The Longitudinal Trajectory of Vitamin D Status from Birth to Early Childhood on the Development of Food Sensitization

Xin Liu[1,2,‡], **Lester Arguelles**[2], **Ying Zhou**[3], **Guoying Wang**[4], **Qi Chen**[1], **Hui-Ju Tsai**[1,5], **Xiumei Hong**[4], **Rong Liu**[1], **Heather E Price**[6], **Colleen Pearson**[7], **Stephanie Apollon**[7], **Natalie Cruz**[7], **Robert Schleimer**[8], **Craig B. Langman**[6], **Jacqueline Pongracic**[9], and **Xiaobin Wang**[1,4]

[1]Mary Ann and J. Milburn Smith Child Health Research Program, Department of Pediatrics, Northwestern University Feinberg School of Medicine and Children's Hospital of Chicago Research Center, Chicago, IL, USA

[2]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

[3]Biostatistics Research Core, Children's Hospital of Chicago Research Center, Chicago, IL, USA

[4]Center of Early Life Origins of Disease, Department of Population, Family and Reproductive Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

[5]Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan

[6]Division of Kidney Disease, Department of Pediatrics, Northwestern University Feinberg School of Medicine and Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

[7]Department of Pediatrics, Boston University School of Medicine and Boston Medical Center, Boston, MA, USA

[8]Division of Allergy-Immunology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

[9]Division of Allergy and Immunology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Abstract

Background—Increasing evidence supports the immunomodulatory effect of vitamin D on allergic diseases. The combined role of prenatal and postnatal vitamin D status in the development of food sensitization (FS) and food allergy remains under-studied.

[‡]**Correspondence and reprint requests should be addressed to:** Xin Liu, MD, PhD, Mary Ann and J. Milburn Smith Child Health Research Program, Children's Hospital of Chicago Research Center, Department of Pediatrics, Feinberg School of Medicine, Northwestern University, 225 E. Chicago Avenue, Box 157, Chicago, IL, USA, Telephone: 312-227-7025, Fax: 312-227-9523, xnliu@luriechildrens.org.

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Category of study: Clinical

Methods—460 children in the Boston Birth Cohort had plasma 25(OH)D measured at birth and early childhood, and were genotyped for rs2243250 (C-590T) in the *IL4* gene. We defined FS as specific IgE 0.35kUA/L to any of eight common food allergens; and persistently low vitamin D status as cord blood 25(OH)D <11ng/ml and postnatal 25(OH)D <30ng/ml.

Results—We observed a moderate correlation between cord blood 25(OH)D at birth and venous blood 25(OH)D measured at 2–3 years (r=0.63), but a weak correlation at <1 year (r=0.28). There was no association between low vitamin D status and FS at any single time point alone. However, in combination, persistence of low vitamin D status at birth and early childhood increased the risk of FS (OR=2.03, 95%CI:1.02–4.04), particularly among children carrying the C allele of rs2243250 (OR=3.23, 95%CI:1.37–7.60).

Conclusions—Prenatal and early postnatal vitamin D levels, along with individual genetic susceptibility, should be considered in assessing the role of vitamin D in the development of FS and food allergy.

