asthma. Studies are needed to determine whether such FENO information will improve future asthma care and outcomes.

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Age- and atopy-dependent effects of vitamin D on wheeze and asthma

To the Editor:

The role of vitamin D in a myriad of physiologic processes has recently become a focus of controversy. Growing evidence suggests a role for vitamin D in the regulation of IgE and the development of allergic sensitization, as well as in lung development, incident asthma, and asthma exacerbation, although the studies are not all consistent.[1-3] Despite these data, the Institute of Medicine recently reviewed the literature about vitamin D and concluded that there were insufficient data to recommend supplementation with vitamin D for the prevention of non–bone-related diseases.[4] Here we use nationally representative data from the National Health and Nutrition Examination Survey (NHANES) to assess the relationship between vitamin D levels and respiratory outcomes.

Study participants included 6857 US subjects 6 years of age and older who participated in NHANES 2005-2006, as discussed in the Methods section and Table E1 of this article's Online Repository at www.jacionline.org. The relationships between serum vitamin D levels and wheeze, history of asthma, and asthma exacerbation were assessed by means of logistic regression in analyses that accounted for the complex survey methods and were adjusted for age, sex, race/ethnicity, household income, and body mass index (BMI) z score. Analyses were performed with STATA 11.0/SE (StataCorp, College Station, Tex) and R 2.12.2 (R Foundation, Vienna, Austria) software.

Serum vitamin D levels were inversely associated with both current wheeze and asthma in adjusted analyses (Table I and see Table E2 in this article's Online Repository at www.jacionline.org). Each 10 ng/mL decrease in vitamin D level was associated with a 26% greater odds (odds ratio [OR], 1.26 [95% CI, 1.09-1.46]) of current wheeze and an 8% greater odds of asthma (OR, 1.08 [95% CI, 1.01-1.16]). Among those with asthma, lower vitamin D levels were associated with increased odds of both emergency department visit and exacerbation in the past year (OR for each 10 ng/mL decrease in vitamin D level: 1.53 [95% CI, 1.01-2.32] and 1.38 [95% CI, 1.06-1.80], respectively; see Table E3 in this article's Online Repository at www.jacionline.org). Results relating to asthma are described in more detail in the Results section in this article's Online Repository at www.jacionline.org.

The association between a lower vitamin D level and wheeze was similar for asthmatic and nonasthmatic subjects ($P = .37$ for interaction term). The higher odds of current wheeze associated with lower vitamin D levels was driven by a strong inverse relationship between vitamin D level and current wheeze in older subjects ($P = .007$ for interaction term, Table I, Fig 1). This was not due to a stronger relationship between vitamin D level and wheeze in patients who reported chronic obstructive pulmonary disease (COPD; OR per 10 ng/mL vitamin D: 1.23 [95% CI, 1.02-1.55] for those with COPD and 1.32 [95% CI, 1.13-1.55] for those without COPD). Nor was the vitamin D effect among older subjects on current wheeze caused by smoking: the relationship between vitamin D level and wheeze was similar in current, former, and never smokers (ORs of 1.28 [95% CI, 1.04-1.57], 1.35 [95% CI, 1.03-1.81], and 1.24 [95% CI, 0.88-1.74], respectively, for every 10 ng/mL decrease in vitamin D level).

In addition to age, there was a suggestion that the relationship between vitamin D level and current wheeze was also modified by atopy and total IgE level, with a stronger relationship found in nonatopic subjects and among those with lower IgE levels ($P = .096$ and .08 for the interaction between vitamin D level and atopy and total IgE level, respectively; Table I). Moreover, the relationship between vitamin D level and wheeze was not mediated by either atopy or total IgE level (see Table E4 in this article's Online Repository at www.jacionline.org).

