



Neonatal vitamin D status and childhood peanut allergy: a pilot study

Raymond James Mullins, MB BS, PhD, FRACP, FRCPA ^{*,†,‡}; Sunday Clark, MPH, ScD [§];
Veronica Wiley, PhD, FHGSA, FFS_c(RCPA) ^{¶,||}; Darryl Eyles, PhD ^{**}; and Carlos A. Camargo Jr, MD, DrPH ^{††,‡‡}

^{*} John James Medical Centre, Deakin, Australia, Medical School, Canberra, Australia

[†] Australian National University, Canberra, Australia

[‡] Department of Clinical Immunology, Faculty of Health, University of Canberra, Canberra, Australia

[§] Division of General Internal Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

[¶] New South Wales Newborn Screening Program, The Children's Hospital at Westmead, Westmead, New South Wales, Australia

^{||} Departments of Genetic Medicine and Pediatrics and Child Health, The University of Sydney, Sydney, Australia

^{**} Queensland Brain Institute, University of Queensland, Brisbane, Australia

^{††} Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

^{‡‡} Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

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ABSTRACT

Background: Although a number of factors have been proposed to explain the increase in food allergy during the last decade, the possibility that vitamin D status may play a pathogenic role has received recent attention.

Objective: To determine whether lower levels of neonatal 25-hydroxyvitamin D (25[OH]D) would be observed in children with peanut allergy compared with in population controls.

Methods: The concentration of 25(OH)D was measured from neonatal dried blood samples by liquid chromatography tandem mass spectrometry. Levels were compared between children with IgE-mediated peanut allergy younger than 72 months assessed during 2008–2011 in a specialist referral clinic in the Australian Capital Territory and population births matched by sex, birth date, and birth location. Odds ratios were calculated for the matched pairs across quintiles of 25(OH)D.

Results: Neonatal 25(OH)D levels ranged from 8 to 180 nmol/L (median, 66 nmol/L; interquartile range, 46–93 nmol/L); only 4 children (3%) had levels less than 25 nmol/L, and 24 (20.9%) had levels greater than 100 nmol/L. No significant association was found between socioeconomic or clinical factors and 25(OH)D levels. Compared with the reference group (50–74.9 nmol/L), levels of 75 to 99.9 nmol/L were associated with lower risk of peanut allergy ($P = .02$). No further reduction was found at levels of 100 nmol/L or higher, and the risk of peanut allergy at levels less than 50 nmol/L was not significantly different from the reference group.

Conclusion: The relationship between neonatal 25(OH)D level and childhood peanut allergy was nonlinear, with slightly higher levels (75–99.9 nmol/L) associated with lower risk than those in the reference group (50–74.9 nmol/L). Vitamin D status may be one of many potential factors contributing to childhood peanut allergy pathogenesis.

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Introduction

Food allergy (FA) and anaphylaxis have become increasing public and personal health burdens in developed countries during the last decade,^{1–3} with rates of peanut sensitization and challenge-

confirmed peanut allergy in 12-month-old infants in Southeast Australia of 8.9% and 3%, respectively.⁴ Although a number of factors have been proposed to explain the increase in FA,⁵ the possibility that vitamin D status may play a pathogenic role has received recent attention.^{6,7} In part, this is based on observations of latitudinal variation in epinephrine autoinjector prescription rates in the United States⁸ and Australia⁹; similar variations in infant hypoallergenic infant formula prescriptions in Australia¹⁰; latitudinal variations in hospital anaphylaxis admission rates in the United States^{11,12} and Australia⁸; latitudinal variations in childhood FA in Australia¹³; higher rates of physician-diagnosed FA in children born in the fall/winter compared with the spring/summer in the United States^{14,15} and Australia¹⁶; evidence that low vitamin D intake during pregnancy is associated with higher rates of food sensitization in early life in infants born of mothers with low vitamin D

Reprints: Raymond James Mullins, MB BS, PhD, John James Medical Centre, Suite 1, 175 Strickland Crescent, Deakin ACT 2600, Australia; E-mail address: rmullins@allergycapital.com.au.

