abstract

OBJECTIVE: There has been growing interest in vitamin D insufficiency as a predisposing factor for allergy development based on immunoregulatory properties and epidemiological studies. The aim of this study was to investigate the association between vitamin D exposure in utero and allergic outcomes in the first year of life.

METHODS: Cord blood (CB) vitamin D was measured in 231 high-risk infants from an Australian prospective birth cohort. CB 25-hydroxyvitamin D3 (25(OH)D3) concentration was analyzed in relation to maternal vitamin D intake and the development of infant eczema, allergen sensitization, and immunoglobulin E-mediated food allergy.

RESULTS: Maternal intake of supplemental vitamin D was significantly correlated with CB 25(OH)D3 concentration ($r = 0.244$, $P = .003$), whereas dietary vitamin D did not influence CB levels. There was significant seasonal variation in CB 25(OH)D3 concentration suggesting that sunlight exposure was an important determinant. Lower CB vitamin D status was observed in infants that developed eczema ($P = .018$), and eczema was significantly more likely in those with concentrations <50 nmol/L in comparison with those with concentrations ≥75 nmol/L (odds ratio 2.66; 95% confidence interval 1.24–5.72; $P = .012$). This association remained significant after adjustment for multiple confounding factors. The associations between CB 25(OH)D3 concentration and allergen sensitization, immunoglobulin E-mediated food allergy, and eczema severity (SCORing Atopic Dermatitis) were not significant.

CONCLUSIONS: Reduced vitamin D status in pregnancy may be a risk factor for the development of eczema in the first year of life, reinforcing the need to explore the role of vitamin D exposure during development for disease prevention. Pediatrics 2012;130:e1128–e1135

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KEY WORDS vitamin D, eczema, cord blood, pregnancy, season of birth, maternal diet, supplementation, food allergy, sensitization, SCORAD, infant, DOHaD

ABBREVIATIONS 25(OH)D3—25-hydroxyvitamin D3
CB—cord blood
CI—confidence interval
IgE—immunoglobulin E
OR—odds ratio
SCORAD—SCORing Atopic Dermatitis

Mr Jones contributed to the design of the study, analysis of data, drafting and revising the article, and approval of final version; Dr Palmer contributed to the study design and provided intellectual input in revising the article and approving the final version; Dr Zhang assisted with statistical analysis, revising the article, and approving the final version, and Dr Prescott contributed to the conception and design of the study and acquisition of data, supervised the overall project, and contributed intellectual input in the drafting and revision of the article and approval of the final version.

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Allergic diseases are now the most common chronic disorders of childhood, with a pressing need to define the causal pathways and better prevention strategies. In particular, the rates of food allergy and eczema have continued to increase dramatically in children as part of what appears to be a “second wave” of the allergy epidemic. Progressively earlier presentations with disease clearly implicate early environmental influences such as exposures in pregnancy. Although this is likely to be multifactorial, there has been growing speculation that vitamin D insufficiency in pregnancy may have adverse consequences for early immune development of the fetus.

Previous studies provide a persuasive basis for the hypothesis that vitamin D may protect against allergic disease. Reduced maternal dietary vitamin D intake in pregnancy has been reported as a risk factor for respiratory conditions such as wheezing, asthma, and allergic rhinitis; however, these studies were largely based on questionnaire-derived data rather than biological measures. Other studies have examined “season of birth” as a surrogate marker of vitamin D status through sunlight exposure and found significantly higher rates of food allergy in children born in autumn and winter (compared with spring and summer), providing indirect evidence that seasonal variations in sunlight exposure may make an important contribution to early disease risk. In older children, there is also evidence of lower serum 25-hydroxyvitamin D3 (25(OH)D3) associated with allergen sensitization, eczema severity, and asthma.

Here, we have examined cord blood (CB) serum 25(OH)D3 levels as an indicator of fetal exposure to vitamin D in relation to infant eczema outcomes. Our prospective cohort study with well-defined allergic outcomes, documented maternal dietary and supplement intakes in pregnancy, and CB serum samples provided an ideal opportunity to examine this question in addition to other early allergic outcomes.

