



Complex relationships between vitamin D and allergic sensitization among Puerto Rican 2-year-old children

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ABSTRACT

Background: In the United States, Puerto Ricans have a higher prevalence of asthma than other Latino ethnicities. Low vitamin D levels for children living in northern climates could be a factor.

Objective: To assess serum 25-hydroxyvitamin D [25(OH)D] distributions (a marker of vitamin D) and associations among vitamin D, allergic sensitization, early wheeze, and home/demographic factors.

Methods: Puerto Rican infants born in New York City, with a maternal history of atopy, were enrolled in a birth cohort. Blood was collected at age 2 years (n = 154; 82 males and 72 females). Serum 25(OH)D and immunoglobulin E (IgE) (indoor allergen-specific and total) were determined using immunoassays. Home/demographic characteristics and respiratory symptoms were assessed by questionnaire.

Results: The median concentration of 25(OH)D was 22.6 ng/mL; 32% were at risk of deficiency or inadequacy (<12 or 12–19 ng/mL). Serum 25(OH)D levels were lower in the heating (a surrogate for less sun exposure in colder months) compared with nonheating (26.1 vs 22.7 ng/mL, *P* = .02) season, but were not associated with allergen-specific IgE levels or with level of acculturation (measured by maternal birthplace). However, low 25(OH)D levels (below median) were associated with high total IgE >100 IU/mL (*P* = .01). Also, 25(OH)D concentrations differed between children who attended daycare and those who did not (21.8 vs 24.5 ng/mL; *t* test, *P* = .02). Serum 25(OH)D was not associated with wheeze or asthma by 2 years of age (*P* = .43).

Conclusion: Vitamin D deficiency, possibly linked with allergic pathways, may partially explain the trajectory for disproportionate asthma burden among Puerto Ricans, especially those born and raised in colder climates.

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Introduction

In recent years, awareness of vitamin D's role as an essential micronutrient with immunomodulatory effects^{1,2} has emerged, and its deficiency may predispose to asthma by altering lung development

in early life.³ Chronically low 25-hydroxyvitamin D [25(OH)D] levels, the most common biomarker of vitamin D status, or vitamin D deficiency, is defined as levels of <15 ng/mL,⁴ with levels of 15–29 ng/mL considered insufficient. Specifically, low 25(OH)D in early childhood is inversely associated with the risk of developing acute wheeze,⁵ and may play a role in the pathogenesis of infants with recurrent wheezing.^{6,7} Low 25(OH)D in children >6 years of age has been found to be associated with an increased risk of allergic sensitization and allergic asthma.^{8–11}

Although lower levels of vitamin D and asthma disproportionately burden low-income, ethnic minority children in urban environments,^{12–14} less is known about the “vitamin D protective effect” in inner-city toddlers, who may be exposed to high levels of indoor allergens.¹⁵ Vitamin D deficiency is common among

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inner-city Latino children,^{12–14} and inner-city Puerto Rican children experience disproportionately higher rates of allergic sensitization and asthma.^{16–19} Vitamin D can be synthesized in significant quantities in the skin from exposures to ultraviolet B (UVB) rays, thus serving as the primary determinant of vitamin D status in early childhood.²⁰ However, at northern latitudes, there are insufficient UVB rays for synthesis of vitamin D to occur during the winter months between November and March.^{21,22}

Recent research suggests a relationship between pediatric asthma prevalence and vitamin D deficiency²³ due to shared risk factors, such as ethnic minority status,¹³ inner-city residence,^{24,25} and obesity.³ Other known predictors of low vitamin D status in healthy children include age,⁴ gender⁴ and socioeconomic status,²⁶ lack of sufficient sunlight exposure,²⁷ insufficient activity,²⁸ decreased consumption of vitamin D-containing foods such as fish and fortified dairy products,¹³ and malabsorptive states.⁴ Findings from the literature suggest that the origins of the association between vitamin D deficiency and allergic disease are in early life. Because vitamin D levels are expected to be lower among inner-city infants in northern states, there is a need to examine the possible link between early-life vitamin D deficiency and atopic sensitization in this high-risk group. To our knowledge, however, this association has not been investigated among 2-year-old children, and this presents a novel avenue for exploration.

The goal of the current analysis was to examine the relationship between 25(OH)D deficiency and allergic disease, specifically markers of allergy (eg, total and allergen-specific immunoglobulin E) in 2-year-old Puerto Rican children living in New York City. The specific aims were to: (1) characterize the prevalence of at-risk-of-vitamin D insufficiency and deficiency; (2) identify associations between vitamin D status, allergy, wheeze, and asthma; and (3) find potential factors associated with at-risk-of-vitamin D deficiency (eg, sociodemographic home characteristics, daycare attendance, and season). We hypothesized that Puerto Rican toddlers in New York City would have vitamin D deficiency and that this would be linked with factors in their “atopic march.”