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intake during pregnancy¹⁷; and higher rates of food sensitization among children and adolescents (but not adults) with vitamin D deficiency.¹⁸ The objective of the present pilot study was to prepare for a much larger case-control study that would examine the relationship between neonatal and childhood vitamin D status and risk of childhood peanut allergy.

Methods

Study population

The study was undertaken in a mixed adult-pediatric specialty allergy/immunology practice in the Australian Capital Territory (ACT) in Southeastern Australia, encompassing the city of Canberra. The practice services the local metropolitan population and surrounding regional (including coastal) areas. Referrals were received from general medical practitioners, accident and emergency departments, and pediatricians; patients were assessed by the first author (R.J.M.). Clinical and demographic data were entered prospectively into a searchable database (Blue Chip Clinical Research Module; Health Communication Network, Sydney, Australia: Microsoft Access; Microsoft Corporation, Redmond, Washington). Data (and accuracy) were analyzed and verified retrospectively in January 2011. Case patients were peanut allergic patients younger than 72 months born in the ACT and assessed by the first author (R.J.M.). Children younger than 72 months at the time of assessment were examined because 90% of first peanut reactions occur in this group.¹⁹ The assessment period 2008–2011 (birth years 2003–2010) was selected to maximize the ability to contact parents to obtain permission to access neonatal dried blood spot (DBS) samples for analysis. The Human Research and Ethics committee (Calvary Bruce/Calvary John James Private Hospitals) approved the study.

Patient evaluation and diagnostic criteria

The primary indication for undertaking skin prick testing (SPT) was a history of likely peanut allergy, with secondary indications for testing being another FA (where peanut had not yet been ingested or tolerated), or children with atopic eczema or siblings of a child with documented FA where parents were concerned about possible FA. Peanut, egg, milk, soy, prawn, fish, sesame seed, and all commercially available tree nut extracts were tested unless the patient regularly consumed and tolerated these foods. SPT was performed on the volar aspect of the forearm using metal lancets (Stallergenes, Antony, France) according to standard guidelines.²⁰ Glycerinated allergen extracts (Hollister Stier, Spokane, Washington) and histamine, 10 mg/mL, positive control (Hollister Stier) were purchased from EBOS Australia (Sydney, Australia). A positive SPT result was defined as a wheal size of at least 3 mm greater than a negative control (saline) at 15 minutes.²⁰ IgE-mediated FA was diagnosed only if there was a history of acute systemic allergic reaction (≥ 1 cases of urticaria, vomiting, bronchospasm, or vascular collapse) within 2 hours of known food exposure, combined with a SPT to the relevant food. (Patients with peanut sensitization only without a history of clinical reactivity do not form part of this study). A diagnosis of anaphylaxis was assigned if either of the first 2 criteria of the 2005 National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium definition were fulfilled, specifically if noisy or difficulty breathing (dyspnea, bronchospasm/wheeze, or cyanosis/hypoxia) and/or cardiovascular compromise arose in the setting of acute allergic symptoms.²¹

Ethics approval and access to neonatal blood spots

Dried blood spots (DBSs) DBSs are taken in the first 3 days of life and stored by the New South Wales Newborn Screening Program.²² Access to identifiable DBSs required written parental permission, which was obtained from parents of peanut allergic patients. Ge-

neric access to deidentified DBSs from population controls (but not to identifiable socioeconomic or clinical information) is allowed. The Human Research and Ethics Committee (Calvary Bruce/Calvary John James Private Hospitals) approved the study.

Neonatal blood spot analysis

25-Hydroxyvitamin D (25(OH)D) was measured by liquid chromatography tandem mass spectrometry (LCMS) as previously described²³ from DBSs taken from peanut allergic patients and from deidentified population controls selected by the New South Wales Newborn Screening Program. Paired samples from patients and controls were matched by sex, birth date, and birth location in the ACT. LCMS has been shown to reliably detect seasonal fluctuations, to be strongly correlated with neonatal cord blood measurement, and to be able to detect 25(OH)D after storage times of up to 20 years.²³ Because protein-bound 25(OH)D₃ is excluded from erythrocytes, results are reported as sera concentrations of 25(OH)D₃ in nmol/L, standardized to a hematocrit of 42.4% (as previously described²⁴) in capillary blood. Assay calibration was achieved by means of multipoint calibration curves for 25(OH)D₃ and 25(OH)D₂. All specimens were run in one batch, sorted by study identification number.