INTRODUCTION

Vitamin D has become increasingly recognized as an important regulator of immune responses (1). The vitamin D hypothesis, one of several hypotheses on the development of food allergy, was first suggested in 2007(2), and the potential mechanisms were later proposed in detail by Vassallo et al. (3). Although numerous cross-sectional studies have been conducted to examine the associations between plasma 25(OH)D levels and allergic diseases and associated phenotypes (4–10), findings remain inconsistent. Previous studies (11–15) indicate that the immunomodulatory effects of vitamin D, including its contribution to the development of allergic diseases, begin *in utero*. To date, only three birth cohort studies have examined the effect of prenatal vitamin D exposure on allergic phenotypes using cord blood 25(OH)D concentrations, an objective measure of vitamin D status reflecting both dietary intake and sun exposure. Camargo et al. found that New Zealand newborns with low cord blood 25(OH)D (<10 ng/ml) were at a higher risk for respiratory infection and childhood wheezing but not for incident asthma compared to newborns with higher cord blood 25(OH)D (30 ng/ml) (16). In their Tucson cohort, Rothers et al. (17) reported that both higher (>40ng/ml) and lower (<20 ng/ml) vitamin D levels were associated with high total IgE and detectable inhalant allergen-specific IgE; high vitamin D was also associated with positive allergy skin tests. Our study, conducted primarily in African American children in the U.S., was the first to show that genetic polymorphisms might modify the effects of vitamin D deficiency on the risk of FS (18). However, findings regarding the combined effects of prenatal and postnatal vitamin D status on FS, two of the most critical periods for immune system development (19, 20), are unclear.

In an earlier report, we examined a single time point gene-cord blood vitamin D interaction on FS in the Boston Birth Cohort (16). This study further extends and strengthens our previous work by examining the risk of FS in relation to the longitudinal trajectory of vitamin D status from birth to early childhood in the same birth cohort. Herein, we examined the interaction of a promoter polymorphism (rs2243250: C-590T) in the *IL4* gene and the longitudinal trajectory of vitamin D status from birth to early childhood on the risk of FS.

This particular gene variant was chosen based on our most significant finding from the previous studies (18).

METHODS

The study sample for the analyses included 460 children, a subset of the Boston Birth Cohort (BBC), which is an ongoing birth cohort study that so far has recruited ~7,800 mother-infant pairs at birth from 1998 to 2012. Since 2004, the infants of the BBC who sought pediatric care at the Boston Medical Center and their mothers who gave informed consent have been followed prospectively for postnatal outcomes, including the development of food sensitization, food allergy and other allergic phenotypes. This study focused on children who: 1) had plasma total 25(OH)D measured at two time points: one at birth and the other in early childhood ranging from ~6 months to 36 months, and 2) had available genotype data for rs2243250 (C-590T) in the *IL4* gene, a potentially functional SNP in the promoter region (21). Compared with the 6,255 mother-infant pairs enrolled in the BBC from which this study sample was drawn, this sample included a much lower proportion of preterm infants (19% vs. 27%) (Supplemental Table 1 (online)). Although we also found statistically significant difference between these 460 children and the parent cohort in terms of maternal race, age, BMI, and birth season, the magnitude of the difference was relatively small, and its statistical significance was likely driven by the large sample size. Furthermore, this study sample had over 99% overlap with the children included in our previous report, which only examined plasma total 25(OH)D measured at birth (18). A detailed description of the recruitment (22) and follow-up (23), FS definition, plasma 25(OH)D measures, and genotyping methods has been published (18). The study protocol was approved by the individual Institutional Review Boards of Children's Memorial Hospital, Boston Medical Center and Johns Hopkins University.

Consistent with our previous publications from this cohort (18, 24, 25), we defined FS cases as children who had allergen-specific IgE $\geq$ 0.35kIU/L to any of 8 common food allergens (i.e., egg white, milk, peanut, walnut, soy, shrimp, cod fish, and wheat). Plasma 25(OH)D was measured using an HPLC-tandem mass spectrometry assay. Genotyping was conducted using the Illumina Golden Gate Assay. We grouped the children according to longitudinal trajectory of 25(OH)D based on if a child had: 1) low vitamin D status at birth (< 11ng/ml) as suggested by the Institute of Medicine (26) or 2) low postnatal vitamin D status (< 30ng/ml) according to the Endocrine Society Clinical Practice Guidelines on Vitamin D insufficiency (27, 28). Persistently low vitamin D status was defined as having low levels at both time points.

