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Vitamin D and Pulmonary Function in Obese Asthmatic Children

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Summary

Objective—Asthma-related morbidity is higher among children with vitamin D deficiency and obesity, morbidities that frequently co-exist among minority children. However, the effect of co-existent obesity and vitamin D deficiency on pulmonary function is poorly understood.

Methods—We compared percent-predicted values of pulmonary function across vitamin D categories among 72 obese and 71 normal-weight Hispanic and African-American children with asthma recruited at an urban children's hospital. Serum cytokines associated with Th1 and Th2 inflammation and 25-hydroxyvitamin D (25-OHD) were quantified in fasting serum. 25-OHD levels ≥ 30 ng/ml were categorized as sufficient, <30 and ≥ 20 ng/ml as insufficient, and <20 ng/ml as deficient. The role of inflammation was investigated by regression analysis.

Results—Vitamin D deficiency was present in 50% of children and did not differ by obese status. Forced Expiratory Volume in the first second (84.5 ± 9.4 vs. 94.8 ± 8.4 , $P < 0.001$), and Functional Residual Capacity (67.5 ± 20.1 vs. 79.3 ± 19 , $P = 0.01$) were lower among vitamin D deficient obese asthmatics than their sufficient counterparts, and Total Lung Capacity was lower than their insufficient counterparts (86.9 ± 14.3 vs. 96.6 ± 10 , $P = 0.01$); similar associations were not observed in normal-weight asthmatics and were not influenced by systemic inflammation. No association between Th1 and Th2 inflammatory measures, vitamin D deficiency, and pulmonary function tests was found.

Conclusions—Vitamin D deficiency was associated with pulmonary function deficits among obese children, but not among normal-weight children with asthma, an association that was independent of Th1 and Th2 serum inflammatory measures. Vitamin D deficiency may be one potential mechanism underlying the obese-asthma phenotype.

Keywords

asthma; obesity; vitamin D deficiency; pulmonary function testing

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INTRODUCTION

Asthma is one of the most common chronic pediatric diseases.¹ It disproportionately affects urban minority children, in whom it has been linked to environmental exposures and related allergen sensitization.² More recently, obesity and vitamin D deficiency (25-OHD <20 ng/ml),³ also highly prevalent among minority children,⁴ have been associated with pediatric asthma.^{5,6} However, the mechanistic links between co-existent obesity and vitamin D deficiency and asthma are not well understood.

Vitamin D is inversely associated with asthma severity and exacerbations^{6,7} and its deficiency has been associated with poor asthma control and lower pulmonary function among urban children.⁸ However, not all studies have identified an association between vitamin D and asthma,⁹ suggesting that there may be a mediating factor between vitamin D and asthma.

Obesity is an independent risk factor for asthma and has been correlated with increased asthma morbidity, especially in urban, minority populations.⁵ Obesity is associated with altered pulmonary mechanics, with lower airway obstruction and reduced lung volumes among children with asthma.¹⁰ This association may be due to metabolic dysregulation,¹¹ systemic inflammation,¹² or mechanical load of truncal fat.¹³ Obese asthmatic children have non-atopic systemic inflammation that correlates with metabolic dysregulation and pulmonary function deficits.^{10,12} Obesity is also associated with vitamin D deficiency,⁴ which itself has immunomodulatory properties.¹⁴ However, the relationship of asthma with co-existent obesity and vitamin D deficiency among urban minority children is not well elucidated.

To address these gaps, we investigated the association of vitamin D with pulmonary function among obese and normal-weight asthmatic urban minority children. Since obesity and asthma are pro-inflammatory conditions and vitamin D is known to be an immunomodulator,¹⁴ we also investigated the role of systemic inflammation in the relationship of vitamin D with pulmonary function among urban minority children with asthma. We hypothesized that vitamin D deficiency is associated with pulmonary function deficits in obese asthmatic children and this relationship is influenced by systemic measures of non-atopic inflammation.

