

Original article

Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study

John M. Brehm, MD, MPH,^{a,b,d} Brooke Schuemann, BS,^a Anne L. Fuhlbrigge, MD,^{a,b} Bruce W. Hollis, PhD,^e Robert C. Strunk, MD,^f Robert S. Zeiger, MD, PhD,^g Scott T. Weiss, MD, MS,^{a,b,c,d,*} and Augusto A. Litonjua, MD, MPH,^{a,b,d,*} for the Childhood Asthma Management Program Research Group[‡] Boston, Mass, Charleston, SC, St Louis, Mo, and San Diego, Calif

Background: Asthma exacerbations, most often caused by respiratory tract infections, are the leading causes of asthma morbidity and comprise a significant proportion of asthma-related costs. Vitamin D status might play a role in preventing asthma exacerbations.

Objectives: We sought to assess the relationship between serum vitamin D levels and subsequent severe asthma exacerbations.

Methods: We measured 25-hydroxyvitamin D levels in sera collected from 1,024 children with mild-to-moderate persistent asthma at the time of enrollment in a multicenter clinical trial of children randomized to receive budesonide, nedocromil, or placebo (as-needed β -agonists): the Childhood Asthma

Management Program. Using multivariable modeling, we examined the relationship between baseline vitamin D levels and the odds of any hospitalization or emergency department visit over the 4 years of the trial.

Results: Thirty-five percent of all subjects were vitamin D insufficient, as defined by a level of 30 ng/mL or less 25-hydroxyvitamin D. Mean vitamin D levels were lowest in African American subjects and highest in white subjects. After adjusting for age, sex, body mass index, income, and treatment group, insufficient vitamin D status was associated with a higher odds of any hospitalization or emergency department visit (odds ratio, 1.5; 95% CI, 1.1-1.9; $P = .01$).

Conclusion: Vitamin D insufficiency is common in this population of North American children with mild-to-moderate persistent asthma and is associated with higher odds of severe exacerbation over a 4-year period. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

Key words: Asthma, vitamin D, inhaled corticosteroids, asthma exacerbations

From ^athe Channing Laboratory, ^bthe Division of Pulmonary/Critical Care Medicine, and ^cthe Center for Genomic Medicine, Department of Medicine, Brigham and Women's Hospital, Boston; ^dthe Department of Medicine, Harvard Medical School, Boston; ^eDarby Children's Research Institute, Medical University of South Carolina, Charleston; ^fthe Division of Allergy and Pulmonary Medicine, Department of Pediatrics, Washington University School of Medicine and St Louis Children's Hospital; and ^gthe Department of Allergy, Kaiser Permanente Medical Center, San Diego.

*These authors contributed equally to this work.

[‡]Members of the Childhood Asthma Management Program Research Group are detailed in this article's Online Repository at www.jacionline.org.

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Reprint requests: Augusto A. Litonjua, MD, MPH, Channing Laboratory, 181 Longwood Ave, Boston, MA 02115. E-mail: real@channing.harvard.edu.
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Asthma is a major public health problem affecting an estimated 22 million persons in the United States¹ and 300 million persons worldwide.² Much of the burden of the disease is a consequence of asthma exacerbations, which result in missed time from work, increased absence from school, and increased health care expenditures. Asthma is the third leading cause of hospitalization among children younger than 15 years, with 26.2 discharges per 10,000 population.³ In the United States asthma health care costs are estimated to be \$19.7 billion each year,⁴ and hospitalizations from exacerbations are estimated to be responsible for a third of these costs.⁵

Vitamin D has been shown to have several effects on the innate and adaptive immune systems that might modulate the severity of asthma exacerbations. Airway epithelia contain high levels of the enzyme that converts circulating 25-OH-vitamin D₃ to its active form, 1,25-OH-vitamin D₃. This active form of vitamin D has local effects in response to infections⁶ and might dampen the inflammation that is the consequence of these infections.⁷ Vitamin D also has potentially beneficial effects on the adaptive immune system through its effects on T_H1, T_H2, and regulatory T cells.⁸ Through these mechanisms, vitamin D might also have a therapeutic role in reducing asthma exacerbations.

Our group recently published the first epidemiologic study demonstrating an association between low vitamin D levels and increased markers of asthma severity, including serum IgE levels, eosinophil counts, hospitalizations in the previous year, and

Abbreviations used

AMP: Antimicrobial protein
 BMI: Body mass index
 CAMP: Childhood Asthma Management Program
 ED: Emergency department
 PAR: Population attributable risk

inhaled steroid use.⁹ However, this study was cross-sectional and retrospective and limited to a single geographic location and age group (children 7.5–10.5 years of age) in Costa Rica. We now examine the association between vitamin D levels and risk of hospitalizations or emergency department (ED) visits in a prospective manner in the Childhood Asthma Management Program (CAMP) study, a diverse population of North American asthmatic children.

METHODS

Study population

CAMP was a multicenter, randomized, double-blind, placebo-controlled trial established to investigate the long-term effects of commonly prescribed asthma treatment regimens. In total, 1,041 children were randomized to receive inhaled budesonide, inhaled nedocromil, or placebo. Participants were subsequently followed for a mean of 4.3 years, with lung function studies and questionnaires at regular intervals. Serum IgE levels and eosinophil counts were measured at the time of enrollment in the study, and other outcomes, such as lung function, response to methacholine, and symptom scores as calculated from diary data, were recorded at baseline and at regular intervals over the 4-year follow-up period. At regularly scheduled follow-up visits (approximately every 4 months), children and caretakers were asked about hospitalizations or ED visits specifically caused by an asthma exacerbation. At the screening visit, children and caretakers were also asked about any ED visits or hospitalizations that occurred in the year before enrollment in the study. Trial design, methodology, and the primary outcomes analysis of the CAMP study have been previously published.^{10,11}

At enrollment, CAMP participants had mild-to-moderate persistent asthma based on the presence of symptoms, the use of inhaled bronchodilators at least twice weekly, or the use of daily asthma medication for at least 6 months in the year before screening. Patients with severe persistent and mild intermittent asthma were excluded from the study. Spirometry was performed at least 4 hours after short-acting bronchodilator use and 24 hours after long-acting bronchodilator use. Spirometry was required to meet American Thoracic Society criteria for acceptability and reproducibility. At least 3 spirometric maneuvers were performed, with at least 2 reproducible maneuvers required for each test. Bronchodilator response to albuterol was assessed at randomization and at all subsequent visits, except when a methacholine challenge was performed. Postbronchodilator spirometric values were obtained at least 15 minutes after the administration of 2 puffs of albuterol (90 µg per puff).