In this broadly representative sample of the US population, lower serum vitamin D levels were associated with increased risk of current wheeze, and this relationship varied by age, suggesting an age-dependent relationship between vitamin D level and wheeze that has not previously been reported. In addition, although vitamin D deficiency is known to be associated with higher total IgE levels in this population,[5] the vitamin D/wheeze

TABLE I. Recent wheeze by vitamin D status and group

		Wheeze in past year						
			Age ≥50 y		Atopic		History of asthma	
	Category of vitamin D	Unstratified model	No (5049)	Yes (1808)	No (3530)	Yes (3327)	No (5959)	Yes (998)
OR (95% CI)	≥30 ng/mL				1 by definition			
	20-30 ng/mL	1.25 (0.98-1.60)	1.21 (0.85-1.73)	1.28 (0.80-2.06)	1.09 (0.74-1.61)	**1.37 (1.00-1.86)**	1.23 (0.81-1.87)	1.16 (0.70-1.92)
	<20 ng/mL	**1.64 (1.28-2.28)**	1.25 (0.78-2.00)	**2.48 (1.46-4.23)**	**1.80 (1.19-2.75)**	**1.41 (1.09-1.83)**	**1.70 (1.12-2.59)**	1.57 (0.99-2.49)
	P value for trend	**.007**	.34	**.002**	**.008**	**.02**	**.01**	**.05**
	10 ng/mL decrease in vitamin D	**1.26 (1.09-1.46)**	1.10 (0.92-1.31)	**1.65 (1.30-2.10)**	**1.34 (1.11-1.62)**	**1.17 (1.03-1.32)**	**1.25 (1.04-1.51)**	**1.32 (1.13-1.54)**
	P value for interaction		**.007**		**.097**		.37	

All analyses are adjusted for age, sex, race/ethnicity, income, and BMI *z* score. Boldface type indicates statistically significant ORs.

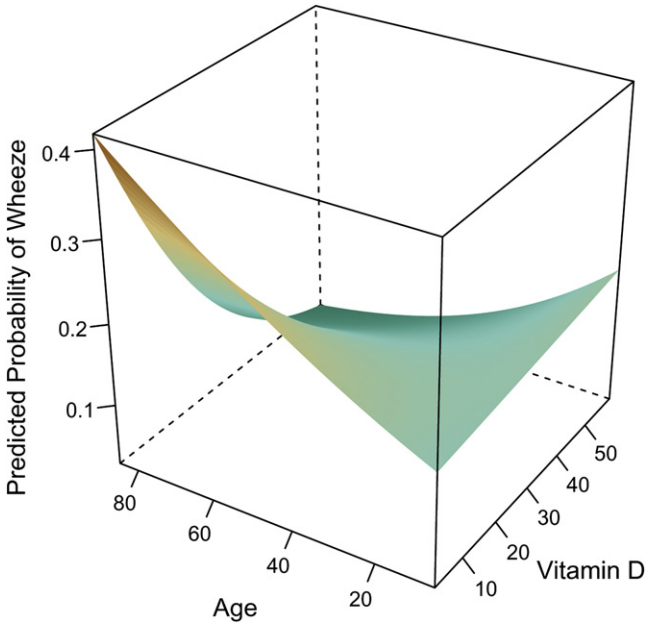

FIG 1. Three-dimensional representation of the predicted probability of wheeze by vitamin D level and age by means of logistic regression. Predicted probabilities of wheeze at a given age and vitamin D level are specified for white female subjects of mean income and BMI *z* score. Age is in years and vitamin D level is in nanograms per milliliter.

relationship found here was independent of total IgE level and atopy, implying that vitamin D protects against wheeze by means of a mechanism other than the downregulation of IgE. Indeed, we found that wheeze might be more strongly associated with vitamin D level in nonatopic subjects and those with lower total IgE levels. Taken together, our findings highlight the complexity of the relationships between vitamin D level and respiratory and allergic diseases, suggesting that vitamin D likely modifies respiratory disease risk through multiple mechanisms that manifest as pleiotropic and age-dependent effects.