Methods

Study Design and Inclusion Criteria

This study leverages the Puerto Rican Asthma Project (PRAP), the general study design and methods for which have been described by Acosta et al.²⁹ Briefly, children of Puerto Rican ethnicity born in New York City to mothers with a self-reported history of inhalant allergy and/or allergic asthma were enrolled in this prospective, longitudinal cohort study ($n = 274$ mother–child pairs) from November 2002 and December 2004.²⁹ Children with major congenital health problems, preterm birth (<36 weeks), or intubation and mechanical ventilation were excluded. Of the 274 pairs, serum samples collected at age 2 years were available for analysis. Reasons for samples not being available were: (i) loss to follow-up; (ii) insufficient amount of blood collected; and (iii) hemolysis of blood sample as described by Kannan et al.³⁰ Informed written consent was obtained from the mothers in accordance with the institutional review boards of the Lincoln Hospital, Albert Einstein Medical Center, Columbia University, and Harvard University.

Data Collection

Home characteristics and sociodemographics were first assessed during the postpartum period and then every 6 months from birth to 2 years of age, and height and weight were assessed at age 2 years. Home visits were conducted shortly after birth (mean age of child, 45 ± 39 days) and at 1 and 2 years of age by 2 technicians, 1 of whom was bilingual in Spanish/English. When the children

reached 2 years of age, blood was drawn from both mother and child (181 mother–child pairs). Depending on participant preference, blood was either drawn in the home or in the pediatric blood-drawing unit at the Columbia University Medical Center. Of the 274 mother–child pairs that constituted the original PRAP²⁹ and completed the baseline interview and home visit, 181 completed the 2-year follow-up visit. One hundred fifty-four of these mother–child pairs were included in the current analysis (82 males and 72 females), based on availability of sufficient serum samples for analysis.

25(OH)D

The 25(OH)D assays were based on a standard radioimmunoassay (RIA) procedure developed by DiaSorin, Inc (Saluggia, Italy). Serum 25(OH)D was extracted using acetonitrile and levels were assayed using an equilibrium RIA with ¹²⁵I. The lower limit of detection was 1.5 ng/mL (DiaSorin, Inc).

Allergic Sensitization

Total and allergen-specific (dust mite, cockroach, cat, mouse) serum IgE was assayed with the PharmaciaCAP (Phadia, Portage, Michigan) system, as described previously.³¹ By design, blood draws for IgE and vitamin D analysis were conducted in the same season. The serum was aliquoted and a portion was analyzed for IgE and a portion was analyzed for 25(OH)D.

Data Analysis

All data were analyzed using SAS version 9.2 (SAS Institute, Inc, Cary, North Carolina). The normality of 25(OH)D distribution was assessed using the Shapiro–Wilk statistic. Vitamin D levels were not transformed, as the distribution was normal.

Vitamin D status was quantified using the Institute of Medicine (IOM) National Academy of Sciences Guidelines,³² with at-risk-of-vitamin D deficiency, inadequacy, and sufficiency defined as serum 25(OH)D levels <12 ng/mL, 12–19 ng/mL, and ≥ 20 ng/mL, respectively. For allergic sensitization, total IgE levels of >100 IU/mL were considered elevated.^{31,33} Children with allergen-specific IgE (to inhalant allergens from dust mites, cockroaches, cats, dogs, and mice) ≥ 0.35 IU/mL were considered sensitized. “Any sensitization” was defined as sensitization to at least 1 of the inhalant allergens. Heating season was defined as October 1 to May 31, when landlords in New York City are required to provide heat to buildings.³⁴

Serum 25(OH)D levels were treated as categorical and as a continuous variables and associations with household characteristics, child characteristics, and other biomarkers were assessed with χ^2 test, logistic regression, and Pearson correlation analyses. Student's t test was used to assess differences in mean vitamin D concentrations for dichotomous variables, such as household and demographic characteristics.