Approval was obtained from the institutional review boards at each of the CAMP-participating institutions before initiation of the trial. Informed consent was obtained from the parent or guardian of the participant, and the child's assent was obtained before study enrollment.

Serum 25-hydroxyvitamin D₃

Serum levels of 25-hydroxyvitamin D₃ (hereafter referred to as vitamin D) are considered the best circulating biomarker of vitamin D metabolic status and reflect contributions from all sources of vitamin D (ie, diet and sun exposure).^{12,13} A single measurement of vitamin D was obtained for 1,024 subjects (98% of enrolled subjects) by using a radioimmunoassay method in Dr Bruce Hollis' laboratory at the Medical University of South Carolina.^{14,15} Vitamin D levels have been shown to be relatively stable when specimens have been properly stored.¹⁶ We categorized vitamin D levels into insufficient (≤30 ng/mL) and sufficient (>30 ng/mL) based on previous recommendations.^{17–19}

Statistical analysis

A descriptive analysis of univariate predictors and outcomes was performed by using a dichotomous vitamin D variable with a cutoff of less than or equal to 30 ng/mL. For the purposes of this analysis, a severe exacerbation was defined as any hospitalization or ED visit specifically caused by an asthma exacerbation over the 4-year course of the study. *P* values were calculated by using 2-sided *t* tests for continuous predictors with equal variance and the Wilcoxon rank sum test for continuous predictor with unequal variances. χ^2 tests were performed to obtain *P* values for binary variables.

Multivariable models were constructed by using linear and logistic regression, and proportional hazards models were used for time-to-event analysis. We initially conducted a retrospective analysis relating baseline vitamin D levels with the subjects' (or parents') report of an ED visit or hospitalization for asthma in the previous year, which was obtained at the initial screening visit. The analysis is retrospective because the events had occurred before measurement of vitamin D levels, and it recapitulate the analysis we conducted in the Costa Rican study.⁹ We then conducted the main prospective analyses relating baseline vitamin D levels with subsequent reports of ED visits or hospitalizations for asthma over the 4 years of the trial. Potential confounders were included in the multivariable models if they were associated with vitamin D insufficiency on a univariate basis at a *P* value of .05 or less or if they were plausibly related to both vitamin D levels and asthma severity. The baseline covariates are age, sex, income, and body mass index (BMI). Prospective models for asthma hospitalizations or ED visits were additionally controlled for treatment group. Additional confounders that are possibly causally related to the relationship between vitamin D and the outcome of interest were then added in a stepwise fashion and include season of vitamin D level draw, baseline asthma severity as determined by a physician, and race. All models were additionally stratified by treatment group (budesonide vs either placebo or nedocromil) to assess for effect modification by inhaled steroid use. In the stratified analysis the term for treatment group was removed from the models. All analyses were performed with SAS version 9.1 and JMP 7 software (both from SAS Institute, Inc, Cary, NC).

RESULTS

Characteristics of the study population

The baseline characteristics of the study population stratified by vitamin D sufficiency are shown in Table I. Thirty-five percent of the children were vitamin D insufficient, as defined by a level of 30 ng/mL or less. In a univariate analysis vitamin D insufficiency was significantly associated with older age, higher BMI, and African American race. A higher proportion of the vitamin D-sufficient group was randomized to the budesonide treatment group, although the blood samples were drawn before randomization. Vitamin D insufficiency was not more common among subjects with low income (<\$30,000 per year) in a univariate analysis.

Distribution and predictors of serum vitamin D levels in the study population

The distribution of vitamin D levels by study center, season, and subjects' self-reported race are shown in Fig 1. The highest average levels were in Denver, Colorado, and Albuquerque, New Mexico, and the lowest were in Boston, Massachusetts. Vitamin D levels also varied by season, with summer having the highest mean level, whereas winter and spring had the lowest levels. African American subjects had the lowest average vitamin D levels, and white subjects had the highest levels, although there was a wide range of levels among the white subjects.

Among the entire cohort of children with asthma, the distribution of vitamin D levels were right skewed, with a few subjects having levels greater than 90 ng/mL, but 95% of subjects had levels between 14 and 72 ng/mL (see Fig E1 in this article's Online Repository at www.jacionline.org). In addition, a plot of the

TABLE I. Baseline characteristics of study participants

Characteristic*	All children (n = 1024)	Vitamin D level		P value†‡
		Insufficient (≤ 30 ng/mL; n = 361 [35%])	Sufficient (> 30 ng/mL; n = 663 [65%])	
Age (y)	8.9 (7.2-10.6)	9.3 (7.6-11.0)	8.7 (7.0-10.4)	.0002
Female sex	413 (40%)	155 (43%)	258 (39%)	.21
BMI (kg/m ²)	17.2 (15.7-19.8)	17.7 (16.2-20.8)	17.0 (15.5-19.2)	<.0001
African American race	134 (13%)	88 (24%)	46 (7%)	<.0001
Income $< \$30,000$	239 (24%)	87 (25%)	152 (24%)	.61
Budesonide group	305 (30%)	89 (25%)	216 (33%)	.008
Moderate severity§	538 (53%)	195 (54%)	343 (52%)	.49
Positive skin test response to any allergen	898 (88%)	326 (90%)	572 (86%)	.06
Total IgE level (IU/mL)	437 (174-1,216)	468 (178-1,380)	427 (170-1,175)	.15
Eosinophil count (cells/mm ³)	398 (200-646)	389 (200-617)	398 (200-676)	.44
Postbronchodilator lung function				
FEV ₁ (L)	1.85 (1.83-1.87)	1.82 (1.78-1.85)	1.87 (1.84-1.89)	.009
FEV ₁ /FVC ratio	86 (82-90)	86 (81-90)	86 (82-90)	.79
Bronchodilator response (% FEV ₁)	8 (4-15)	9 (4-15)	8 (4-15)	.66
Health care use				
Hospitalizations for asthma in the year before randomization	328 (32%)	142 (39%)	186 (28%)	.0002
Any hospitalization or ED visit over 4 y	346 (34%)	136 (38%)	210 (32%)	.05

FVC, Forced vital capacity; FEV₁, forced expiratory volume in 1 second.