METHODS
Study Design and Subjects
The mother-infant pairs included in this study were derived from a larger (n = 669) prospective birth cohort recruited between 2002 and 2009 for the investigation of dietary exposures in relation to infant allergy outcomes. Only nonsmoking mothers with healthy, uncomplicated term pregnancies were recruited. The population used for this study was selected on the basis of (1) ≥2 frozen CB serum samples in storage (317/669), (2) allergic outcomes assessed at 12 months of age (259/317), and (3) at least 1 parent with a history of allergic disease (eczema, asthma, or hay fever) (231/259). The latter criterion was included because infants with a family history of atopy have a greater risk of developing allergic disease (50%-80%) than those with no family history (20%), providing greater statistical power, and results from this population are the most relevant and transferable to allergy prevention strategies. The cohort was recruited in Perth, Western Australia, as approved by the Princess Margaret Hospital Ethics Committee. Mothers provided written, informed consent.

Assessment of Antenatal Vitamin D Intake
In the last trimester of pregnancy, mothers completed a validated semi-quantitative food frequency questionnaire developed and analyzed by the Commonwealth Scientific and Industrial Research Organization in Adelaide, Australia. This recorded the frequency of consumption of 212 individual foods, mixed foods, and beverages from which vitamin D intake in IUs could be calculated. Energy intake cutoffs were applied to identify unreliable records. In addition to food and drink items, details of all dietary supplements taken in the last trimester of pregnancy (including doses, brands, and frequency of consumption) were collected. Reported supplement intake was converted into daily vitamin D intake (IU) by using composition information provided by the manufacturers.

Collection and Analysis of Umbilical CB Samples for 25(OH)D3 Concentration
At delivery, blood was collected from the umbilical cord or placental vein, and an aliquot (7–9 mL) transferred to a serum clot activator tube, which was kept out of light and processed within 8 hours. Aliquots of serum were stored at −80°C and transported in dry ice for analysis by RMIT Drug Discovery Technologies (Melbourne, Australia) by using liquid chromatography-tandem mass spectrometry (Applied Biosystems 4000 Q Trap and Agilent LC-MS/MS). The lower limit of quantification was 4.69 ng/mL for 25(OH)D3, and the intra-assay precision had a coefficient of variation of <5%.

For categorical analysis by CB 25(OH)D3 concentrations we used cutoffs of <50 nmol/L, 50 to 74.99 nmol/L, and ≥75 nmol/L, as described in the literature. Although similar cutoffs have been used by others in relation to CB concentrations, there is evidence to suggest that neonatal 25(OH)D3 concentrations are generally lower than CB concentrations. We therefore used these values as categorical descriptors of vitamin D status rather than diagnostic criteria.
Assessment of Allergic Status

The primary outcome measures in the infants at 12 months of age were eczema and allergen sensitization. Infants were defined as having eczema if they had a doctor’s diagnosis of eczema, or evidence of typical skin lesions. The extent and severity of the eczema was determined by the standardized SCORing Atopic Dermatitis (SCORAD) severity index, measured on the day and as mother-reported worst ever episode. An objective SCORAD of <15 was classified as mild, 15 to 40 as moderate, and >40 as severe. Allergen sensitization was assessed by use of the skin prick test by using common allergen extracts (whole egg, cow’s milk, peanut, house dust mite [Dermatophagoides pteronyssinus], cat, rye grass pollen, mold mix; Hollister-Stier Laboratories, Spokane, WA). A wheal diameter of ≥3 mm was considered positive. The secondary outcome was immunoglobulin E (IgE)-mediated food allergy, which was defined as a history of immediate symptoms (typically within 60 minutes) after contact with and/or ingestion of food and a positive skin prick test to the implicated food. Information on respiratory symptoms (recurrent wheeze) and physician-diagnosed asthma were also collected, but these were not analyzed because of the limitations in diagnosis at this age.

Statistical Analysis

In this high-risk population, we estimated that >40% of infants would have vitamin D deficiency and ~40% infants at age 1 who would have either food allergy, eczema, or atopy (defined by skin prick test). Based on these assumptions, a sample size of 230 was estimated to detect an odds ratio (OR) of 2.5 with a power >0.8 in the vitamin D deficiency group, at a significance of 0.05. The distribution of CB 25(OH)D3 concentration represented approximately normality after adjusting an outlying value. Because all results between the natural and adjusted data set were unaffecte, parametric tests were performed by using adjusted data. Objective SCORAD data and maternal vitamin D intake from diet or supplements were not normally distributed. Means were compared by using the Mann-Whitney U test. Differences in CB 25(OH)D3 concentration by month of birth were analyzed by 1-way analysis of variance and Bonferroni post hoc test. Logistic regression was used to estimate the risk of allergic outcomes by CB 25(OH)D3 status while adjusting for confounders. We included recognized confounders of vitamin D status and allergic disease in our analyses, specifically season of birth, pets in the home, infant gender, maternal age, maternal education, and ethnicity. All statistics were performed by using SPSS software (version 19 for IBM, SPSS Inc, Chicago, IL).