Additional information

Parents of peanut allergic patients were surveyed as part of this study and asked retrospectively about the use of general pregnancy vitamin supplements (containing an average of 400 IU of vitamin D) and specific vitamin D supplements (1000 IU of vitamin D) taken during each trimester of pregnancy, as well as any vitamins given to infants during the first year of infancy. Of note, commercially available pregnancy vitamin preparations in Australia do not contain peanut oil, and vitamin D supplements are generally taken in the form of tablets not cod liver oil. Limited information on patient socioeconomic status was recorded by noting hospital of birth (private vs public) and residential location using Socio-Economic Indexes for Areas codes, which range from 1 (least advantaged) to 10 (greatest advantage).²⁴

Statistical analysis

Consistent with guidelines for categorization of vitamin D deficiency²⁵ and other studies that have examined associations between vitamin D status and other allergic disorders,²⁶ neonatal sera levels of 25(OH)D were categorized into 4 groups: less than 50 nmol/L, 50 to 74.9 nmol/L, 75 to 99.9 nmol/L, and 100 nmol/L or greater. A level of 50 to 74.9 nmol/L was used as the reference group. Because clinical data were not available for the population controls, unadjusted analyses comparing differences between cases of peanut allergy and population controls were not possible. Because age, sex, and season of birth were considered to be potentially strong confounders (and available), we matched cases of peanut allergy and population controls on these factors during study implementation. Analyses were conducted using Stata statistical software, version 12.0 (StataCorp, College Station, Texas). The association between 25(OH)D categories and child characteristics were evaluated using the χ^2 test, Fisher exact tests, and Kruskal-Wallis rank sum test, as appropriate. Conditional logistic regression was used to evaluate the relationship between 25(OH)D categories and peanut allergy. All odds ratios are presented with 95% confidence intervals. A 2-sided $P < .05$ was considered statistically significant.

Results

Of 166 eligible children, 115 case patients (69%) were included in the analysis, with 51 excluded due to inability to contact parents ($n = 45$), absence of samples due to home birth ($n = 3$), refusal to

Table 1
Clinical characteristics of 115 peanut allergic patients stratified by neonatal sera 25(OH)D levels

Characteristic	25(OH)D level				P value
	<50 nmol/L (n = 36)	50–74.9 nmol/L (n = 35)	75–99.9 nmol/L (n = 20)	≥100 nmol/L (n = 24)	
Neonatal 25(OH)D, median (IQR), nmol/L	40 (31–45)	63 (59–70)	88 (80–92)	122 (115–152)	
Male, %	50	71	16	19	.28
Season of birth, %					.77
Winter	14	26	25	21	
Spring	25	26	20	42	
Summer	31	20	30	17	
Fall	31	29	25	21	
Born in private hospital, %	39	34	30	33	.94
SEIFA score, %					.97
<9	3	6	0	0	
9	42	37	45	42	
10	56	57	55	58	
Age evaluated, median (IQR), mo	42 (22–60)	38 (16–59)	32 (19–53)	23 (15–39)	.14
Age first reaction, median (IQR), mo	18 (12–41)	13 (12–18)	17 (12–31)	12 (11–14)	.07
Time between first reaction and clinical assessment, median (IQR), mo	8 (3–19)	11 (2–31)	5 (2–20)	7 (2–26)	.72
Onset time, median (IQR), min	10 (5–10)	10 (5–10)	10 (8–10)	10 (5–10)	.97
Initial SPT, median (IQR), mm	8 (6–11)	8 (6–10)	8 (7–10)	8 (6–10)	.70
Anaphylaxis, %	14	14	10	13	>.99
Eczema, %	86	86	85	88	>.99
Asthma, %	14	11	5	21	.49
Milk allergy, %	8	9	10	0	.48
Milk IgE, %	50	57	50	0	.20
Egg allergy, %	17	29	50	32	.09
Egg IgE, %	67	75	83	73	.81
Tree allergy, %	14	15	6	11	.92
Tree IgE, %	35	35	25	29	.84
Sesame allergy, %	0	6	5	0	.29
Sesame IgE, %	0	18	7	0	.09
Seafood allergy, %	0	3	0	0	.69
Seafood IgE, %	4	4	0	6	>.99
Prenatal multivitamin supplements (400–500 IU of vitamin D per dose), %					
First trimester	73	77	60	79	.49
Second trimester	74	71	50	71	.33
Third trimester	69	72	50	71	.39
Prenatal vitamin D supplements (1,000 IU of vitamin D per dose), %					
First trimester	3	9	5	4	.85
Second trimester	3	6	5	0	.77
Third trimester	3	9	5	0	.53
Child multivitamin supplements, %					
0–5 months	0	9	0	8	.15
6–12 months	3	3	0	0	>.99
Child vitamin D supplements, %					
0–5 months	0	0	0	0	
6–12 months	0	0	0	0	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; IQR, interquartile range; SEIFA, Socio-Economic Indexes for Areas; SPT, skin prick test.