There are several potential mechanisms to explain the relationship between vitamin D level and wheeze and why vitamin D deficiency might be a stronger risk factor for wheeze in those without atopy and in older persons. The first is that a low vitamin D level is a risk factor particularly for respiratory tract infection. Data from both animal models and human subjects support this hypothesis. Vitamin D directly and indirectly induces production of antimicrobial proteins and has other antimicrobial effects.[2,6] In human subjects relative vitamin D deficiency has been associated with recent respiratory tract infection and viral infection accompanying wheeze, and in small interventional studies vitamin D supplementation provided some protection against respiratory tract infection prospectively.[2,7] Alternatively or additionally, vitamin D might protect against inflammatory reactions to environmental pollutants and might be broadly important in regulating chronic inflammation in the lung.[3] Finally, accumulating evidence suggests a role for vitamin D in lung development; vitamin D deficiency in early life might lead to permanent susceptibility to poorer respiratory outcomes that are not related to atopy.[8] Each of these causes of wheeze could be more important in older persons and nonatopic subjects; wheeze in younger persons might be more likely to be related to allergy than it is in older persons. However, because the mechanistic rationale is not entirely clear, this novel finding should be replicated before definitive conclusions can be made.

Ultimately, cross-sectional studies such as this are only a first step in understanding the causal relationships between vitamin D levels and respiratory outcomes. Because data are collected simultaneously on all variables, it is not possible to determine temporal relationships between exposure and outcome. In addition, because vitamin D levels are closely related to both diet and outdoor activity and might be related to socioeconomic status in ways not fully accounted for by the adjustments here, there is potential for unmeasured and residual confounding to complicate the relationships that were evaluated. With those caveats in mind, the strength of this study is that it is of a nationally representative sample of the US population, and the findings extend our current understanding of the role of vitamin D in respiratory and allergic diseases.

In sum, our findings point to a strong protective effect of vitamin D against wheeze and asthma exacerbation in a nationally representative study population, supporting the notion that vitamin D status might influence the risk of respiratory disease. In light of the known association between vitamin D and IgE levels, our findings that the vitamin D/wheeze relationship was strongest for nonatopic subjects and older subjects suggest that vitamin D might modify the risk of allergic and respiratory disease through multiple mechanisms. Taken together, these findings underscore the importance of conducting prospective studies, including clinical trials, to understand better the role of vitamin D in patients with incident asthma and wheeze.

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Profilin: A relevant aeroallergen?

To the Editor:

Profilin is a panallergen that is present in all eukaryotic cells. It is one of the main causes of cross-sensitization between pollen and plant-derived foods.[1] As a food allergen, it usually induces oral allergy syndrome,[1] but its clinical relevance as a respiratory allergen remains unknown.

We sought to investigate the prevalence of nasal and bronchial responses to profilin in patients with pollen allergy with rhinitis, asthma, or both who were sensitized to profilin and also to measure the profilin content in different pollen extracts.

We report 28 patients with rhinitis symptoms compatible with seasonal allergic rhinitis, asthma, or both (23 patients sensitized to pollens and profilin and 5 control subjects sensitized to pollens with negative skin prick test responses and specific IgE results to profilin) enrolled from our outpatient clinic during the winter of 2009-2010. All patients received written information and signed a written informed consent form authorized by our institutional review board.

At the clinic, participants underwent skin prick testing with common aeroallergens and purified natural date palm profilin (Pho d 2; 50 μg/mL; ALK-Abelló, Madrid, Spain),[2] as well as fruit allergens (melon, peach, apple, plum, pear, kiwi, banana, and orange). Histamine and glycerol saline solution were used as controls (all from ALK-Abelló).

Nasal and bronchial tidal volume was measured in all patients after challenge testing by using a face mask with Pho d 2 extract (maximum Pho d 2, 100 μg/mL). Nasal response was assessed by means of acoustic rhinometry, for which the minimal transverse area (MTA) was measured. Results were considered to be positive when a decrease of 30% or greater in the MTA and bronchial response was detected by means of spirometry; positive results were all those reflecting a decrease of 20% or greater in FEV_1, as previously described.[3,4] PC_{20} methacholine values were also determined, as previously described.[4]

Specific serum IgE testing with the microarray technique (ISAC; Phadia, Uppsala, Sweden), which included rBet v 2, nOle e 2, rHev b 8, rMer a 1, and rPhl p 12, was performed in all patients.