*Results are expressed as medians (interquartile ranges) for continuous variables and numbers of subjects (percentage of group) for categorical variables.

†Information is missing on some subjects for eosinophil counts (n = 14), spirometry and bronchodilator response (n = 2), and BMI (n = 10).

‡P values are 2-sided *t* tests or Wilcoxon rank sum tests (depending on equality of variances) for continuous variables and χ^2 tests for binary variables.

§Only subjects with mild persistent or moderate persistent asthma were enrolled in the study.

||FEV₁ is the predicted value from the regression model, including age, sex, and vitamin D status (for stratified columns), for subjects at a mean age of 9 years and of male sex.

probability of having an ED visit or hospitalization over the 4 years of the trial versus serum vitamin D level is demonstrated in Fig 2. A smoothing function was used to fit a line between these points to assess for nonlinear trends over the range of vitamin D levels in the study. At around 30 ng/mL, the probability of having an asthma exacerbation decreases. Given this finding and in keeping with prior recommendations for “sufficient” levels, all subsequent analyses were performed with a dichotomous variable for vitamin D levels.

Severe asthma exacerbations

For the purposes of this analysis, any asthma exacerbation requiring hospitalization or an ED visit was defined as severe, according to Global Initiative for Asthma guidelines.²⁰ Over the 4 years of the study, 106 children were hospitalized for asthma, and 352 children had either a hospitalization or a visit to the ED for an asthma exacerbation. Univariate and multivariable analyses of the relation between vitamin D levels and odds of an ED visit or hospitalization before and during the CAMP study are shown in Table II. The odds of any ED visit or hospitalization in the year before enrolling in the trial (retrospective analysis) were significantly increased in the vitamin D–insufficient group, even after controlling for age, sex, BMI, and physician-determined severity at baseline. We additionally adjusted for race and season of blood draw in a stepwise fashion, although these covariates are strong determinants of vitamin D levels and therefore might be an overadjustment. The effect remained significant after additionally adjusting for these variables, although the effect size was attenuated.

The odds of any hospitalization or ED visit over the 4 years of the CAMP study (prospective analysis) in the vitamin D–insufficient group were also increased after adjustment for age, sex, BMI, and baseline physician-determined severity. We also analyzed the association stratified by treatment group. Subjects who were randomized to inhaled budesonide and were vitamin D

insufficient tended to have higher odds of hospitalizations than subjects who were randomized to nedocromil or placebo and were vitamin D insufficient. This effect was largest in subjects randomized to budesonide and nonsignificant in subjects randomized to placebo or nedocromil.

Because inhaled corticosteroids had a large protective effect on severe exacerbations,¹¹ we calculated the risks of hospitalization or ED visit over 4 years for all combinations of vitamin D status and inhaled corticosteroid use (Table III). Compared with the reference group of children receiving inhaled steroids and with sufficient vitamin D levels, all other combinations had increased odds of severe exacerbation, with the highest risk occurring in children who were not receiving inhaled corticosteroids and were vitamin D insufficient. Because children who were receiving inhaled corticosteroids and were vitamin D insufficient also had increased risks for severe exacerbations, these results also suggest that having sufficient vitamin D levels conferred additional benefit to use of inhaled corticosteroids. Children not receiving inhaled steroids and with insufficient vitamin D levels had the highest risk of hospitalization compared with the reference group.

Because some children had more than one severe exacerbation in the 4 years of the trial, we also conducted a time-to-first-event analysis. With a proportional hazards model, vitamin D insufficiency conferred a higher hazard ratio for hospitalization or an ED visit (see Table E1 in this article's Online Repository at www.jacionline.org). As in the logistic regression analysis, the effect was strongest in the budesonide treatment arm and remained significant after controlling for season of vitamin D draw, baseline asthma severity, and race.

Measures of atopy and asthma symptoms

After adjustment for potential confounders, there was no significant difference in skin test reactivity, total serum IgE levels, or eosinophil counts between the vitamin D–sufficient and vitamin