MATERIALS AND METHODS

Study Population

Our study cohort of 143 Hispanic and African-American children included 72 obese and 71 normal-weight asthmatics. These children were recruited from clinics at the Children's Hospital at Montefiore, Bronx, NY between 7/2008 and 6/2013 as part of two studies, one including pre-adolescent children ages 7–11 years,¹⁰ and the other including adolescents ages 13–18 years.¹² These studies were conducted to investigate systemic inflammatory patterns and their association with pulmonary function among obese children with asthma.^{10,12} Obesity was defined as a body mass index (BMI) greater than the 95th

percentile and normal-weight as less than the 85th percentile for age and gender.^{10,12} Asthma was defined based on physician diagnosis with electronic medical record documentation of medication use, emergency department visits, and hospitalizations for asthma. All study participants completed one study visit at the Clinical Research Center. The study visit comprised of a questionnaire on asthma disease burden, including daytime and nighttime symptom frequency, medication use, and unscheduled health care visits. These responses were used to calculate the Composite Asthma Severity Index (CASI).¹⁵ The children underwent anthropometric measurements, pulmonary function testing, and a fasting blood draw. Consent for subsequent use of samples for research purposes was obtained at the time of recruitment for these two studies (IRB#08-04-107E and 10-06-174E, respectively). 25-OH vitamin D was quantified in residual de-identified serum samples. The study was approved by the Institutional Review Board at Albert Einstein College of Medicine.

Pulmonary Function Testing

A trained respiratory therapist conducted all pulmonary function testing, including spirometry and lung volume quantification in a body plethysmograph (SensorMedics, Yorba Linda, CA), as per the American Thoracic Society (ATS) guidelines.¹⁶ National Health And Nutrition Examination Survey (NHANES) reference values were applied to calculate percent-predicted values of the spirometric indices¹⁷ and those developed by the ATS were applied for lung volume indices.¹⁸ The percent-predicted values of the following pulmonary function variables were included in the analysis: (a) spirometry indices: Forced vital capacity (FVC), forced expiratory volume in 1st second (FEV₁), FEV₁/FVC ratio, mid-expiratory flow rates (FEF_{25–75%}); (b) lung volume indices: Total lung capacity (TLC), residual volume (RV), RV/TLC ratio, expiratory reserve volume (ERV), functional residual capacity (FRC), and inspiratory capacity (IC).

Quantification of Serum Vitamin D

Fasting de-identified serum samples were analyzed for 25-OH vitamin D levels (hereafter referred to as vitamin D) using Tandem Liquid Chromatography-Mass Spectrometry (LC/MS) (Agilent, Santa Clara, CA). Vitamin D levels were categorized as sufficient (levels ≥30 ng/ml), insufficient (levels ≥20 and <30 ng/ml), or deficient (<20 ng/ml) based on prior pediatric literature and endocrine guidelines.³

Quantification of Serum Cytokines

Serum cytokines were quantified as measures of systemic inflammatory response, as previously described.^{10,12} These included cytokines associated with T helper (Th)1 inflammation (IFN γ , TNF, IL-6, IL-8, and interferon gamma-induced protein 10 [IP-10]) and Th2 inflammation (IL-4, IL-5, IL-13, and eotaxin). While IP-10 is a cytokine secreted by immune cells in response to IFN γ stimulation and associated with T cell recruitment, eotaxin is a chemokine associated with eosinophil recruitment to tissues. Among the pre-adolescent participants, the cytokines were quantified on the Bioluminex 100 system (Luminex, TX) and analyzed with StarStation (version2.0; Applied Cytometry Systems, Sheffield, UK). Among the adolescent participants, we used the Luminex xPONENT MAGPIX system (v4.2, Luminex) for quantification followed by analysis on the Milipore

analyst (v3.5.5., Milipore, MA). There were no significant differences in the distribution of these cytokines between the pre-adolescent children and adolescents. Since we have previously reported a consistent direct association of obesity with Th1 cytokines and inverse association with Th2 cytokines,^{10,12} we calculated composite measures of Th1 and Th2 inflammation for each participant as the sum of log₁₀ values of the Th1 and Th2 cytokines, respectively. These values were used to investigate the role of Th1 and Th2 inflammation in the association of vitamin D with pulmonary function.

Statistical Analysis

Demographic variables, pulmonary function, and vitamin D categories were compared between the obese and normal-weight asthmatics using Student's *t*-test for the continuous variables and χ^2 test for the categorical variables. Analysis of Variance (ANOVA) was performed to elucidate the relationship between vitamin D categories and pulmonary function among obese and normal-weight asthmatics. Bonferroni post hoc analysis was done when ANOVA was statistically significant ($P < 0.05$). To elucidate the role of inflammation, multivariate linear regression models were developed for pulmonary function variables that were significantly associated with vitamin D deficiency, including composite Th1 and Th2 measures as predictor variables in the model. Although the equations for deriving percent-predicted values of pulmonary function include age, gender, and height and are ethnicity specific,^{17,18} we recognize the limitation of these equations in predicting pulmonary function among the different Hispanic heritage groups. We therefore included age, gender, height, and ethnicity as covariates in the model. Analysis was conducted on STATA statistical software version 12¹⁹ and statistical significance was defined a priori as $P < 0.05$.

