

Vitamin D Insufficiency and Asthma in a US Nationwide Study



Yueh-Ying Han, PhD, Erick Forno, MD, MPH, and Juan C. Celedón, MD, DrPH Pittsburgh, Pa

What is already known about this topic? Vitamin D deficiency or insufficiency may increase the risk of asthma or morbidity from asthma, particularly in children.

What does this article add to our knowledge? We show racial/ethnic-specific effects of vitamin D insufficiency on current asthma or wheeze. Moreover, we show parallel recent decrements in the prevalence of vitamin D insufficiency and asthma among participants in different study waves.

How does this study impact current management guidelines? At this time, vitamin D cannot be recommended for asthma treatment. Clinicians should consider screening for vitamin D deficiency (which causes musculoskeletal problems) in high-risk groups (eg, blacks, Puerto Ricans, institutionalized individuals, and the obese).

BACKGROUND: Vitamin D insufficiency (a serum 25-hydroxy vitamin D level of <30 ng/mL) has been associated with asthma morbidity.

OBJECTIVE: To examine vitamin D insufficiency, asthma, and lung function among US children and adults.

METHODS: Using data from the National Health and Nutrition Examination Survey from 2001 to 2010, we examined vitamin D insufficiency and (1) current asthma or wheeze in 10,860 children (6-17 years) and 24,115 adults (18-79 years) and (2) lung function in a subset of participants. Logistic or linear regression was used for the multivariable analysis, adjusting for age, sex, race/ethnicity, income, body mass index, smoking, and C-reactive protein level.

RESULTS: Vitamin D insufficiency was associated with current asthma (odds ratio, 1.35; 95% CI, 1.11-1.64) and current wheeze in children, as well as with current wheeze in adults (odds ratio, 1.17; 95% CI, 1.04-1.31). After stratifying the analysis by race/ethnicity and (in adults) current smoking, vitamin D insufficiency was associated with current asthma and wheeze in non-Hispanic white children only; in adults, vitamin D insufficiency was associated with current wheeze in non-Hispanic whites and blacks. Vitamin D insufficiency was also associated with lower FEV₁ and forced vital capacity in children and adults.

When analyzing each National Health and Nutrition Examination Survey wave separately, vitamin D insufficiency prevalence was 72% to 76% from 2001 to 2006, and then decreased from 2007 to 2010 (64%-65%); interestingly, asthma prevalence decreased for the first time from the period 2007 to 2008 (8.2%) to the period 2009 to 2010 (7.4%).

CONCLUSIONS: We show racial/ethnic-specific associations between vitamin D insufficiency and current asthma or wheeze in children and adults. Moreover, we report parallel recent decrements in the prevalence of vitamin D insufficiency and asthma. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:790-6)

Key words: Vitamin D insufficiency; Asthma; Wheezing; Lung function; NHANES

Asthma is a common respiratory disease and a significant public health problem worldwide. In the United States, the prevalence of asthma increased from 3.1% in 1980 to 8.4% in 2010.¹ The causes of this “asthma epidemic” are unclear but likely to be due to changes in the environment or lifestyle. Vitamin D status, which is assessed by measurement of serum or plasma 25-hydroxyvitamin D (25[OH]D), is key to the metabolism of calcium and phosphorus. Although the definition of vitamin D deficiency or insufficiency on the basis of 25(OH)D values is still under debate,² vitamin D insufficiency, defined as a serum 25-hydroxyvitamin D₃ (25[OH]D₃) level of less than 30 ng/mL, is now commonly found in children³ and adults⁴ in the United States, likely due to reduced outdoor activity (and thus sun exposure) over the last few decades. Because vitamin D insufficiency is particularly frequent among members of demographic groups at high risk for asthma, such as African Americans, Puerto Ricans, and obese individuals,^{5,6} there has been considerable recent interest in exploring a potential role of vitamin D in the pathogenesis of asthma.