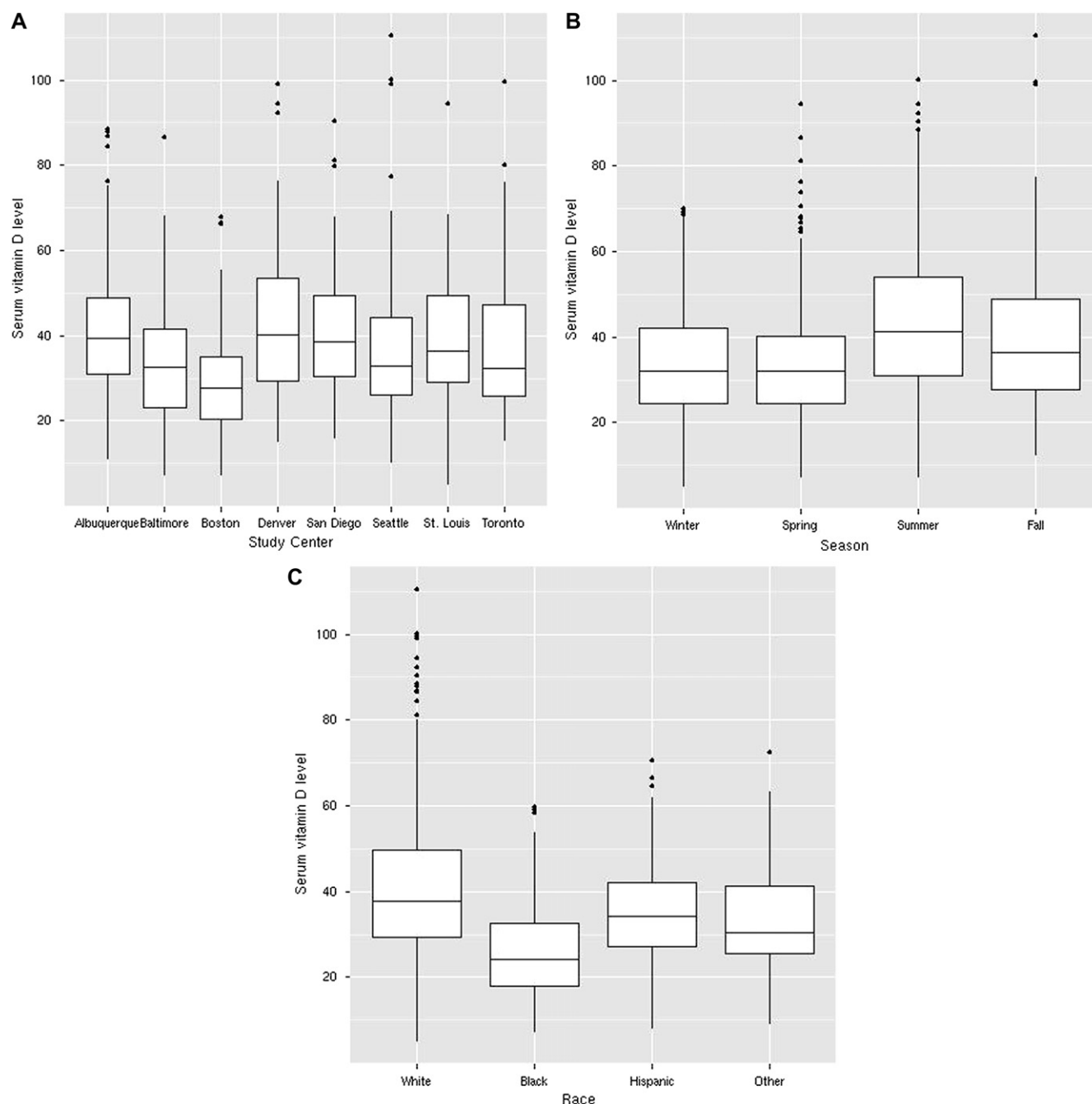


FIG 1. Vitamin D levels and distributions by study center (A), season (B), and race (C).

D-insufficient subjects (see Table E2 in this article's Online Repository at www.jacionline.org). Subjects with insufficient vitamin D at randomization also had a significantly lower percentage of visits with reports of moderate symptoms (defined as ≥ 2 days of symptoms in each of the 4 weeks before the visit). We found no difference in the odds of receiving a prednisone burst over the 4 years of the study in the vitamin D-insufficient children.

Spirometric measures of lung function and airway hyperreactivity

Table E2 also shows the results of multivariate models for prediction of postbronchodilator FEV₁ and FEV₁/forced vital

capacity ratio and the natural log dose of methacholine required to cause a 20% decrease in FEV₁. After controlling for confounders, insufficient vitamin D status predicts a slightly lower postbronchodilator FEV₁ and a trend toward a slightly higher FEV₁/forced vital capacity ratio. There was no difference in airway hyperreactivity as measured by log-transformed PC₂₀ dose.

DISCUSSION

Our group previously reported an inverse relationship with vitamin D levels and several markers of asthma and allergy severity in Costa Rican children.⁹ The present data from the CAMP cohort of 1,024 children confirms the finding in the Costa

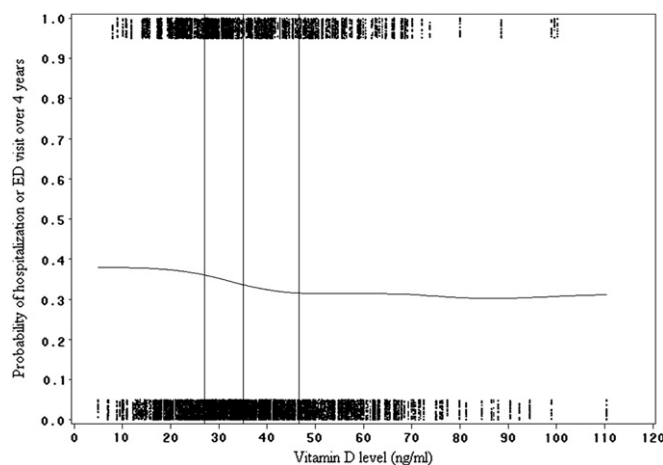


FIG 2. Sensitivity analysis of risk of hospitalization or ED visit by vitamin D level. The probabilities of severe exacerbations were plotted for the range of vitamin D levels in the study, and a smoothing function was used to draw a line through the values. Vertical lines represent quartiles of vitamin D levels. The risk of hospitalization starts to decrease around a vitamin D level of 30 ng/mL.

Rican study that low vitamin D levels are associated with increased odds of asthma-related ED visits or hospitalization in the previous year. In this study we further demonstrate that after adjustment for age, sex, BMI, and baseline asthma severity, vitamin D insufficiency at baseline is associated prospectively with increased odds of severe asthma exacerbations, defined as hospitalizations, ED visits, or both, over the 4-year course of the study. In addition, children with insufficient vitamin D levels had a slightly lower mean FEV₁ compared with children with sufficient levels. However, unlike the Costa Rican study, we did not find any association between vitamin D levels and allergy markers.

Higher vitamin D levels are likely associated with decreased risk of severe exacerbations through multiple mechanisms. One mechanism might be through improved response to respiratory tract infections because vitamin D has been shown to induce the production of antimicrobial proteins (AMPs), such as cathelicidin (which has both antimicrobial and antiviral properties)^{6,21} and defensin β 4.²² Induction of AMPs has been shown to occur at the airway epithelium. In addition to the induction of AMPs, vitamin D might modulate the inflammatory response to viral infections. Airway epithelial cells exposed to vitamin D produce less inflammatory cytokines (without adversely affecting viral clearance) than cells not exposed to vitamin D when infected with viruses.^{6,7} These findings suggest that although higher vitamin D levels might not prevent the occurrence of infections, higher levels might allow improved handling of these infections and decreased inflammatory responses, resulting in less severe disease and sequelae of these viral infections. This is supported by our data, which show no difference in the odds of receiving a prednisone burst in the vitamin D–insufficient group but a higher odds of hospitalization or an ED visit, suggesting that the number of exacerbations are the same but the severity of exacerbations are worse in the vitamin D–insufficient children. However, we are unable to directly test the hypothesis that vitamin D improved the host response to infections because we did not have specific information regarding infections.