Natural profilin (Pho d 2) was prepared by purifying a date palm extract by means of affinity chromatography with a Poly (L-proline)–Sepharose. Purity (99%) was checked by means of SDS-PAGE, mass spectrometry, and amino acid analysis.[2]

An inhibition assay was developed with the ADVIA Centaur platform (Siemens, Berlin, Germany) to determine profilin content in different pollen extracts. This assay uses a reverse sandwich architecture with a monoclonal murine anti-human IgE antibody covalently bound to paramagnetic particles in the solid phase and capturing the sample IgE that reacts with biotin-labeled Pho d 2.[5] In our inhibition assay a pool of patient sera sensitized to profilin was preincubated with known amounts of purified Pho d 2, as well as varying dilutions of the different pollen extracts analyzed. The 8 allergenic preparations were standardized from freeze-dried extracts provided by ALK-Abelló. They were analyzed for total protein content by using the Lowry method[6] and for major allergen content by using specific ELISAs.[7,8]

Table I displays participants' characteristics and test results. The mean age was 39 ± 14 years. Twenty-eight patients had positive specific IgE results to pollen showing a pattern of polysensitization to major pollen allergens.

Twenty-three patients had positive specific serum IgE results to all profilin proteins present in the microarray kit. All 5 control subjects had negative specific serum IgE results for profilin.

Twenty patients from the profilin-sensitized group were sensitized to at least 1 fruit allergen, and 11 presented with oral allergic syndrome to fruit.

In the profilin-sensitized group 16 (69%) patients had a positive methacholine challenge result (PC_{20} <8 mg/mL) and a mean PC_{20} value of 3.00 ± 2.45 mg/mL.

Seventeen (77%) patients had a positive specific bronchial challenge results with Pho d 2, and the mean PC_{20} value was 4.52 ± 2.46 μg/mL. Eight of these 17 patients also had a positive nasal challenge result, and the mean MTA decrease was 41.8% ± 10.1%. Two (9%) patients had positive nasal challenge results only.

In the control group 4 of 5 patients had positive methacholine challenge results, with a mean PC_{20} value of 3.62 ± 2.48 mg/mL.

METHODS

Survey design

NHANES is a cross-sectional survey of the US civilian noninstitutionalized population that uses a complex, multistage sampling design with oversampling of low-income persons, adolescents, those older than 60 years, African American subjects, and Mexican American subjects. Questionnaires are initially administered in the subject's home, with follow-up laboratory and physical examination performed in a mobile van. NHANES data collection was approved by the Institutional Review Board of the National Center for Health Statistics, Centers for Disease Control and Prevention, and informed consent was given by all participants.

Because the diagnosis of asthma cannot be made with certainty in young children, analyses were restricted to subjects 6 years of age and older. Analyses were further limited to subjects who had complete data for the main outcomes, exposures, and confounders. A total of 1556 subjects were excluded because of incomplete data. One thousand one subjects did not have blood drawn for both vitamin D and total IgE measurement, likely as a result of the blood draw exclusion criteria in NHANES. In NHANES laboratory studies were not done on subjects with hemophilia, those who had received chemotherapy within the last 4 weeks, and those who had rashes; gauze dressings; casts; edema; paralysis; tubes; open sores or wounds; withered arms or limbs missing; damaged, sclerosed, or occluded veins; allergies to cleansing reagents; burned or scarred tissue; shunts; or intravenous lines in both arms. An additional 9 subjects were missing data on vitamin D, and 13 were missing data on total IgE levels. Four hundred thirty-eight subjects did not have examination data for height or weight. Data were missing because of refusal or were unknown for the following: income (n = 364), history of asthma (n = 13), wheeze (n = 6), chronic bronchitis (n = 9), and emphysema (n = 13). Finally, 13 subjects were excluded because they had very high vitamin D levels (>60 ng/mL; 1 ng/mL = 2.496 nmol/L), leaving 6857 subjects for analysis of non-COPD and smoking outcomes. COPD and smoking data were collected only on subjects 20 years of age and older. For analyses with COPD and smoking, there were 4133 and 4134 subjects, respectively.