Experimental findings and results from epidemiologic studies have provided suggestive but inconclusive evidence for vitamin D insufficiency as a cause of asthma or morbidity from asthma,

Division of Pediatric Pulmonary Medicine, Allergy, and Immunology, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, Pittsburgh, Pa
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Corresponding author: Juan C. Celedón, MD, DrPH, Division of Pediatric Pulmonary Medicine, Allergy and Immunology, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Ave, Pittsburgh, PA 15224. E-mail: juan.celedon@chp.edu.
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Abbreviations used

BDR-Bronchodilator response

BMI-Body mass index

FVC-Forced vital capacity

NHANES-National Health and Nutrition Examination Survey

RCTs-Randomized clinical trials

25(OH)D-25-hydroxy vitamin D

with generally more consistent findings of a possible link in children than in adults.⁷⁻¹⁶ Such data provided support for 2 ongoing randomized clinical trials (RCTs) of prenatal vitamin D for the prevention of childhood asthma.^{17,18} In the largest of those 2 trials ($n = 876$), children born to women who received vitamin D at 4400 IU/d during pregnancy had a lower incidence of asthma and recurrent wheeze at age 3 years than did those born to women who received 400 IU/d of vitamin D during pregnancy (24.3% vs 30.4%), but this difference (6.1%) was not statistically significant ($P = .05$).¹⁸ However, the study lacked sufficient statistical power to detect an effect of 20% or more,¹⁸ and longer follow-up of the participating children is ongoing to determine whether the observed effect of vitamin D on asthma is persistent and clinically important. With regard to asthma morbidity, 2 RCTs have reported that vitamin D did not reduce the rate of first treatment failure or exacerbation among adults with persistent asthma and vitamin D insufficiency.^{19,20} However, the larger of those 2 trials reported that adults in the vitamin D arm received a significantly lower dose of inhaled corticosteroids than did those in the placebo arm, suggesting steroid-enhancing effects of vitamin D. Moreover, an exploratory analysis in that trial showed that adults who achieved vitamin D sufficiency while in the intervention arm had a significantly lower risk of severe asthma exacerbations than did those in the placebo group.²¹ Small clinical trials in children have shown supportive but inconclusive evidence of beneficial effects of vitamin D in preventing asthma exacerbations^{21,22} and improving asthma control,^{23,24} and a larger clinical trial in US school-aged children is ongoing (NCT02687815; principal investigator J.C. Celedón).

Given continued controversy and a paucity of large-scale studies, we examined the relationship between vitamin D insufficiency and current asthma, current wheeze, and lung function among children and adults who participated in the US National Health and Nutrition Examination Survey (NHANES) from 2001 to 2010. Moreover, we examined temporal trends for vitamin D insufficiency and current asthma during the study period.

METHODS

Subject recruitment and study procedures

NHANES is a cross-sectional nationwide survey of a representative sample of the US population. As part of the study design, ethnic minorities (African Americans and Mexican Americans) and individuals 60 years and older are oversampled, to achieve adequate statistical power for data analysis in these groups.

Serum 25(OH)D level was measured in study participants at the National Center for Environmental Health, using the DiaSorin RIA kit (Stillwater, Minn) for NHANES 2001-2006 and liquid chromatography-tandem mass spectrometry for NHANES 2007-2010 data. To allow comparison of standardized 25(OH)D

levels across the 2 study periods, various regression equations were developed to convert NHANES 2001-2006 RIA measurements to a standardized liquid chromatography-tandem mass spectrometry-equivalent 25(OH)D level.²⁵ Serum total 25(OH)D (in SI units of nmol/L) was defined as the sum of 25(OH)D₃ and 25(OH)D₂ and then converted to conventional units (ng/mL) using the suggested conversion factors: 1 nmol/L = 0.40066 ng/mL.²⁵

Spirometry was available in NHANES 2007-2008 and 2009-2010. Participants were not eligible for spirometry if they were on supplemental oxygen or had painful ear infections, current chest pain or a physical problem with forceful expiration, surgery (of the eye, chest, or the abdomen) in the previous 3 months, heart disease, history of an aneurysm or a detached retina, hemoptysis, or history of a collapsed lung or tuberculosis exposure. Eligible participants performed spirometry following American Thoracic Society recommendations.²⁶ The best FEV₁ and forced vital capacity (FVC) were selected for analysis. Participants whose baseline FEV₁/FVC ratio was below the lower limit of normal^{27,28} and/or whose baseline FEV₁ was below 70% of the predicted value for their demographic characteristics underwent a repeat spirometry, 15 minutes after inhalation of albuterol. Participants were excluded from bronchodilator administration if they had recently used a short-acting inhaled β_2 -agonist or had a previous adverse reaction to albuterol; had a history of congenital heart disease, hypertension, major arrhythmia, or an implanted defibrillator; or were pregnant or breastfeeding. Age-, sex-, and race/ethnicity-specific percent predicted (%predicted) values of FEV₁, FVC, and FEV₁/FVC were calculated adopting normal equations for spirometric parameters of the general US population.²⁷