Multiple logistic regression was used to test the association between persistently low vitamin D and FS after adjustment for maternal age (<20, 20–25, 25–30, 30–35, 35), postnatal exposure to maternal smoking, household income, child's gender, history of breastfeeding, and ancestry proportion estimated based on 144 ancestry informative markers (AIMs) as previously detailed (18). We also conducted the above regression analyses stratified by the genotypes of rs2243250, and then examined the statistical significance for the multiplicative interaction between low vitamin D status and rs2243250. All of the

analyses were performed using SAS software (v. 9.2) (SAS Institute Inc., Cary, North Carolina) and R software (http://www.r-project.org/).

RESULTS

About one-third of the 460 children had detectable IgE to any food allergen by age 3 years and were defined as FS cases (Table 1). The FS children and those without detectable sIgE differed in regards to maternal race, age, maternal smoking, household income, infant gender, breastfeeding pattern, and individual ancestral proportion (p<0.1). When looking at the studied children overall (Figure 1), cord blood total 25(OH)D concentration (ng/ml) was quite low (N=460, purple curve: 14.16 ± 7.90 ng/mL, (mean ± s.d)). Among children whose follow-up measurement was obtained within one year of age, vitamin D levels were dramatically increased (N=232, black curve: 35.63 ± 11.43 ng/mL). Vitamin D measured at 1–2 years of age (N=163, red curve: 33.60 ± 11.04 ng/mL) or 2–3 years of age (N=65, green curve: 31.73 ± 8.40 ng/mL) was slightly lower than measures obtained within one year of age. Similarly, the proportions of children with low vitamin D status at birth (i.e., <11ng/ml), <1year, 1–2 years, and 2–3 years (i.e., <30ng/ml) were 38%, 29%, 36%, and 40%, respectively; and the correlation coefficients between cord blood 25(OH)D concentrations and 25(OH)D measures up to age 1 year, 1–2 years, and 2–3 years were 0.28, 0.39, and 0.63, respectively. Of note, only 31 children reported having doctor diagnosed food allergy. The mean (sd) plasma 25(OH)D concentrations at birth and at early childhood for these children in the FS group (N=21) is 12.19 ng/ml (4.61) and 37.05 ng/ml (13.09), respectively; and 14.53 ng/ml (5.60) and 33.32 ng/ml (8.03) for those in non-FS group (N=10).

Among the FS-associated variables, maternal race, infant African ancestry proportion, and household income were associated with cord blood 25(OH)D concentration (Table 2); while only breastfeeding status was significantly associated with lower post-natal 25(OH)D levels, as compared with formula only (mean ± s.d.: 23.75 ± 14.07 vs. 36.15 ± 9.58 ng/mL, respectively). As such, our analyses have considered not only the possible confounding variables (i.e., ethnicity and household income) but also other FS-associated variables (i.e., infant sex, post-natal maternal smoking, and maternal age) in the regression model for testing the longitudinal effects of 25(OH)D on FS.

When we examined 25(OH)D concentrations across FS status, we found that FS cases had lower cord plasma 25(OH)D than non-sensitized controls (12.86±5.91 vs. 14.87±8.73 ng/mL respectively; p=0.04), but this difference was not apparent in the postnatal measures (34.25±11.11 vs. 34.43±10.93 ng/mL, p=0.86) (Table 1). Individually, neither cord blood nor postnatal low vitamin D status was significantly associated with any FS (Table 3). However, children with persistently low vitamin D status had the highest risk of FS (OR= 2.04, 95%CI: 1.02–4.04), as compared to those with sufficient vitamin D status at birth and follow-up. Similar association patterns between persistently low vitamin D and high risk of FS were seen among children with 25(OH)D measurements within 1 year of age and 1–3 years of age; among children born in Winter and non-winter; among children born preterm (< 37 weeks of gestation) and children born term (>= 37 weeks) (data not shown). Similar association patterns also were observed from weighted logistic regression analyses with two different weights assigned to preterm and term children according to the proportion of

preterm cases in the study samples (19%) and those in the overall baseline sample (27%) (data not shown). Due to small sample size after stratification, the significant association between persistently low vitamin D and risk of FS was only observed in children with 25(OH)D measurements within 1 year of age (OR=2.99, 95%CI: 1.05–8.52).