RESULTS

Patient Characteristics

The demographic and clinical characteristics of the obese and normal weight asthmatics are summarized in Table 1. Obese asthmatic and normal-weight asthmatics did not differ with regards to age, gender, or ethnicity distribution. Few participants in either group were vitamin D sufficient and close to half of subjects in both groups were vitamin D deficient. The mean vitamin D levels ($P = 0.9$) or the proportion of vitamin D sufficient, insufficient, or deficient children ($P = 0.09$) did not differ between the two study groups. While lung volume indices, RV, RV/TLC ratio, ERV, and FRC were lower, and IC was higher in obese asthmatics compared to normal-weight asthmatics, spirometry indices did not differ between the groups (Table 1).

The mean CASI score did not differ between obese and normal-weight asthmatics (3.75 ± 2.33 vs. 3.94 ± 2.19 , $P = 0.6$). However, compared to their sufficient and insufficient counterparts, vitamin D deficient obese asthmatics had a higher CASI score indicating worse disease ($\beta = 1.45$, 95%CI 0.19, 2.71, $P = 0.02$), an association that was not observed in normal-weight asthmatics ($\beta = 0.22$, 95%CI -0.87 , 1.32, $P = 0.68$).

Comparison of Pulmonary Function by Vitamin D Categories

Comparison of pulmonary function by vitamin D categories among the two study groups is summarized in Tables 2 and 3. A significant association between vitamin D categories and FEV₁, TLC, FRC, and IC was observed among obese (Table 2) but not among normal-weight asthmatics (Table 3). Post hoc analysis of these associations showed that vitamin D deficient obese asthmatics had lower FEV₁ compared to the vitamin D sufficient ($P < 0.05$) and insufficient ($P < 0.005$) groups, lower FRC compared to the vitamin D sufficient group ($P < 0.05$) and lower TLC compared to the insufficient group ($P < 0.05$).

Comparing pulmonary function between obese and normal-weight asthmatics by vitamin D status, ERV was lower in vitamin D deficient obese asthmatics than normal-weight asthmatics (61.7 ± 24.5 vs. 79.6 ± 23.2 , $P = 0.003$) but did not differ between their vitamin D sufficient counterparts (73.9 ± 19.3 vs. 80.5 ± 15.2 , $P = 0.55$).

Effect of the Th1 and Th2 Inflammatory Measures on the Association Between Vitamin D Deficiency and Pulmonary Function Among Obese Asthmatic Children

As summarized in Table 4, Th1 cytokines TNF, IL-8, and IP-10 and the composite Th1 measure were higher among obese asthmatics than normal-weight asthmatics. While Th2 cytokine IL-13, was higher among normal-weight asthmatics, the composite Th2 measure did not differ between the two groups. Multivariate linear regression analysis including Th1 and Th2 composite measures as predictor variables, and adjusted for demographic variables, revealed no influence of Th1 and Th2 inflammatory measures on the association of vitamin D deficiency with FEV₁, TLC, or FRC (Tables 5–7), suggesting that these associations are independent of Th1 and Th2 inflammatory measures. Furthermore, the composite Th1 measure was inversely associated with TLC and FRC, an association that was independent of vitamin D deficiency (Tables 6 and 7). There was a direct protective association of Th2 inflammatory measure with TLC and FRC, also independent of vitamin D deficiency (Tables 6 and 7). Age, gender, and ethnicity did not influence these relationships.

DISCUSSION

We investigated the association of vitamin D with pulmonary function, including spirometry and lung volume indices, in urban minority children with asthma and elucidated the influence of obesity on this association. We found that vitamin D deficiency was associated with lower FEV₁, TLC, and FRC among obese children with asthma, but not among normal-weight asthmatic children. Since pediatric obesity-related asthma is associated with systemic Th1 polarization^{10,12} and vitamin D is an immunomodulator,¹⁴ we additionally examined the effect of systemic inflammation on this association of vitamin D with pulmonary function. We found that the relationship of vitamin D with pulmonary function were independent of Th1 and Th2 systemic inflammatory responses. Together, these findings suggest that vitamin D deficiency is a predictor of both lower airway obstruction and reduced pulmonary volumes among obese children with asthma, independent of systemic inflammation. Given prior reports of the effects of obesity on pulmonary function among asthmatic children,^{10,12} our findings suggest that obesity and vitamin D deficiency together may play a role in the asthma morbidity among urban minority children.