Informed consent was obtained from all study participants. NHANES was approved by the institutional review board of the National Center for Health Statistics of the Centers for Disease Control and Prevention. Further details on study measurements and procedures may be found on the NHANES Web site (<http://www.cdc.gov/nchs/nhanes.htm>); specific details on spirometry and bronchodilator administration can be found in the NHANES spirometry procedures manual.²⁹

Statistical analysis

Vitamin D insufficiency was defined as a serum 25(OH)D level of less than 30 ng/mL. *Current asthma* was defined by a positive answer to both of the following questions: "Has a doctor or other health professional ever told you that you have asthma?" and "Do you still have asthma?" Participants who answered no to both questions were selected as controls. *Current wheeze* was defined by a positive answer to the question "In the past 12 months, have you had wheezing or whistling in your chest?" *Bronchodilator response (BDR)* was defined as $[(\text{postbronchodilator FEV}_1 - \text{prebronchodilator FEV}_1) / \text{prebronchodilator FEV}_1] \times 100$.

Sampling weights, stratification, and clusters provided in the NHANES data set were incorporated into the analysis, to account for the complex NHANES survey design and obtain proper estimates and their standard errors. Wald chi-square tests and t tests were used for bivariate analyses of binary and continuous variables, respectively. In children, body mass index (BMI) z scores were calculated on the basis of 2000 US Centers for Disease Control and Prevention growth charts.³⁰ Logistic regression was used for the multivariable analysis of vitamin D insufficiency and current asthma, current wheeze, and BDR. Linear regression was used for the multivariable analysis of vitamin D insufficiency and lung function measures (FEV₁, FVC, and FEV₁/FVC). All multivariable models

TABLE I. Characteristics of participants in NHANES 2001-2010, by current asthma status

Characteristics	Children 6-17 y		Adults 18-79 y	
	Current asthma			
	No (n = 9668)	Yes (n = 1192)	No (n = 22,286)	Yes (n = 1829)
Age (y)	11.7 ± 0.1	12.1 ± 0.1	44.1 ± 0.2	44.2 ± 0.5
Sex: male	4833 (51.2)	655 (53.9)	11,046 (49.8)	662 (36.3)*
Race/ethnicity				
Non-Hispanic white	2779 (60.1)	316 (56.0)*	10,327 (70.1)	967 (74.2)*
Non-Hispanic black	2737 (13.6)	465 (20.8)	4,560 (10.8)	433 (12.4)
Mexican American/other Hispanic	3685 (19.6)	352 (17.7)	4,619 (13.4)	349 (8.4)
Other	467 (6.6)	59 (5.1)	980 (5.7)	80 (5.0)
Health insurance coverage (yes)	8041 (88.0)	1083 (94.0)*	16,672 (80.1)	1507 (85.5)*
Annual household income < \$20,000	2169 (16.3)	288 (17.1)	4,680 (14.8)	518 (21.1)*
BMI (kg/m ²)	20.8 (0.1)	22.2 (0.2)*	28.2 ± 0.1	30.5 ± 0.3*
BMI z score	0.58 (0.02)	0.88 (0.04)*	—	—
Serum cotinine level (ng/mL)	6.7 ± 0.5	9.5 ± 2.0	63.2 ± 2.1	72.0 ± 4.0*
Current smoker	—	—	4,723 (23.8)	453 (26.8)
Serum C-reactive protein (mg/dL)	0.14 ± 0.01	0.18 ± 0.02	0.39 ± 0.01	0.53 ± 0.02*
Serum vitamin D level (ng/mL)	26.9 ± 0.1	25.7 ± 0.4†	25.7 ± 0.2	25.0 ± 0.3
Vitamin D insufficiency (<30 ng/mL)	7685 (67.7)	995 (75.9)*	7,052 (69.9)	1046 (72.3)
Non-Hispanic white	1527 (54.6)	199 (64.6)	6,379 (61.8)	621 (65.5)
Non-Hispanic black	2584 (93.8)	440 (94.4)	4,287 (94.4)	416 (96.5)
Mexican American/other Hispanic	3183 (84.1)	308 (88.0)	5,552 (86.3)	299 (87.8)
Other	391 (83.6)	48 (82.4)	834 (85.3)	70 (86.5)
Prebronchodilator FEV ₁ (L)‡	2.73 ± 0.03	2.76 ± 0.07	3.28 ± 0.02	2.82 ± 0.03*
Prebronchodilator FVC (L)‡	3.14 ± 0.03	3.28 ± 0.08	4.18 ± 0.02	3.77 ± 0.05*
Prebronchodilator FEV ₁ /FVC (%)‡	86.5 ± 0.2	83.4 ± 0.5*	78.5 ± 0.2	74.5 ± 0.4*
BDR as a percent of baseline FEV ₁ (BDR, %)‡	9.0 ± 0.6	13.2 ± 1.5*	5.5 ± 0.2	10.9 ± 1.1*