Results

Study sociodemographic and home characteristics are shown in Table 1. Over one third of the mothers reported educational level beyond high school (38% had attended college) and many reported breastfeeding their infants (47%). The original cohort and the subsample with biomarkers did not differ significantly with regard to sociocultural, demographic, and home characteristics.³⁰ Most mothers were born in the United States (US) mainland (71%), with Puerto Rican ethnicity. Many of the children either attended daycare ($n = 102$; 66%) and slightly over one third (36%) had a grandmother helping to take care of them. Many of the mothers (66%) with a college degree worked outside the home. Most mothers (68%) reported breastfeeding (although not exclusively). A majority of the

Table 1Sociodemographic and Home Characteristics for the New York City Puerto Rican Asthma Project Biomarkers Cohort³⁰

Variables	Sample size (n = 154)	Percent
Sex		
Boy	82	53
Girl	72	47
Maternal birthplace		
Mainland United States	110	71
Puerto Rico or other country	44	29
Overweight or obese (BMI ≥85th percentile) ^a		
No	70	53
Yes	63	47
Daycare attendance at age 2 years		
No	102	66
Yes	52	34
Mother attended college		
No	95	62
Yes	59	38
ETS report of someone in household who smoked		
No	83	54
Yes	71	46
25(OH)D status ^b		
Sufficient (>20 ng/mL)	105	68
Inadequate/insufficient (12–19 ng/mL)	45	29
Deficient (<12 ng/mL)	4	3

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; ETS, environmental tobacco smoke; IgE, immunoglobulin E.

^aThere were 133 in this group due to several children not having valid height and weight measures (eg, child could not stand still).^bAs defined by the Institute of Medicine (2011).³²

children lived in multifamily housing (79%) and had siblings who lived with them at birth (72%).

The mean concentration of 25(OH)D was 23.6 (SD, 7.0) ng/mL with a median concentration of 22.6 ng/mL. Thirty-two percent of the 25(OH)D levels were consistent with vitamin D deficiency <12 ng/mL or insufficient (12–19 ng/mL) (Table 1). Vitamin D levels were lower in heating season compared with nonheating season (26.1 vs 22.7, $P = .02$).

As shown in Table 2, children with a total serum IgE >100 IU/mL were more likely to have a lower serum concentration of 25(OH)D at age 2 years (no = 24.1 vs yes = 21.3, $P = .01$). When adjusting for potential confounders (foreign-born mother, grandmother helper, daycare attendance, and heating season), 25(OH)D over the median level was still associated with total IgE >100 IU/mL (but not “any sensitization” for the allergen-specific IgE). However, 25(OH)D levels were not associated with total IgE concentrations when treated as a continuous variable or when treated as quartiles.

Very few children had detectable (>0.35 IU/mL) allergen-specific IgE ($n = 18$). Mean total IgE concentrations did not differ between children with and without detectable allergen-specific IgE (22.3 vs 23.8, $P = .43$). In multivariable models adjusting for heating season, grandmother helper, daycare attendance, foreign-born mother, and vitamin D status of the child at age 2 years were not statistically significantly associated with “any sensitization.”

By age 2 years, almost one quarter of the children had a diagnosis of asthma (35 of 152; ie, 23%) and/or had wheezing in the past 6 months (37 of 152; ie, 24%), as reported by their mother. When treating vitamin D levels as a dichotomous variable (cutpoint = median), lower vitamin D tended to be associated with more wheezing (15% vs 9%) and self-reported asthma by age 2 years (14% vs 9%), but χ^2 analysis was not significant ($P = .2$ and $P = .1$, respectively).

Children attending daycare had lower mean levels of 25(OH)D than children not attending daycare (21.8 vs 24.5; t test, $P = .02$).

Table 2Associations Between Vitamin D and Sociodemographic Variables, Allergic Sensitization, and Season^a

Variables	n	Mean concentration of vitamin D at age 2 years (ng/mL)	P value (for t test)
Sex			
Boy	82	23.1	.30
Girl	72	24.2	
Maternal birthplace			
Mainland United States	110	23.6	.88
Puerto Rico or other country	44	23.8	
Overweight or obese (ie, BMI ≥85th percentile)			
No	70	23.6	.85
Yes	63	23.9	
Daycare attendance at age 2 years			
No	102	24.5	.02 ^b
Yes	52	21.8	
Mother attended college			
No	95	23.6	.97
Yes	59	23.6	
Season			
Heating	115	22.76	.02 ^b
Nonheating	39	26.14	
ETS report of someone in household who smoked at age 2 years			
No	83	23.6	.94
Yes	71	23.7	
Child sensitized to any inhalant allergen (cat, dust mite, cockroach, mouse)			
No	135	23.8	.43
Yes	18	22.3	
Total IgE >100 IU/mL			
No	126	24.1	.01 ^b
Yes	27	21.3	

Abbreviations: BMI, body mass index; ETS, environmental tobacco smoke; IgE, immunoglobulin E.