Vitamin D insufficiency has been associated with asthma morbidity in several pediatric studies, including Hispanic and Caucasian children.^{6,20,21} In addition, the direct correlation of serum vitamin D levels with FEV₁ alone,⁸ FVC and FEV₁,²¹ and FEV₁ and FEV₁/FVC ratio,²² among children with asthma suggests that altered pulmonary function may be one of the mechanisms by which vitamin D is associated with asthma. While our results validated these studies and extended these findings to an urban minority pediatric population, we observed an association only between FEV₁ and vitamin D levels, and this finding was limited to the obese asthmatic children. Although BMI was included as a demographic variable in these earlier studies of vitamin D and pulmonary function, and its interquartile range suggests inclusion of overweight children,²¹ additional subgroup analysis based on body weight was not available. Therefore, the role of body weight on their reported findings remains unclear and may be one of the factors that could explain the differences in study results.

More importantly, we found vitamin D deficiency to be associated with FRC and TLC, two lung volume indices that are decreased among obese children.^{11,23} Since the pathophysiology of obesity-related asthma is not well understood, these findings identify a potentially novel association that may underlie lung volume deficits among obese asthmatic children. These findings are also pertinent from the clinical perspective. Although weight loss studies have shown improvement in lung function in children²⁴ and adults²⁵ and higher lean mass is associated with higher vitamin D levels in adults,²⁶ weight loss among children is modest and difficult to sustain, particularly among minorities.²⁷ Since vitamin D deficiency is more common among obese children,^{4,28} is influenced by dietary habits,²⁸ and is responsive to therapy,²⁹ the association of vitamin D with lung volume deficits linked to obesity offers a therapeutic option for childhood obesity-related asthma which is known to be less responsive to conventional asthma management.³⁰ Moreover, because pulmonary function improvement after vitamin D supplementation has been reported in some,³¹ and not all studies,^{29,32,33} we hypothesize based on our findings, that differences in responses may be due to differences in baseline BMI. To address this, additional meta-analysis of existing studies investigating the responsiveness to vitamin D supplementation by obesity status may facilitate a better understanding of the differential effect of vitamin D on asthma outcomes by BMI status.

Several mechanisms may underlie the observed links between vitamin D deficiency and pulmonary function among obese asthmatics, including obesity-mediated influences on inflammation, metabolism, microbiome, and bioavailability of vitamin D. Whereas some studies have linked vitamin D deficiency with atopic Th2 inflammatory response,³⁴ others have reported a higher disease burden with vitamin D insufficiency in children with non-atopic asthma.²⁰ Although we have previously reported evidence of non-atopic Th1 polarized systemic inflammation among obese asthmatic children in these study cohorts,^{10,12} Th1 or Th2 inflammatory measures did not influence the association of vitamin D deficiency with pulmonary function. These findings suggest that biological processes other than inflammation may underlie the vitamin D-obesity-asthma relationship in our study, a concept that was recently supported by a trial in adults, where vitamin D supplementation was not associated with greater asthma control³² or decrease in airway or systemic inflammatory measures.³⁵ We additionally investigated the influence of metabolic

measures including insulin resistance and dyslipidemia on the association of vitamin D deficiency with pulmonary function, details that were available for our study cohort,¹² and did not find an effect of either of these measures (data not shown), suggesting that the metabolic effect of vitamin D among children³⁶ also does not explain our observations.

Recent studies suggest that the gut microbiome may play a role in vitamin D availability,³⁷ and thereby posit that the gut microbiome may play a role in the vitamin D, asthma and obesity relationship. The concept of a “common mucosal response” links the immune effects of the gut microbiome with that of the respiratory tract, and there is evidence to suggest that the gut microbiota may influence responses to viral respiratory infections.³⁸ Since altered gut microbiome has been associated with vitamin D,³⁷ asthma,³⁸ and obesity,³⁹ the extent to which it plays a role in their relationship needs investigation.