RESULTS

Population Characteristics

The characteristics of the study population (n = 231) are shown in Table 1. The maternal population was predominantly of white ethnicity and tertiary educated. A history of maternal allergic disease was reported for 86.1% of the infants, and 51.9% of the infants had both parents with a history of allergic disease.

CB 25(OH)D3 Concentrations

The mean (SD) CB 25(OH)D3 concentration was 58.4 (24.1) nmol/L, with a range of 9.18 to 246.34 nmol/L. The distribution of CB 25(OH)D3 concentrations are displayed in Fig 1.

Season of Birth Effect

Concentrations of CB 25(OH)D3 varied significantly by month of birth, with the Australian summer/autumn months of January, February, and March representing significantly higher levels than the winter/spring months of August, September, and October (Fig 2). Summer births showed a significantly greater percentage of CB 25(OH)D3 concentrations ≥75 nmol/L in comparison with spring births (43.9% and 12.1%, respectively) in addition to a smaller proportion with concentrations <50 nmol/L (12.2% and 65.5%, respectively, P < .001) (Fig 3).

Maternal Characteristics

Although the seasons of birth were not significantly different for Asian and white participants, CB 25(OH)D3 concentrations were significantly higher for those of white (59.39 [23.77] nmol/L, n = 184) in comparison with Asian ethnicity (37.01 [18.36] nmol/L, n = 9) (P = .006).

There was no relationship between CB 25(OH)D3 concentrations and maternal age controlling for season of birth, nor was maternal education a significant predictor of vitamin D status.

Maternal Vitamin D Intake From Diet and Supplements in Pregnancy

The reported intakes of vitamin D from background dietary sources suggest that 85.1% of women in the main cohort had dietary vitamin D intakes that were less than the recommended dietary intake during pregnancy of 200 IU/day. Antenatal supplement use was reported by 212/231 (91.8%) mothers, but information on brand, type, and frequency was only provided by 146/231 (63.2%). Vitamin D intake from diet and supplements is presented in Table 1.

The Relationship Between Maternal Intake and CB 25(OH)D3 Concentrations

Maternal intake of vitamin D from supplements was significantly correlated with CB vitamin D status (P = 0.244, P = .003), whereas the relationship between
CB levels and background dietary intake was not significant (\(r = -0.105, P = .173\)).

**Association Between CB 25(OH)D\(_3\) and Allergic Outcomes in Infants**

**Eczema**

Consistent with other similar populations at high risk of allergic disease, eczema was the most common expression of the allergic phenotype, affecting 34% of the infants in this study\(^{22}\). CB 25(OH)D\(_3\) concentrations were significantly (\(P = .018\)) lower in infants who had developed eczema by 12 months of age (Fig 4). The risk of eczema declined significantly as CB 25(OH)D\(_3\) increased, with a 10 nmol/L rise in CB 25(OH)D\(_3\) reducing risk by 13.3% (OR 0.87, 95% confidence interval [CI] 0.77–0.98; \(P = .020\)). The association remained significant after adjustment for multiple confounding factors (Table 3). We found a significant negative dose-response trend across categories of vitamin D status (OR 0.63, 95% CI 0.44–0.90; \(P = .013\)) and an OR 2.66 for infants with CB 25(OH)D\(_3\) < 50 nmol/L compared with the reference group of \(\geq 75\) nmol/L (95% CI 1.24–5.72; \(P = .012\)) (Fig 5). Mean CB 25(OH)D\(_3\) concentration was not significantly different between IgE- and non–IgE-associated eczema.

Objective SCORAD measures were conducted on 65/78 infants with eczema (severity categories described in Table 2). The median (interquartile range) SCORAD score on the day of assessment and worst ever were 7.8 (14) and 18.1 (13), respectively. We found no correlation between CB 25(OH)D\(_3\) concentration and SCORAD on the day of examination (\(r = 0.018, P = .9\)) or worst ever (\(r = 0.092, P = .467\)). There was no difference in SCORAD score between IgE- or non–IgE-associated eczema.