Results are shown as mean ± standard error for continuous variables, and as N (%) for binary variables.

**P* < .01 for current asthma vs no current asthma (within each age group).

†*P* < .05 for current asthma vs no current asthma (within each age group).

‡Data are available only in NHANES 2007-2010.

were adjusted for age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), household income (<\$20,000/y or ≥\$20,000/y), BMI (for adults) or BMI z score (for children), and serum levels of cotinine and C-reactive protein. Multivariable models of BDR were additionally adjusted for baseline (pre-bronchodilator) FEV₁. All statistical analyses were conducted using the SAS SURVEY procedure and SAS 9.3 software (SAS Institute Inc, Cary, NC).

RESULTS

During the study period (2001-2010), a total of 10,860 children aged 6 to 17 years and 24,115 adults aged 18 to 79 years who had serum vitamin D measures and information on asthma status were included in the current analysis. Of these participants, 3001 children and 8347 adults from NHANES 2007-2010 also had baseline spirometry data; 234 (7.8%) of these children and 744 (8.9%) of these adults had a BDR measurement.

The overall prevalence of current asthma among study participants was 10.9% in children and 7.6% in adults. The main characteristics of participants are presented in Table I. Compared with children without asthma (n = 9668), those with asthma (n = 1192) were more likely to be non-Hispanic black and to have health insurance coverage, a higher BMI z score, a lower

serum vitamin D level and a higher prevalence of vitamin D insufficiency, lower FEV₁/FVC, and higher BDR. Compared with adults without asthma (n = 22,286), those with asthma (n = 1,829) were more likely to be female and non-Hispanic white or black, and to have health insurance coverage, an annual household income of less than \$20,000, higher BMI, higher levels of serum cotinine and C-reactive protein, lower FEV₁ and FVC, lower FEV₁/FVC, and higher BDR. Vitamin D insufficiency was common in both children and adults (68%-76%), and most common in non-Hispanic blacks (94%-97%). Figure 1 shows vitamin D levels by race/ethnicity for each NHANES study wave (2001-2002 to 2009-2010). Overall, non-Hispanic blacks had a lower vitamin D level (mean, 16.0-18.6 ng/mL) than did other racial or ethnic groups. Moreover, an upward trend of increased vitamin D levels, specifically in the periods 2007-2008 and 2009-2010, was seen in the US population.

The multivariable analysis of vitamin D insufficiency and current asthma or current wheeze is presented in Table II. After adjusting for age, sex, race/ethnicity, household income, BMI, and serum cotinine and C-reactive protein levels, vitamin D insufficiency was significantly associated with increased odds of current asthma and current wheeze in children, as well as with current wheeze in adults. After stratification by race or ethnicity, vitamin D insufficiency remained significantly associated with