^aMother reported that at least 1 smoking household member lived in the home when child was 2 years old.^bStatistically significant ($P < .05$).

Maternal birthplace, maternal college attendance, and environmental tobacco smoke exposure at home at age 2 were not associated with 25(OH)D levels (data not shown).

Discussion

To our knowledge, this is the first study to evaluate the relationship between early childhood 25(OH)D and allergic sensitization, wheeze, and asthma in Puerto Rican children who were born and raised in a cold climate. The estimated prevalence of at-risk-of-vitamin D inadequacy (<20 ng/mL; 29%) in the current cohort is similar to that reported for US populations (24%) enrolled in the National Health and Nutrition Examination Survey between 2004 and 2006.³⁵ The PRAP vitamin D status data are comparable to those reported for school-age children with asthma from Costa Rica (24.6% insufficient and 3.4% deficient),³⁶ but higher than in Puerto Rican children with (47% insufficient) and without (44%) asthma.³⁷ A study of healthy infants and toddlers from Boston (42°N) also found significant rates of vitamin D deficiency (40%), but used different criteria.³⁸ Of note, however, although the current study results are based on serum 25(OH)D thresholds proposed by the IOM,³² in the aforementioned studies 25(OH)D levels were categorized using different cutoffs for deficiency (<20 ng/mL) and insufficiency (≥20 and <30 ng/mL).

When exposed to UVB radiation, the skin converts 7-dehydrocholesterol to vitamin D₃.³⁹ However, cultural traditions, biology, and the environmental factors associated with living in New York City likely collectively contribute to the varying levels

of sufficient exposure to UVB rays, even during the city's nonheating season months (June–September) in which vitamin D may be synthesized in the skin at a latitude of 40°N.²⁰ As expected, in the current study, vitamin D levels were lower in heating compared with nonheating season (26.1 vs 22.7 ng/mL). Other investigators have reported a paradoxical relationship between 25(OH)D concentration and season in toddlers, with lower concentrations found in summer than in winter.³⁹

Our results show that the levels of 25(OH)D varied depending on the children's caregiving environment (daycare vs grandmother helper, home care). Specifically, a vitamin D–protective effect was noted for family-based child care (ie, non-daycare attendance). This is a novel finding that supports the need for comparing the vitamin D–protective environment in daycare/preschool vs home care. For example, caregivers of Puerto Rican ethnicity may cover their children's skin and apply sunscreen on them before venturing outside.⁴⁰ This may be due in part to educational campaigns in the 1990s about the dangers of the sun in terms of skin cancer.^{41,42} Inner-city children may not spend very much time outdoors.^{43,44} Based on culturally acceptable behaviors, child-care providers can also strongly influence food consumption patterns of toddlers²² when they transition from vitamin D–supplemented breastfeeding or vitamin D–fortified infant formula to vitamin D–fortified cow's milk and solid foods.⁴⁵

Many other factors that can influence the variations in vitamin D concentrations in children, including geographic location, socioeconomic status, ethnicity, age, gender, and maternal educational level.^{46–49} However, we did not find an association between low 25(OH)D concentrations and these other sociocultural, demographic, and anthropometric characteristics or biomarkers. The presence of tall buildings, such as those found in New York City, create what are known as street canyons, or areas where the sun does not reach at all or only during very limited times during the day.

Our analysis has revealed that 25(OH)D was related to total serum IgE, but not with sensitization to the measured inhalant allergens. Even after adjusting for other factors (foreign-born mother, grandmother helper, heating season), vitamin D remained significantly associated with high total IgE. These results are consistent with the many studies that have linked children's 25(OH)D to allergic sensitization. In the 2005–2006 National Health and Nutrition Examination Survey sample (subjects 1–21 years of age), sensitization to 11 allergens was more common in those with 25(OH)D < 15 ng/mL.⁵⁰ A large cross-sectional study of asthmatic children in Costa Rica showed that 25(OH)D levels were inversely associated with total serum IgE levels and with dust mite sensitization.³⁶

Despite the significant finding in the current study for the association between 25(OH)D at age 2 years and total IgE, both those with and without elevated IgE levels were vitamin D insufficient, suggesting a threshold effect. Another study showed a nonlinear, U-shaped association between low and high 25(OH)D with increased serum total IgE levels; however, with a sample size of over 9,000 study participants, the statistical power to observe such a relationship was much greater than for our study.⁵¹ Despite our smaller sample size, we were still able to detect associations with a dichotomous variable [ie, cutpoint = median level of 25(OH)D].