Finally, we observed an interaction effect between rs2243250 and persistently low vitamin D status on the risk of FS ($p_{interaction}$= 0.02). Among children carrying the C allele of rs2243250 (~65% of the study subjects), persistently low vitamin D status was associated with an over 3-fold increased risk of FS (OR = 3.23, 95%CI: 1.37–7.60) compared to those with sufficient vitamin D at both time points. Interestingly, when low vitamin D at birth was followed by sufficient vitamin D in early childhood, children carrying the C allele were not at an increased risk for FS (OR=1.26, 95%CI: 0.65–2.43). However, a decreased risk of FS was observed for those carrying the TT genotype (OR=0.32, 95%CI: 0.12–0.82) compared to the reference group (Table 3).

DISCUSSION

This is the first study to examine the effects of longitudinal trajectory vitamin D status, by measurement of plasma 25(OH)D concentrations from birth to early childhood, on the development of FS. We found that persistently low vitamin D status from birth to early childhood was associated with FS in the BBC. Our findings suggest that both prenatal and early postnatal vitamin D levels appear to play an important role in the development of FS, especially among those with specific genotypes.

The majority of the vitamin D requirement for most people in the U.S. is achieved through both sun exposure and fortified food or vitamin D nutritional supplements. Toddlers' patterns of physical activity (i.e., sun exposure) and dietary habits (i.e., supplementation) are more like their mothers', while infants obtain their vitamin D mainly through fortified formula. This could explain the higher correlations observed between cord and postnatal plasma 25(OH)D concentrations among those beyond age 2 (r=0.63) as compared to the same measures at age 1–2 years (r=0.39) and 6–12 months (r=0.28). We also found high proportions of children with low vitamin D status (i.e., <30ng.ml) during the first year of life, 1–2 years, and 2–3 years (i.e., 29%, 36%, and 40%). Given that fewer than 10% of our subjects were exclusively breastfed (Table 1), these infants and toddlers should have had the highest intake of vitamin D via fortified formulas, which, in the U.S., all contain at least 400 IU/L of vitamin D (29). As such, it is possible that some of the children in this study did not consume 1,000 mL vitamin D-fortified formula per day, and were not fed additional vitamin D supplements to meet the recommended intake of 400 IU/day for infants, children, and adolescents (30). Another explanation is that because these 460 children were predominantly Black (>50%), and they tend to be more likely to have vitamin D insufficiency (10).

Insufficient vitamin D status is undesirable from many viewpoints, especially because of its impact on bone health and immune function. We previously reported the qualitative interactions between vitamin D deficiency, assessed from cord blood and a genetic variant in the gene *IL4* (rs2243250), and FS in the same birth cohort (18). This study included two-thirds of the samples comprised in the previous report; and samples here were included only

if 25(OH)D was measured by age 3 years. The findings from this extended study emphasize the important role of postnatal vitamin D status in the development of FS. Children who had very low vitamin D status at birth but had sufficient vitamin D during their early life had no risk or a lower risk of FS; while children who were exposed to persistently low vitamin D both pre- and post-natally had the highest risk of FA (Table 3). These findings were not materially changed when stratified by birth season or preterm status. Several studies have shown an association between season of birth and risk of food allergy (31–33). Such significant association was not seen for FS in this study (Table 1). Furthermore, our findings remained similar after controlling for season of birth or stratification by season of birth, indicating that birth season is unlikely to mediate the associations between persistently low vitamin D and risk of FS. In addition, the current study sample is a small subset of the parental birth cohort and, in particular, includes much fewer preterm cases than exists among the 6,255 children currently in the database (Supplemental Table 1 (online)). Nevertheless, the lower percentage of preterm births in this study did not appear to substantially affect the observed associations—based on the similar association patterns from preterm-stratified analyses and also from weighted logistic regression analyses. Of note, our findings from the stratified analyses suggested stronger associations between low vitamin D status and high risk of FS among children born preterm, which needs to be further explored in a larger sample. Furthermore, we observed significant interaction effects between the *IL4* gene polymorphism and persistently low vitamin D status on FS in this smaller sized study sample. Among subjects carrying the C allele of rs2243250, persistently low vitamin D status dramatically increased the risk of FS, while sufficient vitamin D status during early childhood attenuated the risk of perinatal vitamin D deficiency on FS to null. Among those carrying the TT genotype, post-natal sufficient vitamin D status even showed a decreased risk of FS. It should be noted that four SNPs showed significant interaction effects with vitamin D deficiency at birth on FS in our previous report (18). For this subset study, we have only presented findings for the *IL4* promoter polymorphism given that rs2243250 has been commonly studied and has already been shown to have the most significant gene-vitamin D deficiency interaction on FS (18). The other three SNPs (*MS4A2* (rs512555), *FCER1G* (rs2070901), and *CYP24A1* (rs2762934)) showed similar interaction patterns as rs2243250, but only one (rs512555) reached the nominal significance level of 0.05 because of the reduced sample size.