Prior studies have also found decreased bioavailability of vitamin D among obese children compared to normal-weight children.⁴⁰ Since vitamin D is a fat-soluble vitamin, the decreased bioavailability is likely due to its deposition and sequestration in adipose tissue⁴⁰ rather than an absolute deficiency. Furthermore, differences have also been found in the vitamin D threshold for its metabolic effects as compared to bone health.⁴¹ Although we did not find similar thresholds in the relationship of vitamin D levels with pulmonary function in our study, these findings may have been influenced by the very high prevalence of vitamin D deficiency and insufficiency in our study sample. For these reasons, the extent to which differential bioavailability and absolute deficiency play a role in the pathophysiology of obesity-related asthma needs to be better elucidated.

Western lifestyle may be a common denominator to several of these factors that underlie obesity and vitamin D deficiency. It includes greater consumption of processed food, especially among Hispanic and African-American populations,⁴² with low consumption of dairy and other vitamin D rich foods, which itself has been associated with an altered microbiome⁴³ and pro-inflammatory profile.⁴⁴ In addition, children are sedentary with more screen time and less time spent outdoors, have a higher BMI, both of which have been associated with asthma.⁴⁵ Together, the composite investigation of these myriad factors and the influence of Western lifestyle will allow an improved understanding of the mechanisms that underlie the inconclusive results of vitamin D supplementation.⁴⁶ Hence, future studies are needed to better define the individual or combined role of inflammation, metabolic dysregulation, gut microbiome, and vitamin D bioavailability in the association between vitamin D deficiency and pediatric asthma.

Our study has certain limitations. Firstly, the cross sectional nature of the study precluded our ability to identify a causal relationship between vitamin D and asthma. Secondly, being a secondary study to the primary outcomes of the links between inflammation and lung function among obese asthmatic pre-adolescents and adolescents, we did not design the study and subject recruitment to address seasonal differences in vitamin D levels, aspects that have been identified to play a role in the vitamin D-asthma association.⁴⁷ However, a prior study has reported little seasonal variation in vitamin D levels among urban minority children.⁴⁸ Thirdly, we did not query the participants on their time spent outdoors or consumption of vitamin supplements. Fourthly, there were few participants in our study who

were vitamin D sufficient and approximately half of all our subjects in both groups were vitamin D deficient. Although these findings are in keeping with previously reported findings of higher prevalence of low vitamin D levels among urban children with asthma,⁸ they are higher than those reported in a national representative sample of Hispanic children.²⁸ Thus, the low proportion of vitamin D sufficient participants may have influenced the power of the study to identify additional associations of vitamin D subcategories with pulmonary function. Furthermore, we do not have data on the Hispanic heritage groups in our participants, as it is possible that vitamin D levels vary between these subgroups. Lastly, although we measured Th1 and Th2 cytokines as inflammatory measures, we did not quantify fractional exhaled nitric oxide, total immunoglobulin E, blood eosinophil counts, or skin testing in these children which may have further delineated the vitamin D-obesity-asthma relationship.

In conclusion, we found high prevalence of vitamin D deficiency in the urban, minority pediatric population with asthma with no difference in this prevalence by obesity status. However, vitamin D deficiency was associated with lower pulmonary function only among obese asthmatic children, including lung volume deficits found in context of obesity. Our findings define a new mechanism that may underlie pediatric obesity-related asthma, a mechanism that may be amenable to supplementation and dietary modification. Given the inconclusive results on the effectiveness of vitamin D supplementation in improving asthma outcomes and pulmonary function,⁴⁶ perhaps additional analyses of these studies based on the participant BMI may identify differential effects of vitamin D supplementation among obese children with asthma.

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ABBREVIATIONS

BMI	Body mass index
FVC	Forced vital capacity
FEV₁	Forced expiratory volume in 1st second
FEF	Forced expiratory flow
TLC	Total lung capacity
RV	Residual volume
ERV	Expiratory reserve volume

FRC	Functional residual capacity
IC	Inspiratory capacity
IL	Interleukin
TNF	Tumor necrosis factor
IFN	Interferon
ANOVA	Analysis of variance
IP-10	Interferon gamma induced protein-10

