

Maternal vitamin D levels are inversely related to allergic sensitization and atopic diseases in early childhood

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Keywords

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Abstract

Background: There are few studies addressing the impact of maternal vitamin D status on the vitamin D levels in offspring, their sensitization to common allergens and atopic disease development.

Methods: Children aged 0 through 4 yr from a birth cohort in the Prediction of Allergies in Taiwanese Children (PATCH) study were enrolled. Time series of serum 25-hydroxyvitamin D (25(OH)D) levels were measured in maternal blood before delivery, cord blood, and at age 1.5, 3, and 4 using an electrochemiluminescence-based assay. Specific IgE antibodies against food and inhalant allergens were measured at 6 months, and 1, 1.5, 2, 3, and 4 yr of age.

Results: A total of 164 mother–child pairs from a birth cohort were recruited in this study. The mean levels of maternal 25(OH)D were 23.2 ± 7.7 ng/ml with a high (up to 80%) prevalence of insufficient vitamin D status (< 30 ng/ml). A significant correlation was seen between maternal and cord blood 25(OH)D levels ($p < 0.001$), and a persistent lower 25(OH)D level was found in children born to mothers with deficient 25(OH)D levels. Deficient maternal 25(OH)D levels (< 20 ng/ml) appeared to be associated with a higher prevalence of allergen sensitization before age 2. Higher maternal 25(OH)D levels were significantly associated with lower risk of eczema (OR 0.12; 95% CI 0.02–0.63; $p = 0.012$) and asthma (OR 0.22; 95% CI 0.06–0.92; $p = 0.038$) at age 4.

Conclusions: Low maternal 25(OH)D levels appear not only to be associated with an increase in the prevalence of allergic sensitization but also the risk of eczema and asthma in early childhood.

Vitamin D levels are known to be associated with allergic diseases and may be implicated in the development of atopic diseases in childhood (1). Many studies have reported an inverse association between maternal intake of vitamin D during pregnancy and risk of the development of atopic diseases in offspring (2, 3). However, it has also been reported that children born to mothers with high vitamin D levels were more likely to develop offspring eczema compared to children born to mothers with low vitamin D levels (4). Early sensitization to allergens has consistently been identified as a risk factor for developing allergic respiratory diseases (5). To

date, there are, however, few studies addressing the association of maternal vitamin D status with allergen sensitization and the risk of developing atopic diseases in early childhood.

The aim of this study was to determine the longitudinal trajectory of vitamin D status from birth to 4 yr of age in children from a birth cohort in the Prediction of Allergies in Taiwanese Children (PATCH) study. The impact of maternal vitamin D status on the newborn vitamin D levels was assessed, and its relationship with sensitization to food and inhalant allergens and atopic disease development was also examined.

Methods

Patients

The Prediction of Allergies in Taiwanese Children (PATCH) study is a joint study initiated in 2007 to investigate the epidemiology and predictive factors of asthma and allergies in Taiwanese children, including subjects from a birth cohort and several cohorts of school and preschool children (6). In this birth cohort study, newborn babies delivered at Chang Gung Memorial Hospital (CGMH), Keelung, from October 1, 2007 to September 30, 2010, were recruited voluntarily and followed up until the age of 4 yr. Neonates born at more than 34 wk of gestation with birth weight ≥ 2500 g were enrolled. Infants with perinatal insult, significant neonatal respiratory difficulties, or congenital anomalies were excluded. Subjects who dropped out during the follow-up period were likewise excluded. This study was approved by the Ethic Committee of Chang Gung Memorial Hospital (No. 102-1842C). Informed written consent was obtained from the parents of all study subjects.

Data collection

The parents of enrolled babies were invited to answer a standardized questionnaire administered by well-trained investigators, at birth, at 6 months, and at 1, 2, 3, and 4 yr of follow-up. The questionnaire was derived from the well-validated International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (7). The details of information regarding demographic data, family atopy history, and the health care of children including breast-feeding and medical conditions were also collected at the same time.

Evaluation and diagnosis of atopic diseases

Information of current and past allergic symptoms for the diagnosis of atopic diseases was obtained from the validated ISAAC questionnaire (7). Specific questions related to the development of allergic/atopic diseases and symptoms were also inquired and evaluated by a pediatric pulmonologist at outpatient clinics. Eczema was diagnosed as a pruritic rash over the face and/or extensors with a chronic relapsing course as described by Hanifin and Rajka (8). Rhinitis was diagnosed as ever having the symptoms representing rhinitis such as sneezing, nasal congestion, itching, rhinorrhea in the last 12 months, or current use of medication for these symptoms (9). Asthma was diagnosed as ever having asthma, with the occurrence of recurrent wheeze in the last 12 months, or current use of asthma medication (10).