participate (n = 2), or sample not found (n = 1). No significant differences were found between included and excluded patients on socioeconomic or clinical factors (data not shown).

Neonatal 25(OH)D ranged from 8 to 180 nmol/L (median, 66 nmol/L; interquartile range, 46 to 93 nmol/L); only 4 children (3%) had levels less than 25 nmol/L. No significant association was found between socioeconomic or clinical factors and 25(OH)D levels (Table 1). Compared with the reference group (50 to 74.9 nmol/L), levels of 75 to 99.9 nmol/L were associated with lower risk of peanut allergy ($P = .02$). Levels of 100 nmol/L or higher were also

associated with a lower risk compared with the reference group, but this was not statistically significant (Table 2). The risk of peanut allergy at levels less than 50 nmol/L was also not significantly different from the reference group.

Approximately two-thirds of the 115 mothers of children with peanut allergy reported use of general multivitamins during their pregnancy: first trimester (85 yes [74%], 27 no, and 3 uncertain), second trimester (79 yes [69%], 33 no, and 3 uncertain), and third trimester (77 yes [67%], 34 no, and 4 uncertain). A total of 69 mothers (60%) consumed a general multivitamin continuously throughout pregnancy. Three additional mothers were known to be vitamin D deficient and took specific vitamin D supplements throughout pregnancy, as did 3 others during the first trimester only. Five children with peanut allergy (4.3%) received general multivitamin supplements during the first 6 months of life and 2 (1.7%) during the second 6 months of life; none were given vitamin D specific supplements.

Discussion

In this pilot study, we found a nonlinear association between neonatal 25(OH)D level and childhood peanut allergy, with evi-

Table 2
Association between neonatal 25(OH)D levels and relative risk of peanut allergy compared with population controls, adjusted for date of birth, sex, and birth location

25(OH)D level	OR (95% CI)	P value
<50 nmol/L	0.65 (0.33–1.30)	.23
50–74.9 nmol/L	1.00 (Reference)	
75–99.9 nmol/L	0.37 (0.17–0.83)	.02
≥100 nmol/L	0.66 (0.28–1.59)	.36

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; OR, odds ratio.

dence that slightly higher levels (75–99.9 nmol/L) were associated with lower risk than among those in the reference group (50–74.9 nmol/L). Children with 25(OH)D levels less than 50 nmol/L did not differ significantly from those in the 50 to 74.9 nmol/L reference group or those with levels of 100 nmol/L or higher. The small numbers of children with DBS levels less than 25 nmol/L ($n = 4$) or greater than 125 nmol/L ($n = 11$) precluded analysis at these extremes of the vitamin D spectrum.