In addition to the response to infections, another mechanism of vitamin D in asthmatic subjects might be through enhancement of

the response to both exogenous and endogenous steroids. This could explain why we saw a stronger beneficial vitamin D effect among the children randomized to the budesonide group. Although inhaled steroids were effective in significantly decreasing exacerbations in this trial,¹¹ children who continued to have severe exacerbations despite inhaled corticosteroids might be a subgroup that is not responding fully to inhaled corticosteroids. Our results suggest that having sufficient levels prevents some of these exacerbations while receiving inhaled corticosteroids. These results, in particular, are consistent with a proposed mechanism, as demonstrated *in vitro* by Xystrakis et al,²³ that vitamin D restores the ability of steroid-treated regulatory T cells from steroid-resistant asthmatic subjects to secrete IL-10, a potent anti-inflammatory cytokine in airway epithelial cells, thus enhancing steroid uptake and effectiveness.

In contrast to our findings on severe exacerbations, vitamin D insufficiency was significantly associated with the report of fewer symptoms. A possible explanation is that daily symptoms and exacerbations might be related to vitamin D through different mechanisms. Because vitamin D likely reduces the severity of viral infections rather than eliminating them, another explanation is that vitamin D reduces severe exacerbations by preventing the severe sequelae of viral infections without affecting the incidence of such infections. Further investigation will be required to resolve these inconsistencies.

Although this study confirms and extends the results of the Costa Rican study with regard to asthma exacerbations, we did not see similar results for markers of allergy, such as serum IgE levels and eosinophil counts. The CAMP and Costa Rican cohorts have important similarities and differences that might explain some of these discrepant findings. Because the Costa Rican study was designed as a genetic epidemiology study, the study population is homogenous by design: all subjects were required to have 6 of 8 grandparents from the Central Valley of Costa Rica, and all subjects live in or near the Central Valley. In contrast, CAMP has a diverse outbred population composed predominantly of white, black, and Hispanic subjects. Subjects were recruited from 8 centers across the country, each at different latitudes and altitudes. Atopy is highly prevalent in both populations, with 88% of CAMP subjects having positive skin test responses to at least 1 allergen compared with 85% of Costa Rican subjects. Unlike equatorial Costa Rica, which does not have much variability in UV exposure throughout the year, the vitamin D levels of CAMP subjects vary by season. Therefore although the overall median values for vitamin D levels in CAMP and the Costa Rican study are similar (35.1 vs 35.7 ng/mL, respectively), there is likely much more variability in vitamin D levels over the course of a year in the CAMP population. To the extent to which this is true, it would represent a null bias in our results. Finally, it is possible that vitamin D influences atopy only in certain environmental backgrounds. As a multicenter trial, the participants in CAMP would be expected to have quite different quantitative and qualitative seasonal allergen exposures when compared with subjects in Costa Rica. An important area of future research is to clarify the interaction between vitamin D and environmental exposures on allergic outcomes, as well as asthma severity.

Because the Costa Rican study was a cross-sectional study, it was difficult to establish causality for the association between vitamin D levels and asthma severity. It is possible that children with more severe disease are more likely to spend time indoors, which can lead to an association that is spurious. A major

TABLE II. Hospitalizations or ED visits: Values are odds ratio (95% CI) (p value) for severe exacerbations in vitamin D insufficient group (≤ 30 ng/ml) vs. vitamin D sufficient group (>30 ng/ml)

	Unadjusted odds ratio	Adjusted for age, sex, BMI, income, treatment group*	Additionally adjusted for season of vitamin D draw	Additionally adjusted for baseline asthma severity	Additionally adjusted for race
Retrospective analysis†: ED or hospitalization in year prior to study					
All subjects*	1.7 (1.3 – 2.2) (.0002)	1.9 (1.4 – 2.5) (<.0001)	2.0 (1.5 – 2.7) (<.0001)	1.9 (1.4 – 2.6) (<.0001)	1.7 (1.2 – 2.7) (.001)
Prospective analysis: ED/Hospitalization over 4 years of study					
All subjects	1.3 (1.0 – 1.7) (.05)	1.5 (1.1 – 1.9) (.01)	1.5 (1.2 – 2.1) (.004)	1.5 (1.1 – 2.0) (.006)	1.4 (1.0 – 1.9) (.03)
Subjects randomized to Placebo or Nedocromil*	1.2 (0.9 – 1.6) (.36)	1.3 (1.0 – 1.9) (.08)	1.4 (1.0 – 2.0) (.03)	1.4 (1.0 – 2.0) (.06)	1.3 (.9 – 1.8) (.15)
Subjects randomized to Budesonide*	1.7 (1.0 – 2.8) (.06)	1.8 (1.0 – 3.2) (.05)	1.8 (1.0 – 3.3) (.06)	1.8 (1.0 – 3.4) (.05)	1.7 (.9 – 3.2) (.11)

*Models for hospitalization prior to randomization and stratified models are not adjusted for treatment group.

†The terms retrospective and prospective refer to the timing of the outcomes relative to the timing of phlebotomy from which vitamin D levels were measured.