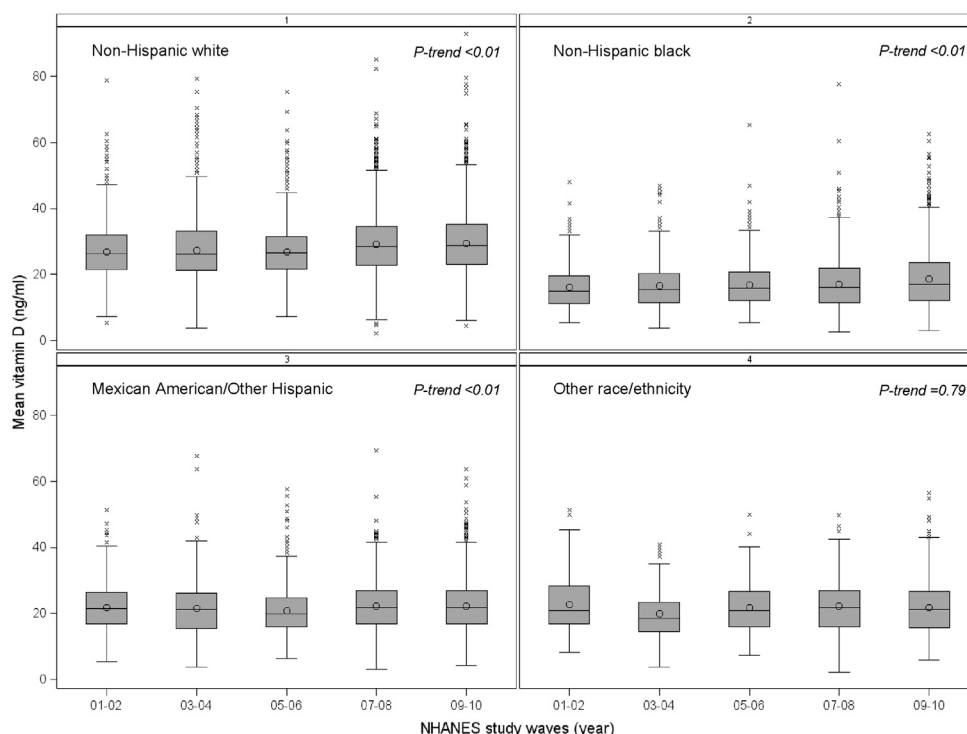


FIGURE 1. Vitamin D level (25[OH]D [ng/mL]) by race/ethnicity and NHANES study waves (2001-2002 to 2009-2010).

TABLE II. Multivariable analysis* of vitamin D insufficiency and current asthma or current wheeze by race/ethnicity (NHANES 2001-2010)

Outcomes	Children (total = 10,860)		Adults (total = 24,115)	
	N†	Odds ratio (95% CI), P value	N†	Odds ratio (95% CI), P value
Current asthma				
All participants	995	1.35 (1.11-1.64), <.01	1046	1.06 (0.93-1.21), .39
Non-Hispanic whites	199	1.41 (1.12-1.77), <.01	621	1.07 (0.93-1.24), .36
Non-Hispanic blacks	440	1.11 (0.69-1.79), .68	416	1.53 (0.91, 2.58), .11
Mexican American/other Hispanic	308	1.35 (0.85-2.14), .20	299	0.95 (0.61-1.48), .83
Current wheeze				
All participants	978	1.24 (1.02-1.52), .03	2597	1.17 (1.04-1.31), <.01
Non-Hispanic whites	228	1.40 (1.11-1.75), <.01	1264	1.22 (1.08-1.38), <.01
Non-Hispanic blacks	383	0.71 (0.47-1.06), .10	660	1.29 (0.91-1.81), .15
Mexican American/other Hispanic	316	0.91 (0.63-1.32), .61	561	1.00 (0.72-1.38), .98

Bold indicates statistically significant results ($P < .05$).

*All multivariable models were adjusted for age, sex, household income, cotinine, C-reactive protein, BMI (in adults), and BMI z score (in children). The model for all participants was additionally adjusted for race/ethnicity.

†N = participants with vitamin D insufficiency and current asthma (or current wheeze). See Table I for the number of participants with vitamin D insufficiency but no current asthma or current wheeze.

current wheeze in non-Hispanic white children and adults, as well as with current asthma in non-Hispanic white children. However, there was no significant association between vitamin D insufficiency and current wheeze or current asthma in children or adults in other racial or ethnic groups. We obtained similar results to those presented in Table II when the multivariable analyses were adjusted for health insurance coverage instead of household income (data not shown).

In a secondary analysis, we repeated the multivariable analysis in adults after stratification by current smoking, to minimize potential misclassification of chronic obstructive pulmonary

disease as current asthma or current wheeze (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). In this analysis, vitamin D insufficiency was significantly associated with current wheeze among nonsmoking non-Hispanic white and black adults. We found no significant association between vitamin D insufficiency and current asthma (regardless of current smoking) or current wheeze in current smokers.