**Allergen Sensitization**

Skin prick tests were conducted on 217/231 infants. Of these 21.2% were found to be sensitized to at least 1 allergen (see Table 2). CB 25(OH)D\(_3\) concentration was not significantly associated with an increased risk for allergen sensitization (OR 1.00, 95% CI 0.99–1.01; \(P = .584\)).

**IgE-Mediated Food Allergy**

IgE-mediated food was present in 24/231 infants. Egg was the most common allergy affecting 6.5% of infants in this study, followed by milk and peanut allergy affecting 1.7% and 1.3%, respectively. Four of the 231 infants (1.7%) displayed allergy to 1 food. The risk of developing IgE-mediated food allergy was not related to CB 25(OH)D\(_3\) (OR 1.00, 95% CI 0.99–1.02; \(P = .584\)).

**Recurrent Wheeze**

There was no significant difference in mean CB 25(OH)D\(_3\) concentration between infants with or without recurrent wheeze (56.44 [24.44] nmol/L and 58.6 [24.1] nmol/L, respectively).
nor was risk of this outcome related to CB 25(OH)D3 concentration (OR 1.00, 95% CI 0.98–1.01; P = .731).

Association Between Maternal Vitamin D Intake and Allergic Outcomes in Infants

Maternal vitamin D intake from supplements was not different for infants with or without eczema (P = .571), allergen sensitization (P = .563), or IgE-mediated food allergy (P = .341). Supplemental intake (analyzed in increments of 50 IU) displayed no association with the risk of eczema (OR 1.02, 95% CI 0.95–1.11; P = .517), allergen sensitization (OR 0.98, 95% CI 0.90–1.07; P = .698), and IgE-mediated food allergy (OR 1.08, 95% CI 0.97–1.19; P = .169).

DISCUSSION

There is an increasing body of evidence linking vitamin D status and immune function, raising important questions about the relationship between fetal vitamin D status and the rising predisposition for allergic disease in young infants. This is the first study to report that reduced CB 25(OH)D3 levels, as an indicator of vitamin D status in utero, are associated with an increased risk of eczema in the first 12 months of life. Interestingly, although 25(OH)D3 concentrations were significantly lower in infants with eczema, there was no association between vitamin D status and allergen sensitization or presence of IgE-mediated food allergy in this cohort. In addition, we found that only 24.2% of participants had adequate vitamin D concentrations (≥75 nmol/L) despite the sunny and temperate climate experienced in Perth, Australia (although we recognize that CB 25(OH)D3 concentrations are generally lower than neonatal concentrations17). We did find marked seasonal variation in CB vitamin D status; summer births displayed significantly greater concentrations.

Consistent with our findings, Miyake et al23 found an association between lower maternal vitamin D consumption in pregnancy and increased risk of eczema in infants. These observations are also in keeping with a series of pregnancy studies that found that lower vitamin D intakes were associated with increased risk of other potential (respiratory-based) indicators of an allergic phenotype including recurrent wheeze,24,25 subsequent asthma, and allergic rhinitis.6 In addition, several studies using indirect measures of nondietary vitamin D such as season of birth (surrogate for sunlight exposure) found that birth in
winter months was associated with higher rates of subsequent eczema and food allergy. Although these studies support a protective role for improving status, they cannot exclude confounding effects of other seasonal factors such as variations in humidity and viral infections. The confirmed seasonal variations in vitamin D levels observed in our study provide support for the hypothesis that vitamin D is independently associated with eczema. Contrary to our results, Gale et al found that maternal serum 25(OH)D concentrations >75 nmol/L were associated with an increased risk of visible eczema on examination at 9 months of age. The method of diagnosis may be key here, because the risk of eczema was not significant when assessed by using the modified UK Working Party’s diagnostic criteria for atopic dermatitis.

There are relatively few other studies that use CB 25(OH)D3 to assess neonatal vitamin D in relation to allergic and immune outcomes. A recent longitudinal study conducted in New Zealand reported a protective association between CB 25(OH)D3 and the risk of wheezing and respiratory infection at 15 months of age, but consistent with our findings, no effect on sensitization. Also supporting our findings that CB 25(OH)D3 was not associated with IgE-mediated outcomes is a study by Liu et al that reports no overall association between vitamin D status and food-specific IgE levels (however, the authors did find that risk was increased for particular genotypes). The protective effects of vitamin D on eczema in our study, together with protective effects on wheezing in other studies, appear to be independent of IgE-related features, raising questions about the potential mechanisms.