Our findings should be interpreted with caution due to the relatively small sample size, and should be duplicated in larger cohorts in the future. The post-natal samples and measurements were not taken at the same time. However, the results remained the same when we reanalyzed the data stratified by follow-up age (i.e., < 1 year and 2–3 years of age). There is no gold standard for how to define low vitamin D status at birth and in early childhood. Therefore, we chose the cut-offs of 11 ng/mL and 30 ng/mL for cord and post-natal 25(OH)D measures, respectively, not only based on the suggestion by the IOM for newborns (26) and the Endocrine Society Clinical Practice Guidelines on Vitamin D Deficiency for both children and adults (27, 28), respectively, but also based on the distributions of the study subjects (Table 1). Note that, approximately 3% of non-FS children reported to have doctor diagnosed food allergy. In this regard, it is possible that FS to relatively rare food allergens might be missed here, but also that these non-FS children

were misreported by parents. However, the results remained similar after excluding these 10 subjects (data not shown). Finally, this study only had plasma 25(OH)D measurements at two time points, which may not comprehensively reflect a longitudinal pattern during early childhood. Nevertheless, our data are valuable to the field given that there is a lack of longitudinal data on vitamin D and allergic outcomes in early childhood.

The biological mechanisms underpinning the associations between persistently low vitamin D and the development of FS and then food allergy include excessive exposure to abundant food allergens caused by increased gastrointestinal barrier permeability and decreased immune tolerance. This so-called "multiple hit" model was recently proposed by Vassallo et al. (3). Due to the small number of food allergy cases (N=31), this study is limited to FS; future studies should examine food allergy as a primary outcome. Future laboratory studies also should be seriously considered to help better understand the molecular basis underlying how the immunomodulatory effect of vitamin D and regulatory effect of the *IL4* gene on IgE production jointly influence the risk of FS. If these findings are replicated in other independent studies, then more attention to vitamin D nutrition should be given to very young children in the toddler age range, and particularly to those with very low cord blood vitamin D measures and specific genotypes. Overall, this study underscores the need to simultaneously consider both cord blood and postnatal vitamin D levels, along with genetic susceptibility, in the development of FS and food allergy. The extent of vitamin D insufficiency in this process may be underestimated by a static, single value, and emphasizes that longer term exposure to a vitamin D deficient state might have profound health consequences in a specific genetic environment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