Table III presents results of the multivariable analysis of vitamin D insufficiency and lung function measures among participants in NHANES 2007-2010. In children, vitamin D insufficiency was significantly associated with 110-mL to

TABLE III. Multivariable analysis* of vitamin D insufficiency and lung function measures (NHANES 2007-2010)

Lung function measures	β (95% CI), <i>P</i> value	
	Children (n = 3001)	Adults (n = 8347)
Prebronchodilator FEV ₁ (mL) [†]	−110.17 (−146.79 to −75.54), <.01	−69.68 (−94.17 to −45.18), <.01
Prebronchodilator FVC (mL) [†]	−129.13 (−176.09 to −82.19), <.01	−118.11 (−150.43 to −85.79), <.01
Prebronchodilator FEV ₁ /FVC (%)	−0.06 (−0.84 to 0.72), .88	0.45 (0.05 to 0.85), .03
BDR (%) ^{‡,§}	0.50 (0.20 to 1.21), .12	0.69 (0.36 to 1.36), .29

Bold indicates statistically significant results ($P < .05$).

*All models were adjusted for age, sex, race/ethnicity, household income, current asthma, cotinine, C-reactive protein, BMI (in adults), or BMI *z* score (in children).

[†]Additionally adjusted for height and height square.

[‡]The model for BDR was additionally adjusted for baseline (prebronchodilator) FEV₁.

[§]BDR defined as $\geq 12\%$ increment from baseline FEV₁ in children, and as $\geq 12\%$ and ≥ 200 -mL increment from baseline in adults.

129-mL decrements in FEV₁ and FVC. In adults, vitamin D insufficiency was significantly and inversely associated with FEV₁ (−70 mL) and FVC (−118 mL), but significantly and positively associated with FEV₁/FVC (0.45%; 95% CI, 0.05%-0.85%). Similar results were obtained when the analysis was repeated using %predicted values of FEV₁, FVC, and FEV₁/FVC (see Table E2 in this article's Online Repository at www.jaci-inpractice.org) and after stratification by current asthma (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). Vitamin D insufficiency was not associated with BDR in either children or adults.

We next examined estimates of the prevalence of vitamin D insufficiency and current asthma for each NHANES study wave from 2001 to 2010 (Figure 2). In this analysis, the estimated prevalence of vitamin D insufficiency was 72% to 76% in 2001-2006, and then decreased to 64% to 65% in 2007-2010. Of interest, the estimated prevalence of current asthma decreased from 8.2% in 2007-2008 to 7.4% in 2009-2010, in parallel with the reduction in the estimated prevalence of vitamin D insufficiency for the same period.

DISCUSSION

To our knowledge, this is the first study to examine the relation between vitamin D insufficiency and current asthma or current wheeze in a large sample of US children and adults. Vitamin D insufficiency was common, being present in two-third of study participants. Vitamin D insufficiency was associated with current asthma and current wheeze in non-Hispanic white children, as well as with current wheeze in non-Hispanic white and black adults without a history of current smoking. Vitamin D insufficiency was not associated with current asthma or current wheeze in nonwhite (black or Mexican) children or Mexican adults. Temporal trends in NHANES showed that a decrement in the estimated prevalence of vitamin D insufficiency was followed by decreased prevalence of current asthma.

Consistent with our findings in the US NHANES, vitamin D insufficiency or vitamin D deficiency (a serum 25[OH]D level of <20 ng/mL) has been associated with asthma or wheeze in population-based studies of Peruvian,⁸ Australian,³¹ and Canadian children³² but not significantly associated with asthma in a large study of Israeli adults.¹² Although 2 recent RCTs of vitamin D supplementation (with 2800 IU/d¹⁷ or 4400 IU/d¹⁸) during pregnancy failed to show a significant effect on asthma or wheeze (recurrent or persistent) in the first 3 years of life, the RCT using the larger dose of vitamin D reported a nonstatistically significant trend ($P = .05$) for a protective effect against asthma or recurrent wheeze, as well as a significant protective

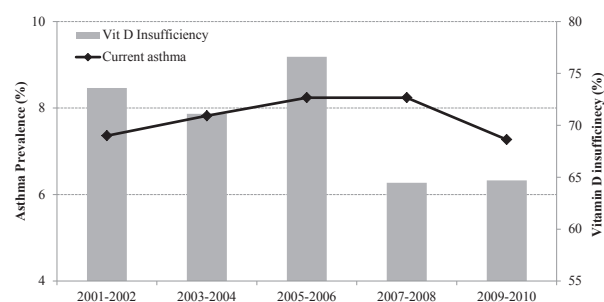


FIGURE 2. Prevalence of current asthma and vitamin D insufficiency (25[OH]D <30 ng/mL) by NHANES study waves (2001-2002 to 2009-2010), in all participants.

effect against degree of allergic sensitization (ie, fewer positive IgE tests to allergens) in a secondary analysis.¹⁸ Both trials had insufficient statistical power to detect small to moderate effects on asthma or wheeze, and continued follow-up of participating children is needed to determine potential effects of vitamin D supplementation on asthma *per se* (because this disease cannot be confidently diagnosed in children younger than 6 years).