Children with higher vitamin D levels had less wheeze or asthma, although this did not reach statistical significance in our study. Nonetheless, our limited findings are in line with recent studies that suggested a link between asthma and low vitamin D levels in children 6–11 years of age,⁵² and others that have identified recurrent wheeze to be associated with deficient levels of 25(OH)D.⁵³ Observational studies of asthmatic school-age children in Costa Rica,³⁶ Puerto Rico,³⁷ and mainland US⁸ have established an inverse association between vitamin D insufficiency and increased asthma morbidity. Other studies showed race/ethnicity-specific associations between vitamin D insufficiency and current asthma or wheeze

in children.⁵² However, not all findings are consistent.^{3,23,54} In the TARGet Kids! research network, early childhood 25(OH)D was not associated with wheezing at 0–5 years of age.⁵⁴

Our study's design was strengthened by the fact that the association between vitamin D and allergic sensitization was explored in a well-defined sample of inner-city children at high risk for limited sunlight exposure, allergies, and asthma. Second, the inclusion of a wide range of data, such as environmental exposures, sociodemographic measures, and immune markers, provided the opportunity to investigate the potential multifactorial influences on vitamin D status and allergic sensitization.

Certain limitations to our study must be noted. First, a single blood draw is unlikely to be representative of vitamin D status over a period of more than a few months.²² Because vitamin D is not synthesized in the skin from November to March at a latitude of 40°N and dietary intake during those months often does not sufficiently compensate for this,²⁰ the measured 25(OH)D concentrations were likely influenced by the variation in season of blood draw among these children. One of the overarching goals of PRAP was to assess risk factors involved in sensitizing atopically predisposed children. Thus, the study's inclusion criteria were rather specific (inner-city children of Puerto Rican ethnicity born in New York City with a maternal history of asthma and/or inhalant allergy). Although the findings presented here have significant implications for other similarly defined high-risk populations, the generalizability of these findings to other, lower risk populations is limited. Nonetheless, our study design (with narrow inclusion criteria) also allowed us to adjust for potential confounders that can obscure associations between exposures and outcomes.

An additional limitation includes the definition of “self” (parent/caregiver) report of “wheeze” or “asthma” as a diagnosis of asthma. Wheezing in 2-year-old children is mostly infectious and not allergic, so a self/parental history of wheezing and/or asthma may not be a good indicator of allergy/sensitization in that age group. Multiple early-life, time-invariant and time-varying causative factors have been established for predicting phenotypic patterns of early childhood wheeze, including cold/flu season,⁵⁵ maternal asthma,^{55,56} maternal stress,⁵⁷ child gender,^{55,58} environmental tobacco smoke exposure,⁵⁹ and high exposure to traffic-related air pollutants.⁶⁰ Wheezing in young children is often attributed to viral infections.⁶¹

In addition, IgE levels in early childhood can vary by life stage.⁶² By limiting our assessment of children at age 2 years, we reduced the likelihood of bias of comparing children at different ages. By limiting our assessment to 2-year-olds, we adjusted for the age-dependent factors of IgE development and concentration. However, the cross-sectional assessment at age 2 years is a limitation not only for self-reported wheeze, but also seasonality of sunlight exposure and vitamin D levels. Having another blood draw in the heating season or the nonheating season would have addressed this limitation; however, obtaining blood samples from children in observational epidemiology studies at such a young age can be difficult and is often not an acceptable component of a study design.

Finally, it is also possible that the observed associations are due to confounding variables that we did not investigate here and other variables that have not yet been identified. Further study into the vitamin D–IgE association and its mechanisms is warranted.

In conclusion, we have identified a strong inverse relationship between vitamin D and allergic sensitization (high levels of total IgE). We also identified heating season and family-based/home care as the 2 most important determinants of 25(OH)D status in this early childhood population residing in inner-city New York City with risk for winter-time 25(OH)D concentrations below those recommended by the US IOM.³² Our findings suggest that clinicians should consider the established risk categories for vitamin D inadequacy. Future work should assess the determinants of risk for suboptimal vitamin D status as part of the health care provided for Puerto

Rican children who live in densely populated northern cities with very little sun exposure throughout the year. Given that the health implications of suboptimal vitamin D status extend far beyond the immune system, ongoing studies of allergic sensitization and asthma in early life should consider sociocultural factors and time-activity patterns related to sun exposure to better understand why the asthma burden among Puerto Ricans is higher than that of other Latino ethnicities.

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