TABLE III. Risk of severe exacerbation over 4 years by a combination of inhaled corticosteroid use and vitamin D status

	No	Yes	Percentage	Odds ratio*
Receiving inhaled steroids, sufficient vitamin D	162	52	24	1.0 (reference)
Receiving inhaled steroids, insufficient vitamin D	58	31	35	1.7 (1.0-2.9)
Not receiving steroids, sufficient vitamin D	289	158	35	1.7 (1.2-2.5)
Not receiving steroids, insufficient vitamin D	166	105	39	2.0 (1.3-2.9)

*Odds ratios are for each stratum in reference to a subject receiving inhaled corticosteroids with sufficient vitamin D. The Cochran-Armitage 2-sided *P* value for trend over the 4 strata is .0009.

advantage of the current study is that we were able to measure vitamin D levels in blood samples collected at the time of enrollment and perform an analysis when the hospitalizations or ED visits occurred after the time of phlebotomy, which is a stronger study design than a retrospective analysis. This prospective design reveals more modest effects of vitamin D than that seen in the retrospective design, but these effects remain statistically significant after adjustment for age, sex, BMI, treatment group, and physician-determined severity. Because vitamin D production in the skin is dependent on skin pigmentation and amount of UVB exposure,¹⁸ covariates such as race and season of vitamin D measurement are strongly related to vitamin D levels, and therefore adjusting for them in a multivariate model likely represents overadjustment for vitamin D. However, because both race and season likely affect asthma severity through pathways independent from vitamin D, they are also likely to confound the association between vitamin D and severe asthma exacerbations. Accordingly, we have presented models with race and season added in a stepwise fashion. Despite this concern for overadjustment, the full models, including race and season, predict a significantly higher odds ratio for ED/hospitalization in the vitamin D–insufficient group. At this point, a randomized, placebo-controlled trial of vitamin D supplementation to prevent asthma exacerbations is needed to confirm the findings from our observational studies.

Another potential confounder of our results is vitamin D supplementation. Although significant vitamin D supplementation will be reflected in higher vitamin D levels, this might also reflect a “healthy user” effect or act as a proxy for intake of other vitamins that might influence asthma severity. For this type of confounding to significantly affect our results, vitamin D supplementation would have to substantially change serum levels, and one would have to postulate that those who were insufficient at the start of the study were supplemented with relatively large doses. As Heaney

et al²⁴ demonstrate, standard recommended replacement doses of vitamin D (400 IU/d) do not have any substantial effect on serum levels, and therefore we believe this is unlikely to be a significant source of error. At the time the CAMP study was conducted, vitamin D supplementation was not as publicized as it is today; thus it is likely that children who were vitamin D insufficient remained in the insufficient range throughout most of the study.

The current study is limited by only having one measure of serum vitamin D at enrollment. An ideal analysis would be to perform repeated measures over time for testing in a proportional hazards model, which would be able to account for seasonal variations in vitamin D levels. Our inability to capture this variability does not invalidate these results; rather a low correlation between repeated measures would reduce power to detect a true association, possibly resulting in a false-negative result.²⁵ Furthermore, work by Hilgenfeld et al²⁶ suggests that although seasonal variation in vitamin D levels in school-aged children occurs, over the course of the year, there was no variation in urinary calcium excretion, suggesting that these fluctuations in serum levels might not be physiologically relevant.

Because asthma exacerbations account for a large proportion of overall asthma-related health care costs and because vitamin D deficiency is so common, we calculated the population attributable risk (PAR) for vitamin D insufficiency on asthma exacerbations. Given the prevalence of insufficiency in our study in both the budesonide group and the total group of children in the CAMP, the PAR% is at least 11%. Although this might appear small, decreasing asthma health care costs by this proportion translates into more than \$2 billion in savings per year if circulating vitamin D levels could be brought up to at least 30 ng/mL in all asthmatic subjects. Furthermore, in a recent analysis of the National Health and Nutrition Examination Survey data collected between 2001 and 2006, 48% of children had levels of less than 30 ng/mL,²⁷ and

therefore our PAR% estimate is likely conservative. Although this prevalence of vitamin D insufficiency is higher than in the CAMP cohort, we point out that CAMP subjects were recruited from 1993 through 1995, and vitamin D insufficiency has become more prevalent in the years since.²⁸

The current recommended level of sufficiency (≥ 30 ng/mL) is thought to be the minimum necessary level for overall health because beneficial effects on musculoskeletal function are seen beginning at this level.¹⁷ However, the circulating level of vitamin D for optimal immune function is unknown, although there are suggestions that this level might very well be greater than 40 ng/mL.^{29,30} Beneficial effects are likely to be greatest in black subjects and in those already receiving inhaled steroids. Given the potential public health benefits, a randomized controlled trial is indicated to confirm the observational results presented here.

In summary, we demonstrate that vitamin D insufficiency is common in childhood asthmatic subjects in the United States, and it predicts increased odds of severe exacerbations over a 4-year period, even after adjusting for a range of potential confounders. Even in those already receiving inhaled steroids, vitamin D insufficiency increased this risk. These results confirm and extend the findings from the Costa Rican cohort in regard to severe exacerbations. A randomized controlled trial should be done to confirm these results and to generalize to other subgroups of asthmatic subject.

Key messages

- Vitamin D insufficiency is common in a North American population of subjects with mild-to-moderate childhood asthma.
- Vitamin D insufficiency is associated with higher odds of severe asthma exacerbation over a 4-year period.
- Having sufficient vitamin D levels conferred protection against severe exacerbations that was in addition to the effect of receiving inhaled corticosteroids.

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MEMBERS OF THE CAMP RESEARCH GROUP

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Clinical centers

ASTHMA, Inc, Seattle, Wash: Gail G. Shapiro, MD (Director); Thomas R. DuHamel, PhD (Co-Director); Mary V. Lasley, MD (Co-Director); Tamara Chinn, MSN, ARNP (Coordinator); Michele Hinatsu, MSN, ARNP; Clifton T. Furukawa, MD; Leonard C. Altman, MD; Frank S. Virant, MD; Paul V. Williams, MD; Michael S. Kennedy, MD; Jonathan W. Becker, MD; Grace White. C. Warren Bierman, MD (1992-1997); Dan Crawford, RN (1996-2002); Heather Eliassen, BA (1996-1999); Babi Hammond (1996-1999); Dominick A. Minotti, MD (1992-2003); Chris Reagan (1992-2003); Marian Sharpe, RN (1992-1994); Timothy G. Wighton, PhD (1994-1998).