Allergen-specific serum immunoglobulin E

Serum samples were collected and measured at 6 months, and 1, 1.5, 2, 3, and 4 yr of age. Allergen-specific IgE was determined by a commercial assay for IgE (ImmunoCAP Phadiatop Infant; Phadia), and a mix of three most common

food allergens (egg white, milk, and wheat) and three most common inhalant allergens (*D. pteronyssinus*, *D. farina*, and *C. herbarum*) was measured (11). Values of ImmunoCAP Phadiatop Infant of ≥ 0.35 kU/l ($\geq$ class 1) were considered indicative of allergic sensitization (12).

Measurement of serum 25(OH)D levels

The levels of 25(OH)D were examined in mother–child pairs followed up regularly at clinics for a four-year follow-up period. Time series of serum 25(OH)D levels were measured in maternal blood before delivery, cord blood, and at age 1.5, 3, and 4 by a new automated electrochemiluminescence-based assay, Elecsys Vitamin D Total assay, which measures both 25(OH)D₂ and 25(OH)D₃ as the total 25(OH)D level (Roche Diagnostics, Mannheim, Germany). This assay has shown good precision (coefficient of variation (CV) <13.6%), as well as excellent correlation vs. the reference method, LC-MS/MS (13). Maternal 25(OH)D levels were categorized as being sufficient when ≥ 30 ng/ml, insufficient when between 20 and 29.9 ng/ml, and deficient when <20 ng/ml, as described in the literature (14).

Covariates

Detailed information on potential confounders related to maternal 25(OH)D levels and the development of atopic diseases was collected. The confounder of season of birth has been reported to be associated with both serum 25(OH)D levels and respiratory infections (14, 15). Exclusive breast-feeding has also been reported to be associated with reduced milk sensitization in early childhood (16). Other potential confounding variables of atopic diseases associated with maternal 25(OH)D levels were also included and analyzed.

Statistical analysis

Distribution of baseline characteristics categorized by maternal 25(OH)D levels was performed with univariable parametric and nonparametric tests such as ANOVA, chi-squared, Fisher's exact test, and Kruskal–Wallis rank sum test. Pearson's correlation test was performed to analyze the correlation between maternal and cord blood 25(OH)D levels. The associations of atopic diseases measured as a binary outcome with maternal 25(OH)D status were calculated by the odds ratio (OR), using standard methods of logistic regression analysis. Potential confounders of vitamin D levels were included in the analysis, and multiple logistic regression analysis was used to adjust for the confounding factors. Statistical analysis was performed using the Statistical Program for Social Sciences (IBM SPSS Statistics for Windows, version 20.0. Armonk, NY, USA: IBM), and graphs were plotted using GraphPad Prism Version 5.01 software (GraphPad Software Inc., San Diego, CA, USA). All statistical hypothesis tests were two tailed, and a p-value of <0.05 was considered to be significant.

Results

Characteristics of study population

A total of 258 children who fulfilled the inclusion criteria were voluntarily enrolled; 226 (87.6%), 210 (81.4%), 198 (76.7%), and 182 (70.5%) children were regularly followed up at clinics for a one-, two-, three-, and four-year follow-up period. The major reasons for dropout were the fear of blood drawing and parents' unwillingness of regular outpatient follow-up (17). Atopic diseases including eczema, rhinitis, and asthma were diagnosed in 21, 60, and 29 children, respectively, at 4 yr of age. Serum 25(OH)D levels were measured in final blood samples of 164 mother–child pairs who completed follow-up. There was no significant difference in the baseline characteristics of these 164 mother–child pairs and the full 258 pairs, indicating that the 164 mother–child pairs enrolled could be a representative sample of the full cohort. In these 164 pairs, the mean levels of maternal 25(OH)D were 23.2 ± 7.7 ng/ml. The distribution of maternal 25(OH)D concentrations was as

follows: 32 (20%) children with sufficient levels, 72 (44%) with insufficient levels, and 60 (36%) with deficient levels. Table 1 shows the baseline characteristics of 164 mother–child pairs enrolled in relation to maternal 25(OH)D status. Maternal serum levels of 25(OH)D varied significantly with increased maternal age ($p < 0.001$) and season of birth ($p = 0.049$). A relatively higher levels of maternal 25(OH)D were found in those born in winter as compared to those in spring (26.6 ± 7.3 vs. 21.4 ± 6.6 ng/ml).