In examining possible caveats to this pilot study, we were able to compare vitamin D status in patients and population controls by location of birth location and residence but not by location of pregnancy. Although we were able to measure 25(OH)D status in only 69% of consecutive children with physician-diagnosed peanut allergy, there were no discernible socioeconomic or clinical differences between those included or excluded. Although the population controls were not necessarily disease free (because some would have peanut or other FA) and could only be matched by birth date and sex (not other potential clinical or socioeconomic factors for ethical reasons), this is unlikely to have influenced the results given that all of our cases had FA or peanut allergy compared with expected population control rates of 10% for FA and 3% for peanut allergy in Southeast Australia.⁴ Furthermore, the presence of FA in controls would more likely have obscured the relationship between 25(OH)D status and FA risk rather than enhanced it. Particular caution should be taken when interpreting the absolute 25(OH)D levels described and making assumptions about the degree of vitamin D insufficiency in our population, given the possibility that sample deterioration may have occurred during drying and storage. Such conclusions will require confirmation using matched frozen cord blood and DBS samples. Nonetheless, the gaussian distribution of 25(OH)D data together with matching of patients and controls by birth date make it unlikely that this would influence the *relative* difference between patients and controls.

Until now, the relationship between childhood sun exposure/vitamin D status and FA has been indirect and based on ecologic studies alone.^{8–11,13–16} Our pilot data provide provisional *direct* evidence that early childhood vitamin D status may contribute to FA pathogenesis. We also collected data on the use of vitamin supplementation during pregnancy and infancy, which is of potential relevance to our planned studies of vitamin D status in later infancy and risk of FA and is of importance given recent evidence that peanut allergy is often established by 12 months of age.⁴ Nonetheless, we specifically examined the relationship between vitamin D status at birth (whether achieved by sunlight exposure or by dietary supplements) and later peanut allergy development; our pilot data do not allow us to comment on the relationship between vitamin D status in later childhood and FA development.

It is possible that observational data linking vitamin D status to FA risk might also reflect reverse causation (eg, less outdoor activity undertaken by atopic mothers). This is relevant to the familial nature of atopic disease, the greater likelihood of inheritance of allergic disease from atopic mothers than fathers,²⁷ and the relationship between maternal and neonatal vitamin D status.²⁸ Furthermore, it is also important to be aware of published evidence that vitamin D supplementation might also increase the risk of allergic disease.²⁹ For example, maternal 25(OH)D levels greater than 30 ng/mL during pregnancy have been associated with a higher risk of offspring eczema at 9 months and asthma at 9 years compared with children born of women with levels of less than 10 ng/mL.³⁰ High daily doses ($\geq 2,000$ IU/d) of vitamin D–containing cod liver oil during infancy have also been linked to increased risk of sensitization to inhalant and food allergens, allergic rhinitis, and asthma.^{31–33} In interpreting the results of these studies, it is important to be aware that cod liver oil also contains vitamin A and that normal vitamin D signaling occurs via the heterodimerization of both ligand-bound vitamin A and D receptors. Therefore, their

presence in the same preparation has the potential to be mutually antagonistic,³⁴ although we did not examine vitamin A status in our study.

The lack of a linear relationship between vitamin D status and peanut allergy risk is not immediately intuitive but has been observed in other studies demonstrating a higher risk of aeroallergen sensitization for low (<50 nmol/L) and high (≥ 100 nmol/L) cord blood 25(OH)D levels.²⁶ This lack of linearity may be related to (1) type II error, (2) the absence of a relationship between vitamin D status and FA, or (3) the potential for a detrimental effect of very high levels of vitamin D to increase the risk of sensitization/allergy, as previously observed,²⁷ helping to explain apparently contradictory studies.

The biological plausibility of the vitamin D–allergy hypothesis is informed by growing evidence of the pleiotropic effects of vitamin D on the developing immune system. Recent studies have demonstrated associations between vitamin D receptor polymorphism and asthma risk³⁵; among genetic variants in the vitamin D activation enzyme, vitamin D levels, and total IgE³⁶; and between low vitamin D intake during pregnancy and higher cord blood interleukin 10 levels,³⁷ known to suppress IgE production.³⁴ Furthermore, vitamin D receptor agonists have been shown to suppress allergen specific IgE synthesis in vitro and in vivo,^{38,39} modulate dendritic cell maturation to induce tolerogenic dendritic cells, and induce regulatory CD4⁺CD25⁺Foxp3⁺ T cells but also Foxp3⁺T_H1 cells expressing interleukin 10,⁴⁰ thus affecting both T_H1 and T_H2 cell function, as recently reviewed.³⁴