Brigham & Women's Hospital, Boston, Mass: Scott Weiss, MD, MS (Director); Anne Fuhlbrigge, MD (Principal Investigator); Anne Plunkett, NP, MS (Coordinator); Nancy Madden, RN, BSN; Peter Barrant, MD; Christine Darcy; Kelly Thompson, MD; Walter Torda, MD (Co-Investigator Director, 1993-2003); Martha Tata, RN (1993-2002); Sally Babigian, RN (1997-1999); Linda Benson (1998-2004); Jose Caicedo (1998-1999); Tatum Calder (1998-2001); Anthony DeFilippo (1994-2000); Cindy Dorsainvil (1998-2001); Julie Erickson (1998-1999); Phoebe Fulton (1997); Mary Grace, RN (1994-1996); Jennifer Gilbert (1997-1998); Dirk Greineder, MD (1993-2000); Stephanie Haynes (1993-1998); Margaret Higham, MD (1996-1998); Deborah Jakubowski (1999); Susan Kelleher (1993-1997); Jay Koslof, PhD (1993-1995); Dana Mandel (1996-1998); Patricia Martin (2001-2003); Agnes Martinez (1994-1997); Jean McAuliffe (1994-1995); Erika Nakamoto (2002-2004); Paola Pacella (1993-1998); Paula Parks (1993-1995); Johanna Sagarin (1998-1999); Kay Seligsohn, PhD (1995-2004); Susan Swords (2003-2005); Meghan Syring (1998-2001); June Traylor, MSN, RN (1996-1998); Melissa Van Horn, PhD (1996-1999); Carolyn Wells, RN (1993-1995); Ann Whitman, RN (1994-1996).

The Hospital for Sick Children, Toronto, Ontario, Canada: Ian MacLusky, MD, FRCP(C) (Director); Joe Reisman, MD, FRCP(C), MBA (Director, 1996-1999); Henry Levison, MD, FRCP(C) (Director, 1992-1996); Anita Hall, RN (Coordinator); Jennifer Chay; Melody Miki, RN, BScN; Renée Sananes, PhD; Yola Benedet (1994-1999); Susan Carpenter, RN (1998-2001); Michelle Collinson, RN (1994-1998); Jane Finlayson-Kulchin, RN (1994-1998); Kenneth Gore, MA (1993-1999); Noreen Holmes, RRT (1998-1999); Sharon Klassen, MA (1999-2000); Joséé Quenneville, MSc (1993-1995); Christine Wasson, PhD (1999).

Johns Hopkins Asthma & Allergy Center, Baltimore, Md: N. Franklin Adkinson, Jr, MD (Director); Peyton Eggleston, MD (Co-Director); Elizabeth H. Aylward, PhD; Karen Huss, DNSc (Co-Investigator); Leslie Plotnick, MD (Co-Investigator); Margaret Pulsifer, PhD (Co-Investigator); Cynthia Rand, PhD (Co-Investigator); Nancy Bollers, RN (Coordinator); Deborah Bull, LPN; Robert Hamilton, PhD; Kimberly Hyatt; Susan Limb, MD; Mildred Pesaro; Stephanie Philips, RN; Barbara Wheeler, RN, BSN.

National Jewish Medical and Research Center, Denver, Colo: Stanley Szefer, MD (Director); Harold S. Nelson, MD

(Co-Director); Bruce Bender, PhD (Co-Investigator); Ronina Covar, MD (Co-Investigator); Andrew Liu, MD (Co-Investigator); Joseph Spahn, MD (Co-Investigator); D. Sundström (Coordinator). Melanie Phillips; Michael P. White; Kristin Brelsford (1997-1999); Jessyca Bridges (1995-1997); Jody Ciacco (1993-1996); Michael Eltz (1994-1995); Jeryl Feeley, MA (Coordinator, 1992-1995); Michael Flynn (1995-1996); Melanie Gleason, PA-C (1992-1999); Tara Junk-Blanchard (1997-2000); Joseph Hassell (1992-1998); Marcia Hefner (1992-1994); Caroline Hendrickson, RN (1995-1998; Coordinator, 1995-1997); Daniel Hettelman, MA (1995-1996); Charles G. Irvin, PhD (1992-1998); Jeffrey Jacobs, MD (1996-1997); Alan Kamada, PharmD (1994-1997); Sai Nimmagadda, MD (1993-1996); Kendra Sandoval (1995-1997); Jessica Sheridan (1994-1995); Trella Washington (1993-1997); Eric Willcutt, MA (1996-1997). We also thank the pediatric allergy and immunology fellows for their participation (Kirstin Carel, MD; Neal Jain, MD; Harvey Leo, MD; Beth Macomber, MD; Chris Mjaanes, MD; Lora Stewart, MD; Ben Song, MD).

University of California, San Diego, and Kaiser Permanente Southern California Region, San Diego, Calif: Robert S. Zeiger, MD, PhD (Director); Noah Friedman, MD (Co-Investigator); Michael H. Mellon, MD (Co-Investigator); Michael Schatz, MD (Co-Investigator); Kathleen Harden, RN (Coordinator); Elaine M. Jenson; Serena Panzlau; Eva Rodriguez, RRT; James G. Easton, MD (Co-Director, 1993-1994); M. Feinberg (1997-1998); Linda L. Galbreath (1991-2002); Jennifer Gulczynski (1998-1999); Ellen Hansen (1995-1997); Al Jalowayski, PhD (Co-Investigator, 1991-2005); Alan Lincoln, PhD (Co-Investigator, 1991-2003); Jennie Kaufman (1994); Shirley King, MSW (1992-1999); Brian Lopez (1997-1998); Michaela Magiari-Ene, MA (1994-1998); Kathleen Mostafa, RN (1994-1995); Avraham Moscona (1994-1996); Catherine A. Nelle, RN (1991-2005); Jennifer Powers (2001-2003); Karen Sandoval (1995-1996); Nevin W. Wilson, MD (Co-Director, 1991-1993).