Growing evidence indicates that vitamin D affects innate and adaptive immune responses relevant to childhood asthma. In murine models, vitamin D deficiency is associated with airway hyperresponsiveness, as well as with increased proinflammatory cytokines and reduced regulatory T cells in bronchoalveolar lavage fluid.³³ Moreover, vitamin D supplementation attenuates allergen-induced inflammation and airway hyperresponsiveness in sensitized mice.^{33,34} Among children, 3 common genetic variants in the class I MHC-restricted T-cell-associated molecule gene (CRTAM) have been associated with asthma exacerbations in those with vitamin D deficiency,³⁵ and polymorphisms in the gene for the vitamin D receptor have been associated with asthma.³⁶ Whether gene-by-vitamin D interactions explain inconsistent results across observational studies of asthma is uncertain.

We found a significant association between vitamin D insufficiency and decreased FEV₁ or FVC in children and adults, regardless of coexisting asthma. Our results for lung function are thus consistent with those of previous reports in children³⁷⁻³⁹ and adults.⁴⁰ In a study of adults followed for 11 years, those with asthma and low serum 25(OH)D (<20 ng/mL) level at baseline had larger declines in FEV₁, FVC, and FEV₁/FVC than did those with a serum 25(OH)D level of 20 ng/mL or more. In general agreement with our results, that study showed that the

inverse association between vitamin D deficiency and lung function was more pronounced among adults who were non-smokers and did not use inhaled corticosteroids.¹⁴ In contrast to our results, serum or plasma 25(OH)D level was not associated with lung function in a Danish population-based study of 4999 adults¹⁵ or in a Canadian Health Measure Survey that included 1421 children.⁴¹ Moreover, the Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma trial found no significant effects of vitamin D on lung function (a secondary outcome) in adults with persistent asthma and vitamin D insufficiency.¹⁹ The discrepant findings for vitamin D and lung function may be explained by differences in age, race/ethnicity, number of participants, or degree of residual confounding across studies.

In our study, vitamin D insufficiency was significantly associated with asthma or wheeze in non-Hispanic white children, but not in non-Hispanic black or Mexican children. We found similarly negative results for asthma or wheeze in non-Hispanic black children when lower cutoff points for vitamin D (eg, <20 ng/mL or <25 ng/mL) were used (data not shown). Such negative findings may be explained by lack of variability in vitamin D status. Among non-Hispanic black children, more than 90% had a vitamin D level of less than 30 ng/mL and more than 50% had a vitamin D level of less than 20 ng/mL. In contrast to our results in children, vitamin D insufficiency was significantly associated with current wheeze among nonsmoking white and black adults, suggesting that age may modify the effect of vitamin D on wheeze in non-Hispanic blacks. Similarly, Mexican ethnicity may modify the effects of vitamin D insufficiency on asthma, given null results among Mexican children and adults in our study.

A recent study reported that trends in overall childhood asthma prevalence plateaued in 2008, and then declined significantly in 2013.⁴² Although our finding of parallel decrements in asthma and vitamin D insufficiency must be cautiously interpreted because of inherent limitations of ecological results, they are both intriguing and worth exploring in future longitudinal studies.

Our study has considerable strengths, including large and ethnically diverse cohorts of both children and adults, and ability to adjust for potential confounders such as cigarette smoking (measured by serum cotinine), low-grade systematic inflammation (measured by C-reactive protein), and obesity. We also acknowledge several limitations of our findings. First, we cannot determine a temporal relationship between vitamin D insufficiency and asthma or lung function in a cross-sectional study. Second, we cannot exclude residual confounding by unmeasured variables, including atopy, use of asthma medications, outdoor activities, seasonal variation in vitamin D measurements, and dietary intake of other nutrients. Third, we cannot stratify the analysis of vitamin D insufficiency and lung function by race or ethnicity because of small sample size. Finally, the cutoff points for serum vitamin D levels associated with optimal general (nonmusculoskeletal) health are uncertain and under study.^{2,43} The potential effects of vitamin D on asthma and lung health and what adequate levels should be recommended require further investigation.

