burke F, Mura M, Zheng Y, Qureshi OS, Hewison M, et al. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. *J Immunol* 2009;**183**:5458–67.
27. Heine G, Niesner U, Chang HD, Steinmeyer A, Zugel U, Zuberbier T, et al. 1,25-dihydroxyvitamin D(3) promotes IL-10 production in human B cells. *Eur J Immunol* 2008;**38**:2210–8.
28. Drozdenko G, Scheel T, Heine G, Baumgrass R, Worm M. Impaired T cell activation and cytokine production by calcitriol-primed human B cells. *Clin Exp Immunol* 2014;**178**:364–72.
29. Wittke A, Weaver V, Mahon BD, August A, Cantorna MT. Vitamin D receptor-deficient mice fail to develop experimental allergic asthma. *J Immunol* 2004;**173**:3432–6.
30. Hartmann B, Heine G, Babina M, Steinmeyer A, Zugel U, Radbruch A, et al. Targeting the vitamin D receptor inhibits the B cell-dependent allergic immune response. *Allergy* 2011;**66**:540–8.
31. Milovanovic M, Heine G, Hallatschek W, Opitz B, Radbruch A, Worm M. Vitamin D receptor binds to the epsilon germline gene promoter and exhibits transrepressive activity. *J Allergy Clin Immunol* 2010;**126**:1016–23. e1–4.
32. Széles L, Keresztes G, Töröcsik D, Balajthy Z, Krenács L, Póliska S, et al. 1,25-dihydroxyvitamin D3 is an autonomous regulator of the transcriptional changes leading to a tolerogenic dendritic cell phenotype. *J Immunol* 2009;**182**: 2074–83.
33. Unger WW, Laban S, Kleijwegt FS, van der Slik AR, Roep BO. Induction of Treg by monocyte-derived DC modulated by vitamin D3 or dexamethasone: differential role for PD-L1. *Eur J Immunol* 2009;**39**:3147–59.
34. Bakdash G, van Capel TM, Mason LM, Kapsenberg ML, de Jong EC. Vitamin D3 metabolite calcidiol primes human dendritic cells to promote the development of immunomodulatory IL-10-producing T cells. *Vaccine* 2014;**32**:6294–302.
35. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006;**311**:1770–3.
36. Kong J, Zhang Z, Musch MW, Ning G, Sun J, Hart J, et al. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. *Am J Physiol Gastrointest Liver Physiol* 2008;**294**:G208–16.
37. Ooi JH, Li Y, Rogers CJ, Cantorna MT. Vitamin D regulates the gut microbiome and protects mice from dextran sodium sulfate-induced colitis. *J Nutr* 2013;**143**:1679–86.
38. Lagishetty V, Misharin AV, Liu NQ, Lisse TS, Chun RF, Ouyang Y, et al. Vitamin D deficiency in mice impairs colonic antibacterial activity and predisposes to colitis. *Endocrinology* 2010;**151**:2423–32.

39. Assa A, Vong L, Pinnell LJ, Avitzur N, Johnson-Henry KC, Sherman PM. Vitamin D deficiency promotes epithelial barrier dysfunction and intestinal inflammation. J Infect Dis 2014;**210**:1296−305.

40. Heine G, Tabeling C, Hartmann B, Gonzalez Calera CR, Kuhl AA, Lindner J, et al. 25-hydroxyvitamin D3 promotes the long-term effect of specific immunotherapy in a murine allergy model. J Immunol 2014;**193**:1017−23.

41. Matsui T, Yamashita H, Saneyasu KI, Tanaka H, Ito K, Inagaki N. Vitamin D deficiency exacerbates sensitization and allergic diarrhea in a murine food allergy model. Allergol Int 2018;**67**:289−91.

42. Wu J, Zhong Y, Shen X, Yang K, Cai W. Maternal and early-life vitamin D deficiency enhances allergic reaction in an ovalbumin-sensitized BALB/c mouse model. Food Nutr Res 2018;**62**.

43. Sharief S, Jariwala S, Kumar J, Muntner P, Melamed ML. Vitamin D levels and food and environmental allergies in the United States: results from the national health and nutrition examination survey 2005−2006. J Allergy Clin Immunol 2011;**127**:1195−202.

44. Baek JH, Shin YH, Chung IH, Kim HJ, Yoo EG, Yoon JW, et al. The link between serum vitamin D level, sensitization to food allergens, and the severity of atopic dermatitis in infancy. J Pediatr 2014;**165**:849−54. e1.