If sunlight/vitamin D status is one of the many factors playing a role in childhood FA pathogenesis, the relationship between sunlight/vitamin D status and risk may not be linear. As with any hormone, supraphysiologic vitamin D levels might also be harmful. Furthermore, any effect of vitamin D status on disease risk may not be uniform across all age groups or applicable to all disorders traditionally classified as “atopic.” These data provide the rationale for larger case-control and community-based studies examining the relationship between vitamin D status in early childhood and FA development. If consistent associations are found, observational studies could be followed by randomized controlled trials to more formally test causality and monitor for adverse effects from vitamin D supplementation.⁴¹ Such studies would need to be undertaken in a number of age and ethnic groups and would have to take into account the significant genetic variability of the response to dietary supplementation and metabolism of vitamin D.⁴²

References

- [1] Australasian Society for Clinical Immunology and Allergy. The economic impact of allergic disease in Australia: not to be sneezed at. ASCIA/Access Economics Report. November 2007. <http://www.allergy.org.au/health-professionals/report-economic-impact-of-allergies>. Accessed March 1, 2012.
- [2] Patel DA, Holdford DA, Edwards E, Carroll NV. Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States. *J Allergy Clin Immunol*. 2011;128:110–115.
- [3] Lieberman JA, Sicherer SH. Quality of life in food allergy. *Curr Opin Allergy Clin Immunol*. 2011;11:236–242.
- [4] Osborne NJ, Koplin JJ, Martin PE, et al; HealthNuts Investigators. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol*. 2011;127:668–676.
- [5] Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol*. 2008;121:1331–1336.
- [6] Vassallo MF, Camargo CA Jr. Potential mechanisms for the hypothesized link between sunshine, vitamin D and food allergy in children. *J Allergy Clin Immunol*. 2010;126:217–222.
- [7] Mullins RJ, Camargo CA. Latitude, sunlight, vitamin D, and childhood food allergy/anaphylaxis. *Curr Allergy Asthma Rep*. 2012;12:64–71.
- [8] Camargo CA Jr, 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;120:131–136.
- [9] Mullins RJ, Clark S, Camargo CA Jr. Regional variation in EpiPen prescriptions in Australia: more evidence for the vitamin D–anaphylaxis hypothesis. *Ann Allergy Asthma Immunol*. 2009;103:488–495.