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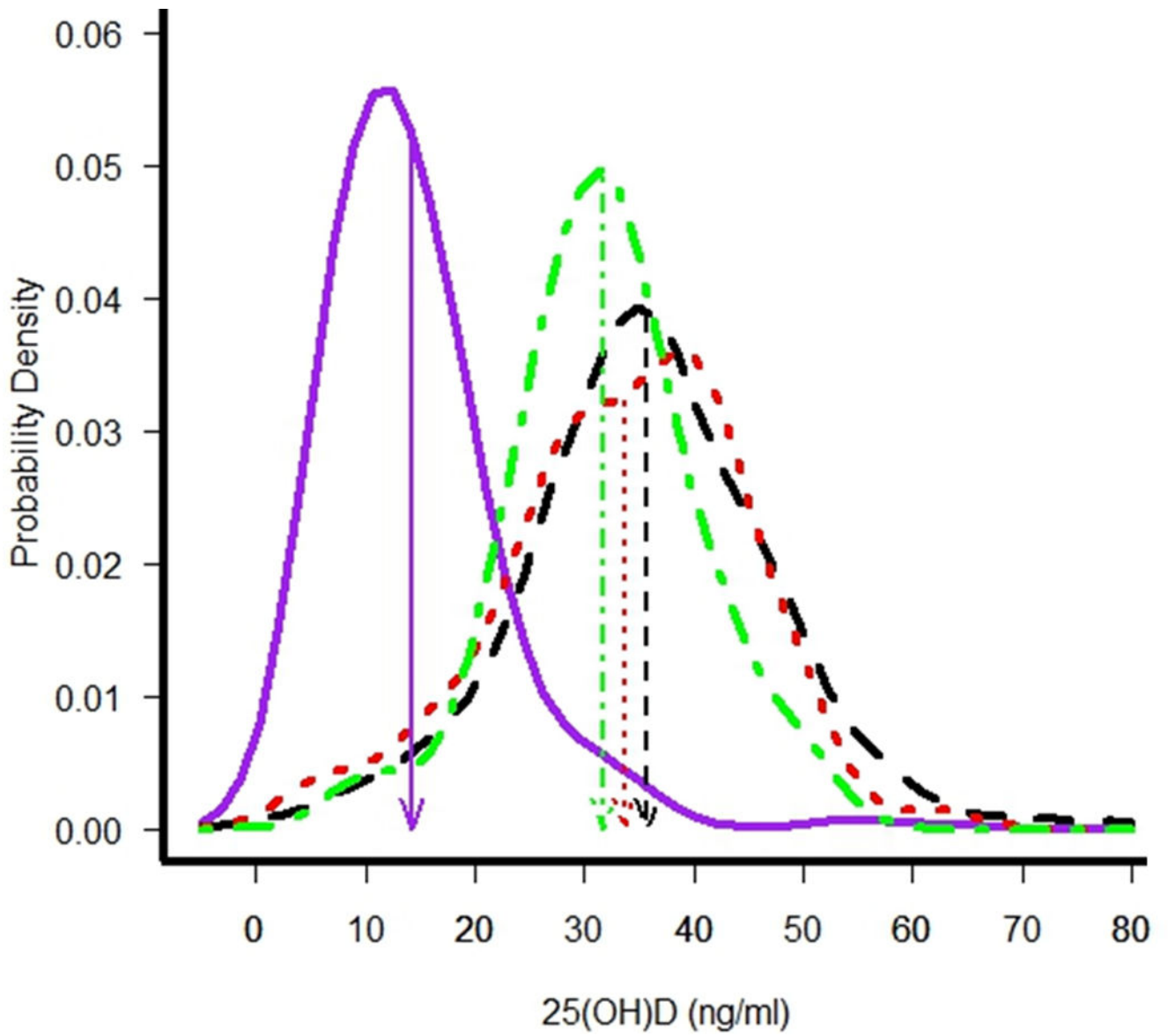
Figure 1.
Distributions of plasma 25(OH)D at birth (cord blood) (solid purple line), <1 year (black dashed line), 1–2 years (red dotted line), and 2–3 years (green dashed-dot line) (means: vertical lines) among 460 subjects from the Boston Birth Cohort.

Table 1

Major characteristics of 460 subjects in the Boston Birth Cohort.