The role of vitamin D in both skin barrier function and local antimicrobial defense could contribute to protective effects at mucosal and cutaneous surfaces. In the skin, the CYP27B1 enzyme (possessed by keratinocytes and monocytes) is required to hydroxylate 25(OH)D3 to the active 1,25(OH)2D3. This active form facilitates the production of the antimicrobial peptide cathelicidin. Notably, in subjects with atopic dermatitis, 25(OH)D3 levels are positively correlated with serum cathelicidin and its production in both keratinocytes and neutrophils. It is possible that insufficient vitamin D levels contribute to the impaired barrier function characteristic in eczema, because diminished CYP27B1 and reduced production of 1,25(OH)2D3 result in hyperproliferation of the basal layers and disrupted barrier integrity, coupled with impaired antimicrobial activity. Cathelicidin levels in lesional skin of established eczema increase significantly in response to oral 25(OH)D3 supplementation, supporting a role of vitamin D in promoting antimicrobial functions and barrier integrity. As in the study by Kanda et al, we did not find that serum vitamin D levels predicted the severity of disease (SCORAD).

A limitation of this study is that the high-risk nature of the population may not be reflective of other populations. In the absence of serial blood collections throughout pregnancy and infancy, it is

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TABLE 2  Allergy Characteristics of the 231 Infants at 1 Year of Age

<table>
<thead>
<tr>
<th>Infant Characteristics at 1 y</th>
<th>n (%)</th>
<th>Otherwise Stated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any allergic disease</td>
<td>100 (43.3)</td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>78 (34.1)</td>
<td></td>
</tr>
<tr>
<td>Objective SCORAD at 12 mo</td>
<td>7.8 (14)</td>
<td></td>
</tr>
<tr>
<td>Mild (&lt;15)</td>
<td>51 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Moderate (15–40)</td>
<td>13 (20)</td>
<td></td>
</tr>
<tr>
<td>Severe (&gt;40)</td>
<td>1 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Objective SCORAD at worst in preceding 12 mo</td>
<td>18.1 (13)</td>
<td></td>
</tr>
<tr>
<td>Mild (&lt;15)</td>
<td>20 (30.8)</td>
<td></td>
</tr>
<tr>
<td>Moderate (15–40)</td>
<td>42 (64.6)</td>
<td></td>
</tr>
<tr>
<td>Severe (&gt;40)</td>
<td>3 (4.6)</td>
<td></td>
</tr>
<tr>
<td>IgE-mediated food allergy</td>
<td>24 (10.4)</td>
<td></td>
</tr>
<tr>
<td>Sensitized to ≥1 allergen (SPT+)</td>
<td>46 (21.2)</td>
<td></td>
</tr>
<tr>
<td>Egg</td>
<td>36 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Peanut</td>
<td>15 (6.9)</td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td>4 (1.8)</td>
<td></td>
</tr>
<tr>
<td>HDM</td>
<td>7 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Cat</td>
<td>2 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Rye grass pollen</td>
<td>2 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Mold mix</td>
<td>1 (0.5)</td>
<td></td>
</tr>
</tbody>
</table>

SPT, skin prick test.
* Median (interquartile range).

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FIGURE 4  Mean CB 25(OH)D3 concentrations for infants that were positive or negative for allergic outcomes by 12 months of age.
also not possible to determine if variations in vitamin D levels at different stages of development differentially influence eczema risk. Likewise, although infant vitamin D supplementation and food fortification is not standard practice in Australia, we have not accounted for variations in infant vitamin D intake. Although we acknowledge that CB 25(OH)D₃ concentrations reflect recent vitamin D status, mainly in the last trimester, this biological measure remains a more accurate indicator of vitamin D status than dietary intake or other surrogate measures.

**CONCLUSIONS**

The findings of this study provide new evidence that reduced fetal exposure to vitamin D increases the risk of eczema in infants by 12 months of age. This adds to the growing body of evidence that vitamin D status is important for many aspects of health and that interventions to improve vitamin D status in pregnancy may be an important part of preventive strategies. This will be more definitively assessed through randomized controlled trials to assess the effects of maternal and/or infant vitamin D supplementation on immune development and clinical outcomes in childhood.

**ACKNOWLEDGMENTS**

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