In summary, vitamin D insufficiency was highly prevalent among children and adults who participated in a large US survey (NHANES). In NHANES, vitamin D insufficiency was associated with current asthma or current wheeze in non-Hispanic

white children, as well as with current wheeze in nonsmoking non-Hispanic white and black adults. Moreover, vitamin D insufficiency was associated with reduced FEV₁ and FVC in children and adults. Ongoing RCTs should help determine whether vitamin D supplementation prevents asthma or severe asthma exacerbations during childhood.

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APPENDIX

TABLE E1. Vitamin D insufficiency and current asthma or current wheeze by race/ethnicity and current smoking status in adults (NHANES 2001-2010)

Vitamin D insufficiency 25(OH)D < 30 ng/mL	Current smoker (n = 5176) OR (95% CI), P value	Not current smoker (n = 16,891) OR (95% CI), P value
Current asthma		
All participants*	0.96 (0.73-1.26), .77	1.09 (0.91-1.31), .36
Non-Hispanic whites	1.07 (0.74-1.39), .93	1.08 (0.89-1.31), .44
Non-Hispanic blacks	0.96 (0.23-4.07), .96	1.74 (0.95-3.20), .07
Mexican American/other Hispanic	0.68 (0.35-1.35), .27	0.96 (0.61-1.51), .85
Current wheeze		
All participants*	1.10 (0.90-1.35), .34	1.17 (0.99-1.38), .06
Non-Hispanic whites	1.17 (0.94-1.45), .17	1.20 (1.02-1.42), .03
Non-Hispanic blacks	0.66 (0.31-1.41), .28	1.55 (1.01-2.38), .04
Mexican American/other Hispanic	0.72 (0.42-1.24), .24	1.13 (0.76-1.68), .53

All models adjusted for age, sex, household income, cotinine, C-reactive protein, BMI (in adults), and BMI z score (in children). Bold indicates statistically significant results ($P < .05$).

*Additionally adjusted for race/ethnicity.

TABLE E2. Vitamin D insufficiency and lung function measures (as percent of predicted values) (NHANES 2007-2010)

Lung function measures	β (95% CI), P value	
	Children (n = 2036)	Adults (n = 7611)
% predicted FEV ₁	-2.93 (-4.02 to -1.85), <.01	-0.56 (-1.33 to 0.21), .15
% predicted FVC	-3.67 (-4.86 to -2.47), <.01	-2.96 (-4.01 to -1.90), <.01
% predicted FEV ₁ /FVC	-0.30 (-1.23 to 0.63), .52	0.58 (0.14 to 1.02), .01

All models adjusted for household income, current asthma, cotinine, C-reactive protein, BMI (in adults), and BMI z score (in children). Bold indicates statistically significant results ($P < .05$).

TABLE E3. Vitamin D insufficiency and lung function measures by current asthma (NHANES 2007-2010)

Lung function measures	β (95% CI), P value	
	Children (n = 3001)	Adults (n = 8347)
No current asthma	n = 2654	n = 7743
Prebronchodilator FEV ₁ (mL)*	-118.95 (-156.49 to -81.42), <.01	-67.39 (-89.43 to -45.35), <.01
Prebronchodilator FVC (mL)*	-133.36 (-180.55 to -86.17), <.01	-116.23 (-148.06 to -84.40), <.01
Prebronchodilator FEV ₁ /FVC (%)	0.25 (-0.67 to 1.17), 0.58	0.51 (0.12 to 0.91), .01
Current asthma	n = 347	n = 604
Prebronchodilator FEV ₁ (mL)*	-174.40 (-300.13 to -48.67), <.01	-112.73 (-230.65 to 5.19), 0.06
Prebronchodilator FVC (mL)*	-70.73 (-168.54 to 27.08), .15	-145.35 (-271.92 to -18.78), .03
Prebronchodilator FEV ₁ /FVC (%)	-2.95 (-4.64 to -1.26), <.01	-0.53 (-2.40 to 1.35), .57

All models adjusted for age, sex, household income, serum cotinine, C-reactive protein, BMI (in adults), and BMI z score (in children). Bold indicates statistically significant results ($P < .05$).

*Additionally adjusted for height and height square.

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