45. Chiu CY, Yao TC, Chen SH, Tsai MH, Tu YL, Hua MC, et al. Low cord blood vitamin D levels are associated with increased milk sensitization in early childhood. Pediatr Allergy Immunol 2014;**25**:767−72.

46. Chiu CY, Huang SY, Peng YC, Tsai MH, Hua MC, Yao TC, et al. Maternal vitamin D levels are inversely related to allergic sensitization and atopic diseases in early childhood. Pediatr Allergy Immunol 2015;**26**:337−43.

47. Liu X, Arguelles L, Zhou Y, Wang G, Chen Q, Tsai HJ, et al. Longitudinal trajectory of vitamin D status from birth to early childhood in the development of food sensitization. Pediatr Res 2013;**74**:321−6.

48. Kim SH, Ban GY, Park HS, Kim SC, Ye YM. Regional differences in vitamin D levels and incidence of food-induced anaphylaxis in South Korea. Ann Allergy Asthma Immunol 2016;**116**:237−43. e1.

49. Neeland MR, Koplin JJ, Dang TD, Dharmage SC, Tang ML, Prescott SL, et al. Early life innate immune signatures of persistent food allergy. J Allergy Clin Immunol 2018;**142**:857−64.

50. Silva CM, Silva SAD, Antunes MMC, Silva G, Sarinho ESC, Brandt KG. Do infants with cow's milk protein allergy have inadequate levels of vitamin D? J Pediatr (Rio J) 2017;**93**:632−8.

51. Molloy J, Koplin JJ, Allen KJ, Tang MLK, Collier F, Carlin JB, et al. Vitamin D insufficiency in the first 6 months of infancy and challenge-proven IgE-mediated food allergy at 1 year of age: a case-cohort study. Allergy 2017;**72**: 1222−31.

52. Nwaru BI, Ahonen S, Kaila M, Erkkola M, Haapala AM, Kronberg-Kippila C, et al. Maternal diet during pregnancy and allergic sensitization in the offspring by 5 yrs of age: a prospective cohort study. Pediatr Allergy Immunol 2010;**21**:29−37.

53. Norizoe C, Akiyama N, Segawa T, Tachimoto H, Mezawa H, Ida H, et al. Increased food allergy and vitamin D: randomized, double-blind, placebo-controlled trial. Pediatr Int 2014;**56**:6−12.

54. Tuokkola J, Luukkainen P, Kaila M, Takkinen HM, Niinisto S, Veijola R, et al. Maternal dietary folate, folic acid and vitamin D intakes during pregnancy and lactation and the risk of cows' milk allergy in the offspring. Br J Nutr 2016;**116**: 710−8.

55. Savage JH, Lee-Sarwar KA, Sordillo J, Bunyavanich S, Zhou Y, O'Connor G, et al. A prospective microbiome-wide association study of food sensitization and food allergy in early childhood. Allergy 2018;**73**:145−52.

56. Willits EK, Wang Z, Jin J, Patel B, Motosue M, Bhagia A, et al. Vitamin D and food allergies in children: a systematic review and meta-analysis. Allergy Asthma Proc 2017;**38**:21−8.

57. Hypponen E, Berry DJ, Wjst M, Power C. Serum 25-hydroxyvitamin D and IgE - a significant but nonlinear relationship. Allergy 2009;**64**:613−20.

58. Rothers J, Wright AL, Stern DA, Halonen M, Camargo Jr CA. Cord blood 25-hydroxyvitamin D levels are associated with aeroallergen sensitization in children from Tucson, Arizona. J Allergy Clin Immunol 2011;**128**:1093−99. e1−5.

59. Cairncross C, Grant C, Stonehouse W, Conlon C, McDonald B, Houghton L, et al. The relationship between vitamin D status and allergic diseases in New Zealand preschool children. Nutrients 2016;**8**:326.

60. Peters RL, Allen KJ, Dharmage SC, Lodge CJ, Koplin JJ, Ponsonby AL, et al. Differential factors associated with challenge-proven food allergy phenotypes in a population cohort of infants: a latent class analysis. Clin Exp Allergy 2015;**45**: 953−63.

61. Liu X, Wang G, Hong X, Wang D, Tsai HJ, Zhang S, et al. Gene-vitamin D interactions on food sensitization: a prospective birth cohort study. Allergy 2011;**66**:1442−8.