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TABLE 1

Characteristics of the Study Sample

	Obese asthmatics (n = 72)	Normal-weight asthmatics (n = 71)	P-value
Demographics			
Age ^a	13.1 ± 3.5	12.9 ± 3.8	0.82
Male ^b	38 (52)	37 (50)	0.87
Hispanic ^b	41 (56)	38 (52)	0.68
Vitamin D levels ^a and categories ^b			
25-OHD levels (ng/ml)	20.9 ± 8.4	21.1 ± 6.5	0.92
25-OHD sufficient	11 (15.2)	5 (7)	0.09
25-OHD insufficient	23 (31.9)	34 (47.8)	
25-OHD deficient	38 (52.9)	32 (45.2)	
Pulmonary function indices ^{a,c}			
FVC	95.5 ± 15.6	92.7 ± 11.5	0.22
FEV ₁	89.3 ± 11.9	86.7 ± 13	0.20
FEV ₁ /FVC	81.2 ± 6.8	82.4 ± 8.1	0.35
FEF _{25-75%}	77.8 ± 21.8	76.4 ± 24.6	0.72
TLC	89.8 ± 13	90.3 ± 16.3	0.83
RV	80.2 ± 31.3	96.9 ± 45.1	0.01
RV/TLC ratio	20.3 ± 5.7	24 ± 6.9	0.0006
ERV	65.9 ± 23.5	77.3 ± 25	0.001
FRC	72.4 ± 20.2	86.7 ± 24.9	<0.001
IC	96.7 ± 17.2	84.8 ± 81.6	<0.001

^aVariables are reported mean ± standard deviation, *P*-value was derived by *t*-test.

^bVariables are reported as proportions (n%), *P*-value was derived by χ^2 test.

^cPercent predicted values of pulmonary function were compared between study groups.

TABLE 2

Association of Pulmonary Function With Vitamin D in Obese Children With Asthma^a

	25-OHD sufficient	25-OHD insufficient	25-OHD deficient	P-value ^b
FVC	99.7 ± 4.7	98.4 ± 24	92.5 ± 10.4	0.23
FEV ₁	94.8 ± 8.4 ^c	94.7 ± 14.1 ^d	84.5 ± 9.4 ^{c,d}	0.009
FEV ₁ /FVC	84 ± 5.7	80.3 ± 6.1	80.9 ± 7.4	0.32
FEF _{25–75%}	87.8 ± 25	80.5 ± 23.2	73.2 ± 19.5	0.11
TLC	86.3 ± 9	96.6 ± 10 ^e	86.9 ± 14.3 ^e	0.01
RV	68.5 ± 27.2	92 ± 36.3	76.8 ± 28.2	0.079
RV/TLC	18.5 ± 6.3	21.5 ± 6.4	20 ± 5	0.35
ERV	73.9 ± 19.3	67.8 ± 22.6	61.7 ± 24.5	0.29
FRC	79.3 ± 19 ^f	73.5 ± 19.3	67.5 ± 20.1 ^f	0.04
IC	92.1 ± 13.6	104.3 ± 12.2	93.9 ± 19.3	0.049

^aPercent predicted values of pulmonary function were compared between the vitamin D categories.^bP-value derived by ANOVA. Post hoc Bonferroni analysis was conducted for the ANOVA test that reached statistical significance. The two vitamin D groups that contributed to the statistical significance, identified on Bonferroni post hoc analysis, are marked by symbols in each row and the results are detailed below.^{c,d}FEV₁ was lower among 25-OHD deficient obese children with asthma, as compared to 25-OHD sufficient ($P < 0.05$) and insufficient children ($P < 0.005$).^eTLC was lower among 25-OHD deficient obese children with asthma, as compared to 25-OHD insufficient children ($P < 0.05$).^fFRC was lower among 25-OHD deficient obese children with asthma, as compared to 25-OHD sufficient children ($P < 0.05$).

TABLE 3Association of Pulmonary Function With Vitamin D in Normal-Weight Children With Asthma^a

Vitamin D level	25-OHD sufficient	25-OHD insufficient	25-OHD deficient	P-value ^b
FVC	97.8 ± 4.3	93.9 ± 12.5	91.1 ± 11.1	0.38
FEV ₁	88.6 ± 17.3	89 ± 12.7	84.3 ± 12.8	0.67
FEV ₁ /FVC	80. ± 15.6	83.3 ± 7.5	81.4 ± 7.5	0.57
FEF _{25–75%}	75.2 ± 35.8	79.1 ± 24	73.8 ± 24.7	0.69
TLC	90.7 ± 18.4	89.7 ± 17.1	90.6 ± 15.6	0.61
RV	105.6 ± 81.1	93.2 ± 44.1	101.3 ± 41.1	0.72
RV/TLC	24.6 ± 13.9	23.1 ± 6.4	25.1 ± 6.3	0.49
ERV	80.5 ± 15.2	74.9 ± 28.5	79.6 ± 28.2	0.75
FRC	109 ± 38.2	83.8 ± 24.7	87 ± 22.3	0.11
IC	87.3 ± 19.1	88.6 ± 14.2	80.6 ± 11.4	0.06

^aPercent predicted values of pulmonary function were compared between the vitamin D categories.^bP-value derived by ANOVA. Post hoc Bonferroni analysis was conducted for the ANOVA test that reached statistical significance. The two vitamin D groups that contributed to the statistical significance, identified on Bonferroni post hoc analysis, are marked by symbols in each row and the results are detailed below.