- [10] Mullins RJ, Clark S, Camargo CA Jr. Regional variation in infant hypoallergenic formula prescriptions in Australia. *Pediatr Allergy Immunol*. 2010;21:e413–e420.
- [11] Sheehan WJ, Graham D, Ma L, et al. Higher incidence of pediatric anaphylaxis in northern areas of the United States. *J Allergy Clin Immunol*. 2009;124:850–852.
- [12] Mulla ZD, Lin RY, Simon MR. Perspectives on anaphylaxis epidemiology in the United States with new data and analyses. *Curr Allergy Asthma Rep*. 2011;11:37–44.
- [13] Osborne NJ, Ukoumunne OC, Wake M, Allen KJ. Prevalence of eczema and food allergy is associated with latitude in Australia. *J Allergy Clin Immunol*. 2012;129:865–867.
- [14] Vassallo MF, Banerji AS, Rudders SA, Clark S, Mullins RJ, Camargo CA Jr. Season of birth is associated with food allergy in children. *Ann Allergy Asthma Immunol*. 2010;104:307–313.
- [15] Vassallo MF, Banerji A, Rudders SA, Clark S, Camargo CA Jr. Season of birth and food-induced anaphylaxis in Boston. *Allergy*. 2010;65:1492–1493.
- [16] Mullins RJ, Clarke S, Katelaris CH, Smith V, Solley G, Camargo CA Jr. Season of birth and childhood food allergy in Australia. *Pediatr Allergy Immunol*. 2011;22:583–589.
- [17] Nwaru BI, Ahonen S, Kaila M, 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.
- [18] 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;127:1195–1202.
- [19] Mullins RJ, Dear KB, Tang ML. Characteristics of childhood peanut allergy in the Australian Capital Territory, 1995 to 2007. *J Allergy Clin Immunol*. 2009;123:689–693.
- [20] Bernstein IL, Li JT, Bernstein DI, et al. Allergy Diagnostic Testing: An Updated Practice Parameter. *Ann Allergy Asthma Immunol*. 2008;100:s1–s148.
- [21] Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391–397.
- [22] The Children's Hospital Westmead. The NSW Newborn Screening Programme. <http://www.chw.edu.au/prof/services/newborn/>. Accessed June 1, 2012.
- [23] Eyles D, Anderson C, Ko P, et al. A sensitive LC/MS/MS assay of 25OH vitamin D3 and 25OH vitamin D2 in dried blood spots. *Clin Chim Acta*. 2009;403:145–151.
- [24] Australian Bureau of Statistics. Research Paper: Socio-Economic Indexes For Areas: Getting a Handle on Individual Diversity Within Areas, September 2011. Catalogue No. 1351.0.55.036. <http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/1351.0.55.036Sep%202011?OpenDocument>. Accessed March 1, 2012.
- [25] Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press; 2011.
- [26] Rothers J, Wright AL, Stern DA, et al. Cord blood 25 hydroxyvitamin D levels are associated with aeroallergen sensitization in children from Tucson, Arizona. *J Allergy Clin Immunol*. 2011;128:1093–1099.
- [27] Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma: does mother confer more risk than father? *Am J Respir Crit Care Med*. 1998;158:176–181.
- [28] De-Regil LM, Palacios C, Ansary A, Kulier R, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev*. 2012;2:CD008873.
- [29] Wjst M. Introduction of oral vitamin D supplementation and the rise of the allergy pandemic. *Allergy Asthma Clin Immunol*. 2009;5:8.
- [30] Gale CR, Robinson SM, Harvey NC, et al; Princess Anne Hospital Study Group. Maternal vitamin D status during pregnancy and child outcomes. *Eur J Clin Nutr*. 2008;62:68–77.
- [31] Hyppönen E, Sovio U, Wjst M, et al. Infant vitamin d supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. *Ann N Y Acad Sci*. 2004;1037:84–95.
- [32] Kull I, Bergström A, Melén E, et al. Early-life supplementation of vitamins A and D, in water-soluble form or in peanut oil, and allergic diseases during childhood. *J Allergy Clin Immunol*. 2006;118:1299–1304.
- [33] de Montis G, Truong M, Toussaint B, et al. Peanut sensitization and oily solution vitamin preparations. *Arch Pediatr*. 1995;2:25–28.
- [34] Moro JR, Iwata M, von Andriano UH. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol*. 2008;8:685–698.
- [35] Raby BA, Lazarus R, Silverman EK, et al. Association of vitamin D receptor gene polymorphisms with childhood and adult asthma. *Am J Respir Crit Care Med*. 2004;170:1057–1065.
- [36] Hyppönen E, Berry DJ, Wjst M, Power C. Serum 25-hydroxyvitamin D and IgE: a significant but nonlinear relationship. *Allergy*. 2009;64:613–620.
- [37] Zittermann A, Dembinski J, Stehle P. Low vitamin D status is associated with low cord blood levels of the immunosuppressive cytokine interleukin-10. *Pediatr Allergy Immunol*. 2004;15:242–246.
- [38] Hartmann B, Heine G, Babina M, et al. Targeting the vitamin D receptor inhibits the B cell-dependent allergic immune response. *Allergy*. 2011;66:540–548.
- [39] Milovanovic M, Heine G, Hallatschek W, et al. Vitamin D receptor binds to the ϵ germline gene promoter and exhibits transrepressive activity. *J Allergy Clin Immunol*. 2010;126:1016–1023.
- [40] van der Aar AM, Sibiryak DS, Bakdash G, et al. Vitamin D3 targets epidermal and dermal dendritic cells for induction of distinct regulatory T cells. *J Allergy Clin Immunol*. 2011;127:1532–1540.
- [41] Roth DE. Vitamin D supplementation during pregnancy: safety considerations in the design and interpretation of clinical trials. *J Perinatol*. 2011;31:449–459.
- [42] Wang TJ, Zhang F, Richards JB, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. *Lancet*. 2010;376:180–188.