Changes in serum 25(OH)D levels categorized by maternal 25(OH)D status

The mean levels of 25(OH)D in cord blood and at ages 1.5, 3, and 4 were 23.8 ± 9.5 , and 40.8 ± 10.6 , 32.8 ± 9.4 , and 28.3 ± 8.6 ng/ml, respectively. A positive significant correlation was seen between maternal and cord blood 25(OH)D levels ($r = 0.644$, $p < 0.001$) (Fig. 1a). During early childhood, serum 25(OH)D levels appeared to decrease

Table 1 Baseline characteristics of 164 mother–child pairs enrolled in relation to maternal 25(OH)D status

	Maternal 25(OH)D levels			
Characteristics	< 20 ng/ml (n = 60)	20–29.9 ng/ml (n = 72)	≥ 30 ng/ml (n = 32)	p-value
<i>Family</i>				
Maternal atopy	25 (41.7%)	31 (43.7%)	12 (37.5%)	0.842
Eczema	9 (15.0%)	6 (8.5%)	2 (6.2%)	0.327
Rhinitis	21 (35.0%)	27 (38.0%)	10 (31.2%)	0.796
Asthma	2 (3.3%)	6 (8.5%)	2 (6.2%)	0.477
Paternal atopy	29 (48.3%)	37 (52.1%)	22 (68.8%)	0.159
Eczema	3 (7.7%)	3 (6.8%)	3 (15.8%)	0.490
Rhinitis	24 (40.0%)	36 (50.0%)	20 (62.5%)	0.116
Asthma	0 (0.0%)	2 (4.7%)	0 (0.0%)	0.291
Passive smoking				
Maternal smoking	4 (6.7%)	3 (4.2%)	2 (6.2%)	0.803
Paternal smoking	26 (43.3%)	18 (25.0%)	11 (34.4%)	0.084
Parental smoking	27 (45.0%)	21 (29.2%)	12 (37.5%)	0.169
Older siblings	26 (43.3%)	25 (34.7%)	16 (50.0%)	0.304
Household income				
Low, ≤ 500,000 NTD	26 (43.3%)	21 (29.6%)	11 (34.4%)	0.417
Medium, 500,000–1,000,000 NTD	24 (40.0%)	39 (54.9%)	14 (43.8%)	
High, > 1,000,000 NTD	10 (16.7%)	11 (15.5%)	7 (21.9%)	
<i>Infant</i>				
Sex				
Male	35 (58.3%)	37 (51.4%)	20 (62.5%)	0.521
Female	25 (41.7%)	35 (48.6%)	12 (37.5%)	
Maternal age (yr)	29.6 ± 5.2	30.2 ± 3.7	32.5 ± 4.3	0.009
Gestational age (wk)	38.1 ± 2.0	38.2 ± 1.7	38.3 ± 1.7	0.806
Birth BMI (kg/m ²)	12.3 ± 1.3	12.7 ± 2.6	13.0 ± 2.7	0.274
Season of birth				
Spring (March to May)	20 (33.3%)	21 (29.2%)	8 (25.0%)	0.049
Summer (June to August)	18 (30.0%)	22 (30.6%)	3 (9.4%)	
Fall (September to November)	12 (20.0%)	12 (16.7%)	6 (18.8%)	
Winter (December to February)	10 (16.7%)	17 (23.6%)	15 (46.9%)	

Data shown are mean $\pm$ s.d. or number (%) of patients as appropriate. 25(OH)D, 25-hydroxyvitamin D; NTD, new Taiwan dollar; yr, year; wk, week; BMI, body mass index.