TABLE 4

Comparison of Serum Cytokines and Composite Th1 and Th2 Inflammatory Measures Between Obese and Normal-Weight Children With Asthma

Immune measure ^a	Obese asthmatics	Normal-weight asthmatics	P-value
Th1 measures			
IFN γ	0.56 $\pm$ 0.87	0.46 $\pm$ 0.99	0.54
TNF	0.92 $\pm$ 0.57	0.68 $\pm$ 0.69	0.03
IL-6	0.58 $\pm$ 0.98	0.32 $\pm$ 0.98	0.11
IL-8	1.12 $\pm$ 0.95	0.78 $\pm$ 1.08	0.046
IP-10	2.39 $\pm$ 0.25	2.10 $\pm$ 0.74	0.003
Composite Th1	5.57 $\pm$ 2.85	4.34 $\pm$ 3.72	0.03
Th2 measures			
IL-4	0.38 $\pm$ 0.77	0.51 $\pm$ 0.77	0.32
IL-5	-0.29 $\pm$ 0.72	-0.4 $\pm$ 0.68	0.34
IL-13	0.03 $\pm$ 0.75	0.37 $\pm$ 0.96	0.02
Eotaxin	1.70 $\pm$ 0.36	1.44 $\pm$ 0.71	0.009
Composite Th2	1.71 $\pm$ 1.80	2.03 $\pm$ 2.32	0.37

^a All cytokines were quantified in pg/ml and the values were log₁₀ transformed for analysis.

TABLE 5

Multivariate Analysis of the Association of FEV₁ With Vitamin D Deficiency and Inflammation Among Obese Children With Asthma^a

	β (95%CI)	P-value
Vitamin D deficient	−9.25 (−15.25, −3.25)	0.003
Th1 composite measure of inflammation	0.50 (−0.54, 1.55)	0.34
Th2 composite measure of inflammation	−1.32 (−2.84, 0.21)	0.09

^aIn the above multivariate analysis, the reference group was vitamin D insufficient and sufficient groups combined together, given the association of vitamin D deficiency with these pulmonary function indices in univariate analysis and the small number of participants that were 25-OH vitamin D sufficient.

β denotes a unit change in pulmonary function index among children with vitamin D deficiency relative to those that were vitamin D sufficient or insufficient. It also denotes the unit change in pulmonary function index for unit change in Th1 or Th2 composite measure of inflammation. All models included demographic variables, age, gender, height, and ethnicity as covariates.

TABLE 6

Multivariate Analysis of the Association of TLC With Vitamin D Deficiency and Inflammation Among Obese Children With Asthma^a

	β (95%CI)	P-value
Vitamin D deficient	−9.31 (−15.58, −3.04)	0.004
Th1 composite measure of inflammation	−2.21 (−3.31, −1.10)	<0.001
Th2 composite measure of inflammation	1.84 (0.25, 3.44)	0.02

^aIn the above multivariate analysis, the reference group was vitamin D insufficient and sufficient groups combined together, given the association of vitamin D deficiency with these pulmonary function indices in univariate analysis and the small number of participants that were 25-OH vitamin D sufficient.

TABLE 7

Multivariate Analysis of the Association of FRC With Vitamin D Deficiency and Inflammation Among Obese Children With Asthma^a

	β (95%CI)	<i>P</i>-value
Vitamin D deficient	−14.98 (−24.88, −5.09)	0.004
Th1 composite measure of inflammation	−3.50 (−5.26, −1.73)	<0.001
Th2 composite measure of inflammation	3.30 (0.80, 5.80)	0.01

^aIn the above multivariate analysis, the reference group was vitamin D insufficient and sufficient groups combined together, given the association of vitamin D deficiency with these pulmonary function indices in univariate analysis and the small number of participants that were 25-OH vitamin D sufficient.