University of New Mexico, Albuquerque, NM: H. William Kelly, PharmD (Director); Aaron Jacobs (Co-Investigator); Mary Spicher, RN (Coordinator); Hengameh H. Raissy; Robert Annett, PhD (Co-Investigator, 1993-2004); Teresa Archibeque (1994-1999); Naim Bashir, MD (Co-Investigator, 1998-2005); H. Selda Bereket (1995-1998); Marisa Braun (1996-1999); Shannon Bush (2002-2006); Michael Clayton, MD (Co-Investigator, 1999-2001); Angel Colon-Semidey, MD (Co-Investigator, 1997-2000); Sara Devault (1993-1997); Roni Grad, MD (Co-Investigator, 1993-1995); David Hunt, RRT (1995-2004); Jeanne Larsson, RN (1995-1996); Sandra McClelland, RN (Coordinator, 1993-1995); Bennie McWilliams, MD (Co-Investigator, Director, 1992-1998); Elisha Montoya (1997-2000); Margaret Moreshead (1996-1999); Shirley Murphy, MD (Co-Investigator, 1992-1994); Barbara Ortega, RRT (1993-1999); David Weers (1997-1998); Jose Zayas (1995-1996).

Washington University, St Louis, Mo: Robert C. Strunk, MD (Director); Leonard Bacharier, MD (Co-Investigator); Gordon R. Bloomberg, MD (Co-Investigator); James M. Corry, MD (Co-Investigator); Denise Rodgers, RFPT (Coordinator); Lila Kertz, MSN, RN, CPNP; Valerie Morgan, RRT; Tina Oliver-Welker, CRTT; Deborah K. White, RPFT, RRT.

Resource centers

Chair's Office, National Jewish Medical and Research Center, Denver, Colo: Reuben Cherniack, MD (Study Chair).

Coordinating Center, the Johns Hopkins University, Baltimore, Md: James Tonascia, PhD (Director); Curtis Meinert, PhD (Co-Director). Patricia Belt; Karen Collins; Betty Collison; Ryan Colvin, MPH; John Dodge; Michele Donithan, MHS; Judith Harle; Rosetta Jackson; Hope Livingston; Jill Meinert; Kapreena Owens; Michael Smith; Alice Sternberg, ScM; Mark Van Natta, MHS; Margaret Wild; Laura Wilson, ScM; Robert Wise, MD; Katherine Yates, ScM.

Project Office, National Heart, Lung, and Blood Institute, Bethesda, Md: Virginia Taggart, MPH (Project Officer); Lois Eggers; James Kiley, PhD; Gang Zheng, PhD. Paul Albert, PhD (1991-1999); Suzanne Hurd, PhD (1991-1999); Sydney Parker, PhD (1991-1994); Pamela Randall (1992-2003); Margaret Wu, PhD (1991-2001).

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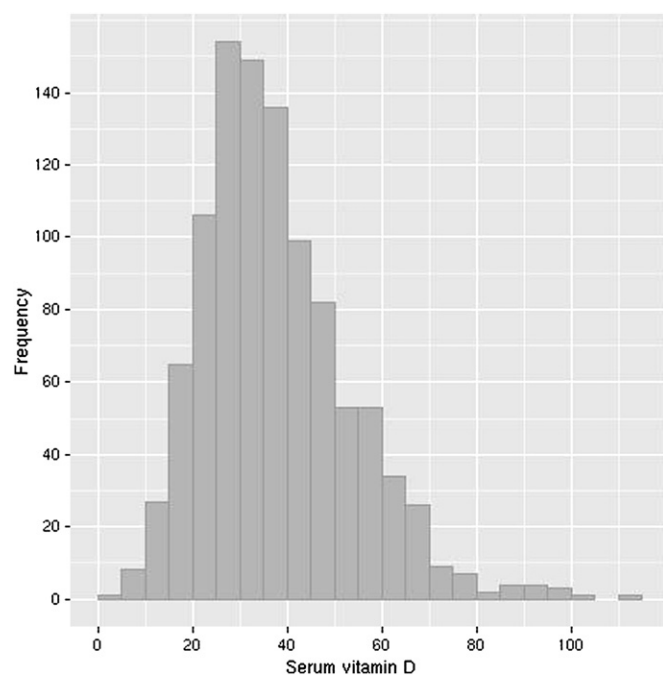


FIG E1. Distribution of vitamin D levels at randomization in all subjects.

TABLE E1. Proportional hazards model time-to-event analysis

	Unadjusted hazards ratio	Adjusted for age, sex, BMI, income, treatment group	+ Season	+ Physician severity	+ Race
First ED/hospitalization over course of the study (all subjects)*	1.2 (.05)	1.3 (.02)	1.4 (.005)	1.3 (.01)	1.3 (.06)
First ED/hospitalization (placebo or nedocromil)	1.1 (.4)	1.2 (.14)	1.3 (.06)	1.3 (.11)	1.2 (.29)
First ED/hospitalization (budesonide)	1.6 (.04)	1.7 (.02)	1.8 (.02)	1.8 (.02)	1.7 (.03)

Values are hazards ratio (*P* values) for time to first ED visit or hospitalization in the vitamin D–insufficient group (≤ 30 ng/mL) versus the vitamin D–sufficient group (>30 ng/mL).

*Models for all subjects are adjusted for treatment group (budesonide vs placebo/nedocromil).

TABLE E2. Markers of asthma and allergy severity, adjusting for age, sex, BMI, baseline severity, and income

	IgE level	Eosinophil count	FEV ₁ (mL)	FEV ₁ /FVC ratio (%)	Log PC ₂₀ dose	Average no. of visits with moderate symptoms
Vitamin D ≤30 ng/mL	−55 (.75)	−19 (.52)	−0.07 (.0003)	0.31 (.46)	0.03 (.72)	−0.07 (.002)
Vitamin D ≤30 ng/mL (placebo or nedocromil group)	−214 (.32)	−11 (.76)	−0.08 (.0004)	0.31 (.53)	0.08 (.46)	−0.10 (.0003)
Vitamin D ≤30 ng/mL (budesonide group)	301 (.20)	−59 (.22)	−0.05 (.23)	0.34 (.66)	−0.11 (.48)	−0.04 (.36)

Results are shown as β coefficients (P values).

FVC, Forced vital capacity.