Variables	Food Sensitization (N=162)	Non-Food Sensitization (N=298)	P-value
	N (%)		
Maternal Race			
Black	100 (62)	143 (48)	
White	4 (2)	23 (8)	
Hispanic	33 (20)	82 (28)	
Other	25 (15)	50 (17)	0.01
Maternal BMI (kg/m^2) (pre-pregnancy)			
<20	18 (11)	24 (8)	
20–24.9	57 (35)	115 (39)	
25–29.9	49 (30)	94 (32)	
30	38 (23)	63 (21)	0.64
Maternal Age (yrs)			
<20	16 (10)	16 (5)	
20–24.9	30 (19)	89 (30)	
25–29.9	33 (20)	92 (31)	
30–34.9	45 (28)	54 (18)	
35	38 (23)	47 (16)	0.0004
Maternal Education			
Middle School	44 (27)	92 (31)	
High School	66 (41)	111 (37)	
> High School	52 (32)	95 (32)	0.66
Maternal Atopy	60 (37)	97 (33)	0.34
Maternal Smoking During Pregnancy	12 (7)	38 (13)	0.08
Infant Sex (Male)	97 (60)	145 (49)	0.02
Preterm (< 37 GWs)	27 (17)	60 (20)	0.36
Birth Season			
Winter (Jan. to Mar.)	37 (23)	61 (20)	
Spring (April to June)	40 (25)	84 (28)	
Summer (July to Sept.)	35 (22)	72 (24)	
Fall (Oct. to Dec.)	50 (31)	81 (27)	0.67
Maternal Smoking (post-natal)	20 (12)	55 (18)	0.09
Household Income			
<$30,000	71 (44)	129 (43)	
$30,000	11 (7)	40 (13)	
Unknown	80 (49)	129 (43)	0.08
Breast Feeding			
Breast Feeding only	9 (6)	23 (8)	
Formula only	31 (19)	81 (27)	

Variables	Food Sensitization (N=162)	Non-Food Sensitization (N=298)	P -value
	N (%)		
Both	122 (75)	193 (65)	0.07
Food Allergy	21 (13)	10 (3)	<0.0001
	Mean ± SD		
African Ancestry Proportion	0.68 ± 0.30	0.55 ± 0.34	0.0002
Cord Blood 25(OH)D (ng/ml)	12.86 ± 5.91	14.87 ± 8.73	0.04
Follow-up Blood 25(OH)D (ng/ml)	34.24 ± 11.12	34.43 ± 10.93	0.86

Note. Due to rounding, percentages for certain variables do not add up to 100%.

Table 2

Distribution of pre- and post-natal plasma 25(OH)D concentration by major characteristics of 460 subjects in the Boston Birth Cohort.

Variables	Cord Blood 25(OH)D (ng/ul)	Post-Natal 25(OH)D (ng/ul)
	Mean (SD)	
Maternal Race ****		
Black	12.13 (5.84)	33.69 (11.00)
White	21.26 (10.55)	38.89 (12.39)
Hispanic	16.34 (9.62)	34.69 (10.13)
Other	14.86 (7.38)	34.40 (11.43)
Maternal BMI (kg/m^2) (pre-pregnancy) *		
<20	14.69 (7.98)	34.85 (10.01)
20–24.9	15.01 (8.48)	34.60 (11.52)
25–29.9	14.64 (8.28)	34.82 (11.34)
30	11.87 (5.68)	32.90 (9.90)
Maternal Age (yrs)		
<20	12.60 (5.66)	32.59 (12.19)
20–24.9	14.14 (8.59)	34.97 (10.46)
25–29.9	13.91 (7.49)	33.28 (11.25)
30–34.9	14.45 (8.98)	36.22 (10.91)
35	14.82 (6.90)	33.59 (10.80)
Maternal Education		
Middle School	14.19 (7.74)	34.99 (10.75)
High School	13.48 (8.13)	33.99 (10.73)
> High School	14.95 (7.75)	34.22 (11.53)
Maternal Atopy		
No	14.43 (7.88)	34.94 (11.30)
Yes	13.40 (7.30)	33.22 (10.31)
Maternal Smoking During Pregnancy		
No	13.90 (7.56)	34.36 (11.24)
Yes	16.29 (10.12)	34.38 (8.68)
Infant Sex		
Male	13.59 (7.16)	34.96 (11.50)
Female	14.79 (8.63)	33.69 (10.36)
Preterm (< 37 GWs) *		
No	13.63 (7.20)	34.17 (11.37)
Yes	16.44 (10.13)	35.19 (9.16)
Birth Season *		
Winter (Jan. to Mar.)	13.05 (8.29)	35.36 (9.95)
Spring (April to June)	14.08 (7.75)	32.80 (11.31)
Summer (July to Sept.)	15.37 (7.90)	34.17 (10.14)