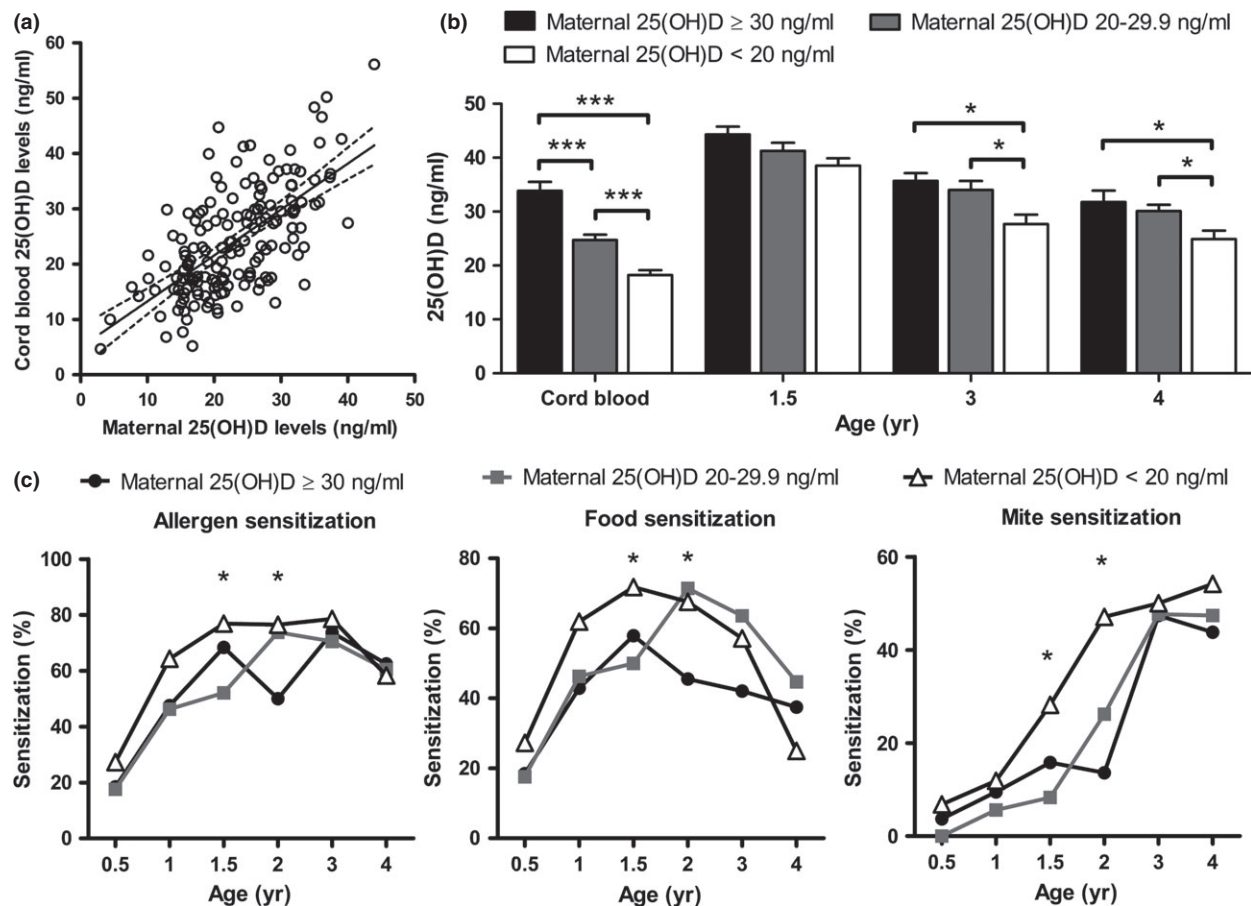


Figure 1 Association of maternal 25(OH)D status with serum 25(OH)D levels and allergen sensitization at different years of age. Correlation between maternal and cord blood 25(OH)D levels (ng/ml) (a). Comparisons and differences between maternal 25(OH)D status and serum 25(OH)D levels (b) and allergen sensitization (c) to any allergen and food and mite at different years of age. Data shown are mean $\pm$ s.e.m. or percent of subjects as appropriate. p-values referred to the comparisons of any allergen and food and mite sensitization at age 1.5 [maternal 25(OH)D < 20 ng/ml vs. maternal 25(OH)D 20–29.9 ng/ml] and at age 2 [maternal 25(OH)D < 20 ng/ml vs. maternal 25(OH)D ≥ 30 ng/ml] are indicated by the marker. * $p < 0.05$; *** $p < 0.001$.

gradually with increasing age. The prevalence of vitamin D deficiency (< 20 ng/ml) was 5%, 11%, and 18% at 1.5, 3, and 4 yr of age, respectively. A statistically significant lower 25(OH)D level was found in children born to mothers with deficient 25(OH)D levels compared to mothers with insufficient or sufficient 25(OH)D levels at 3 and 4 yr of age (Fig. 1b).