62. Koplin JJ, Suaini NH, Vuillermin P, Ellis JA, Panjari M, Ponsonby AL, et al. Polymorphisms affecting vitamin D-binding protein modify the relationship between serum vitamin D (25[OH]D) and food allergy. J Allergy Clin Immunol 2016;**137**:500−6.

63. Junge KM, Bauer T, Geissler S, Hirche F, Thurmann L, Bauer M, et al. Increased vitamin D levels at birth and in early infancy increase offspring allergy risk-evidence for involvement of epigenetic mechanisms. J Allergy Clin Immunol 2016;**137**:610−3.

64. Lockett GA, Soto-Ramirez N, Ray MA, Everson TM, Xu CJ, Patil VK, et al. Association of season of birth with DNA methylation and allergic disease. Allergy 2016;**71**:1314−24.

65. Lack G. Epidemiologic risks for food allergy. J Allergy Clin Immunol 2008;**121**: 1331−6.

66. du Toit G, Tsakok T, Lack S, Lack G. Prevention of food allergy. J Allergy Clin Immunol 2016;**137**:998−1010.

67. Aoki T, Kojima M, Adachi J, Fukuzumi T, Endo K, Sumitsuji H, et al. Seasonla variation in the month of first visit for atopic dermatitis patients. Allergol Int 1998;**47**:137−42.

68. Egeberg A, Andersen YM, Gislason G, Skov L, Thyssen JP. Neonatal risk factors of atopic dermatitis in Denmark − results from a nationwide register-based study. Pediatr Allergy Immunol 2016;**27**:368−74.

69. Sasaki M, Yoshida K, Adachi Y, Furukawa M, Itazawa T, Odajima H, et al. Environmental factors associated with childhood eczema: findings from a national web-based survey. Allergol Int 2016;**65**:420−4.

70. Kim MJ, Kim SN, Lee YW, Choe YB, Ahn KJ. Vitamin D status and efficacy of vitamin D supplementation in atopic dermatitis: a systematic review and meta-analysis. Nutrients 2016;**8**:789.

71. Yamazaki S, Nishioka A, Kasuya S, Ohkura N, Hemmi H, Kaisho T, et al. Homeostasis of thymus-derived Foxp3+ regulatory T cells is controlled by ultraviolet B exposure in the skin. J Immunol 2014;**193**:5488−97.

72. Ng RL, Scott NM, Bisley JL, Lambert MJ, Gorman S, Norval M, et al. Characterization of regulatory dendritic cells differentiated from the bone marrow of UV-irradiated mice. Immunology 2013;**140**:399−412.

73. Schwarz A, Navid F, Sparwasser T, Clausen BE, Schwarz T. 1,25-dihydroxyvitamin D exerts similar immunosuppressive effects as UVR but is dispensable for local UVR-induced immunosuppression. J Invest Dermatol 2012;**132**:2762−9.

74. Tsakok T, Marrs T, Mohsin M, Baron S, du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. J Allergy Clin Immunol 2016;**137**:1071−8.

75. Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH, et al. Emollient enhancement of the skin barrier offers effective atopic dermatitis prevention. J Allergy Clin Immunol 2014;**134**:818−23.

76. Lowe AJ, Su JC, Allen KJ, Abramson MJ, Cranswick N, Robertson CF, et al. A randomized trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitization: the PEBBLES pilot study. Br J Dermatol 2018;**17**:e19−21.

77. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. J Allergy Clin Immunol 2014;**134**:824−30.

78. Balk SJ. Council on environmental health, section on dermatology. Ultraviolet radiation: a hazard to children and adolescents. Pediatrics 2011;**127**:e791−817.

79. Moan J, Grigalavicius M, Baturaite Z, Dahlback A, Juzeniene A. The relationship between UV exposure and incidence of skin cancer. Photodermatol Photoimmunol Photomed 2015;**31**:26−35.

80. Hoel DG, Berwick M, de Gruijl FR, Holick MF. The risks and benefits of sun exposure 2016. Dermatoendocrinology 2016;**8**:e1248325.

81. Reichrath J. The challenge resulting from positive and negative effects of sunlight: how much solar UV exposure is appropriate to balance between risks of vitamin D deficiency and skin cancer? Prog Biophys Mol Biol 2006;**92**:9−16.