Variables	Cord Blood 25(OH)D (ng/ul)	Post-Natal 25(OH)D (ng/ul)
	Mean (SD)	
Fall (Oct. to Dec.)	14.09 (7.71)	35.25 (11.97)
Maternal Smoking (post-natal)	NA	35.55 (8.51)
No	NA	34.13 (11.40)
Yes		35.55 (8.51)
Household Income *		
<$30,000	12.95 (6.94)	33.69 (11.38)
$30,000	14.89 (7.23)	34.98 (11.05)
Unknown	15.14 (8.76)	34.86 (10.58)
Breast Feeding ****		
Breast Feeding only	NA	23.75 (14.07)
Formula only		36.15 (9.58)
Both		34.81 (10.56)
	Pearson Correlation Coefficient (p-value)	
African Ancestry Proportion	−0.27 (<0.0001)	−0.07 (0.11)
Cord Blood 25(OH)D (ng/ml)	1	0.07 (0.15)
Follow-up Blood 25(OH)D (ng/ml)	0.07 (0.15)	1

*
p 0.05;

****
P<0.0001: non-parametric tests of plasma 25(OH)D by the variables.

Significant symbols apply only to cord blood 25(OH)D concentration except for breastfeeding.

Table 3

Associations between plasma total 25(OH)D and Food Sensitization in the Boston Birth Cohort, stratified by *IL4* promoter polymorphism (rs2243250: C-590T).

25(OH)D (ng/ml)		Whole Sample			rs2243250=CC/CT			rs2243250=TT			
Cord Blood	Postnatal	Case/Control[a]	OR (95%CI)[b]	p-value	Case/Control[a]	OR (95%CI)[b]	p-value	Case/Control[a]	OR (95%CI)[b]	p-value	p_{int}[c]
≥11		93/193	Ref		45/138	Ref		48/55	Ref		
<11		69/105	1.28 (0.84–1.95)	0.26	51/67	**2.04 (1.18–3.54)**	**0.01**	18/38	**0.46 (0.21–0.98)**	**0.04**	**0.003**
	≥30	106/203	Ref		63/141	Ref		43/62	Ref		
	<30	56/95	1.10 (0.71–1.70)	0.66	33/64	1.06 (0.60–1.87)	0.84	23/31	1.21 (0.56–2.59)	0.63	0.62
≥11	≥30	64/121	Ref		34/89	Ref		30/32	Ref		
≥11	<30	29/72	0.73 (0.42–1.29)	0.28	11/49	0.52 (0.23–1.18)	0.12	18/23	0.74 (0.29–1.90)	0.53	
<11	≥30	42/82	0.90 (0.54–1.51)	0.69	29/52	1.26 (0.65–2.43)	0.49	13/30	**0.32 (0.12–0.82)**	**0.02**	
<11	<30	27/23	**2.03 (1.02–4.04)**	**0.04**	22/15	**3.23 (1.37–7.60)**	**0.007**	5/8	0.80 (0.21–3.04)	0.74	**0.02**

[a] Case and control refer to food sensitization cases and non-food sensitization controls.

[b] All OR estimates were adjusted for a child's sex and ancestry proportion, breastfeeding, post-natal maternal smoking, household income, and maternal age.

[c] P-value for interaction