Association between maternal 25(OH)D status and allergic sensitization

Comparisons and differences between maternal 25(OH)D status and sensitization to food and inhalant allergens at different years of age are shown in Fig. 1c. There was a tendency of low maternal 25(OH)D levels (< 20 ng/ml) being associated with higher risk of allergen sensitization within the first 2 yr. Deficient maternal 25(OH)D levels were significantly associated with higher prevalence of allergen sensitization at

age 1.5 and age 2 in comparison with insufficient and sufficient maternal 25(OH)D levels, respectively.

Association of maternal 25(OH)D status and children's 25(OH)D levels with atopic diseases

Maternal 25(OH)D status was not associated with the risk of atopic diseases within the first two years of life. However, compared with deficient maternal 25(OH)D levels, high maternal 25(OH)D levels appeared to be associated with a significantly lower risk of eczema (OR 0.12; 95% CI 0.02–0.63; $p = 0.012$) and asthma (OR 0.22; 95% CI 0.06–0.92; $p = 0.038$) at age 4. The mean levels of 25(OH)D at age 1.5 and 3 were both > 30 ng/ml, which is classified as sufficient, and were not associated with the risk of allergic sensitization and atopic diseases within the first three years of life. Children with higher serum 25(OH)D levels at age 4 appeared to have reduced risk of eczema (OR 0.10; 95% CI 0.01–1.09; $p = 0.059$) and asthma

(OR 0.18; 95% CI 0.03–1.08; $p = 0.061$) with a nearly significant statistical difference at age 4 (Table 2).

Discussion

The association of maternal vitamin D status with allergen sensitization and atopic disease development remains uncertain. This study has demonstrated that maternal vitamin D deficiency (<20 ng/ml) is associated with higher risk of allergen sensitization, which may risk in the development of atopic diseases later in childhood. A significantly association of higher maternal vitamin D status with lower risk of developing eczema and asthma suggests that vitamin D supplementation during pregnancy may be recommended for the prevention of atopic diseases in early childhood.

In Taiwan, vitamin D deficiency is an under-recognized public health issue and more than half of children have vitamin D deficiency (12). Two cups of cow's milk per day have been shown sufficient to maintain healthy vitamin D for most young children (18). The average level of vitamin D was high at age 1.5 in this study; however, serum vitamin D levels decreased gradually with increasing age and the prevalence of vitamin D deficiency increased from 5% to 18% by the age of 4 yr. These findings raise the possibility that the change in baby's eating habits from milk to solids may play an important role in vitamin D deficiency in early childhood.

Vitamin D metabolites are important immune-modulatory hormones and are able to suppress Th2-mediated allergic airway disease (19). Genes associated with vitamin D have been reported to be involved in early lung development and asthma-related phenotypes (20). During pregnancy, the fetus is exposed to vitamin D through cord blood supply and its ability to cross the placenta (21). A strong association between maternal and infant 25(OH)D concentrations has been identified as in this

study (22). In addition, children born to mothers with a deficient vitamin D status appeared to have persistent and significantly lower serum vitamin D levels by the age of 4 yr compared to mothers with insufficient or sufficient vitamin D level. It is therefore postulated that vitamin D deficiency in pregnancy may directly affect fetal lung maturity that influences childhood asthma susceptibility.

There is lack of consistent data addressing the relationship between maternal vitamin D levels and allergen sensitization. In this study, maternal vitamin D levels appeared to be inversely associated with sensitization to food allergens, which is consistent with the report from the Finnish cohort (23). By contrast, a recent study reported that high vitamin D levels in pregnancy may contribute to a higher risk for food sensitization (24). One group even showed that both low vitamin D status (<20 ng/ml) and high vitamin D levels (>40 ng/ml) at birth were associated with total serum IgE levels and aeroallergen sensitization in early childhood (25). Despite discrepancies in some studies, the results demonstrated here are potentially important because of the long, sequential follow-up of our study at very close intervals.

Sensitization to allergens has been recognized as the most important risk factor for atopic diseases. The occurrence and severity of atopic diseases in later childhood have been reported to be directly related to allergen sensitization in infancy (17, 26). In this study, children born to mothers with a deficient vitamin D status appeared to have not only a significantly higher prevalence of food sensitization but also house dust mite sensitization within the first 2 yr of life. There is growing evidence suggesting linkage between vitamin D deficiency and increased incidence and severity of asthma in children (27). This study indicates that an inverse association of maternal vitamin D status with allergen sensitization may particularly explain the reports relating low maternal vitamin

Table 2 Association of maternal 25(OH)D status and children's serum 25(OH)D levels with the risk of developing atopic diseases at age 4

Atopic diseases		Maternal 25(OH)D levels (n = 164)					Serum 25(OH)D levels at age 4 (n = 102)				
		Crude		Adjusted*			Crude		Adjusted*		
		OR (95% CI)	p	OR (95% CI)	p		n (%)	OR (95% CI)	p	OR (95% CI)	p
Eczema (n = 21)											
<20 ng/ml	11 (28)	1.00 (Reference)		1.00 (Reference)			3 (17)	1.00 (Reference)		1.00 (Reference)	
20–29.9 ng/ml	4 (6)	0.25 (0.07–0.94)	0.041	0.12 (0.02–0.63)	0.012		4 (9)	0.33 (0.06–1.70)	0.185	0.25 (0.03–1.84)	0.174
≥30 ng/ml	6 (22)	0.96 (0.28–3.30)	0.941	0.51 (0.12–2.28)	0.379		4 (10)	0.13 (0.02–0.89)	0.038	0.10 (0.01–1.09)	0.059
Rhinitis (n = 60)											
<20 ng/ml	20 (51)	1.00 (Reference)		1.00 (Reference)			11 (61)	1.00 (Reference)		1.00 (Reference)	
20–29.9 ng/ml	28 (52)	0.80 (0.34–1.90)	0.619	0.79 (0.31–2.05)	0.634		17 (40)	0.37 (0.11–1.28)	0.116	0.43 (0.11–1.58)	0.201
≥30 ng/ml	12 (44)	0.78 (0.27–2.23)	0.642	0.75 (0.22–2.50)	0.639		15 (37)	0.29 (0.08–1.02)	0.053	0.52 (0.13–2.04)	0.352
Asthma (n = 29)											
<20 ng/ml	14 (35)	1.00 (Reference)		1.00 (Reference)			6 (33)	1.00 (Reference)		1.00 (Reference)	
20–29.9 ng/ml	10 (19)	0.34 (0.11–1.03)	0.057	0.22 (0.06–0.92)	0.038		7 (16)	0.26 (0.06–1.18)	0.081	0.18 (0.03–1.08)	0.061
≥30 ng/ml	5 (19)	0.52 (0.14–1.91)	0.328	0.40 (0.09–1.80)	0.228		9 (22)	0.25 (0.06–1.12)	0.070	0.49 (0.08–3.14)	0.449

Y, year; CI, confidence interval; OR, odds ratio. All p-values < 0.05, which is in bold, are significant.

*Adjusted for season of birth, maternal age at delivery, and exclusive breast-feeding for 6 months or longer.

D levels and risk for developing atopic disease in early childhood.

It is still debated that a vitamin D supplementation during pregnancy or in early childhood may reduce the allergy risk of the child. Some studies have even shown that excessive vitamin D supplementation in early childhood increased the risk of allergen sensitization and allergic respiratory diseases in children and adults (28, 29). In this study, compared with low maternal vitamin D levels (<20 ng/ml), children with high maternal vitamin D levels appeared to have significantly lower risk of eczema and asthma at age 4. In contrast, children's vitamin D levels were sufficient and not related to the development of atopic diseases during early childhood. These findings indicate that a vitamin D supplementation during pregnancy may be recommended for protecting against atopic diseases in offspring.

Limitations of this study include a relatively low response rate and small sample size of only 164 mother-child pairs with a limited power to detect a statistically significant association for subanalyses. There is also a limitation on the interpretation of our findings, because without correction for multiple comparisons. However, the strength of the present study lies in its longitudinal design, allowing sequential and concurrent measurements of serum vitamin D levels, allergen-

specific IgE for allergic sensitization and the accurate diagnostic evaluations for atopic diseases at outpatient clinics.

In conclusion, insufficient maternal vitamin D status (<30 ng/ml) is common with a prevalence rate as high as 80% in this study. Low maternal 25(OH)D levels (<20 ng/ml) appear to be associated with a significantly higher prevalence of allergen sensitization, which may risk in the development of atopic diseases in early childhood. Furthermore, high maternal vitamin D levels are significantly associated with reduced risk of developing eczema and asthma in later life. These findings suggest that vitamin D supplementation during pregnancy may not only against allergen sensitization but also reduce the risk of atopic diseases in early childhood. Further studies, however, are required to determine whether vitamin D helps prevent atopic diseases.

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