Definition and measurement of variables

Vitamin D levels were measured in serum. The vitamin D assay is a 2-step method using the DiaSorin RIA kit (DiaSorin, Stillwater, Minn). Vitamin D data were adjusted by the National Center for Health Statistics to account for assay drift caused by reagent and calibration lot changes (n = 38). Vitamin D level was categorized as less than 20 ng/mL, 20 to 30 ng/mL, and 30 ng/mL or greater. Total and allergen-specific IgE levels were analyzed by using the Pharmacia Diagnostics Immunocap 1000 system (Kalamazoo, Mich). The limit of detection for this assay was 0.35 kU/L.

Atopy was defined as at least 1 detectable IgE level (≥0.35 kU/L) to one of the following allergens: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat, dog, cockroach, *Alternaria* species, peanut, egg, milk, ragweed, rye grass, Bermuda grass, oak, birch, shrimp, *Aspergillus* species, thistle, mouse, and rat. Total IgE levels were log transformed.

In exploratory analyses age was noted to modify the relationship between vitamin D level and wheeze. Further examination of the relationship by decile of age revealed 50 years as a useful cut point for characterizing the interaction between age and vitamin D status, and therefore age was categorized as 50 years and older and less than 50 years for the analysis of interaction.

Covariates known or thought to be associated both with vitamin D levels and the outcomes evaluated were included in the model. Age, sex, and race/ethnicity were reported by participants. Income was classified as a ratio of reported household income/poverty threshold income (poverty income ratio). The BMI z score was calculated from measured height and weight, as described in this section. Ethnicity was defined as non-Hispanic white, Hispanic, African American, and other. Current wheeze was defined by self-report of "wheezing or whistling in your chest" in the past 12 months, and asthma was assessed by means of self-report of a history of health professional's diagnosis of asthma.

COPD was defined as a self-report of a health professional's diagnosis of either chronic bronchitis or emphysema. Smoking was defined as never (<100 cigarettes ever smoked), former, and current smoking and was only queried in subjects older than 20 years.

BMI z scores were calculated from measured weight and height because BMI changes substantially by age among children. The z score was calculated against age- and sex- appropriate Centers for Disease Control and Prevention growth charts from 2000 by using Epi Info Software 3.5.1 (Division of Integrated Surveillance Systems and Services of the National Center for Public Health Informatics at the Centers for Disease Control and Prevention). For subjects older than 20 years of age, 20-year-old healthy subjects were used to calculate the z score to adjust for a uniform measure of BMI across the age span.

Season of blood draw was accessed through the National Center for Health Statistics Research Data Center and was evaluated as a potential confounder of the association between vitamin D level and asthma, wheeze, IgE level, and atopy. Because it did not change the association between vitamin D level and any of the outcomes (data not shown), it was not included in the final model. Analyses with this restricted variable included only the continental United States.

RESULTS

Vitamin D levels in this population

Thirty-four percent of subjects had serum vitamin D levels less than the level considered at risk of deficiency by the Institute of Medicine (20 ng/mL).[E1] An additional 43% had serum vitamin D levels in the range considered insufficient by some experts (20-30 ng/mL), and 23% had fully sufficient vitamin D levels (>30 ng/mL).

Association of vitamin D levels with potential confounders

Age, ethnicity, income, and BMI were all significantly associated with vitamin D levels in a multivariate model that also included sex. The mean serum vitamin D level decreased by 5.2 ng/mL (95% CI, 3.7-6.7 ng/mL) for every 10 years of increased age, 1.4 ng/mL (95% CI, 1.1-1.7 ng/mL) for each unit increase in BMI z score, and 0.32 ng/mL (95% CI, 0.05-0.57 ng/mL) for each unit decrease in poverty income ratio.

Association of vitamin D levels with history of asthma

Each 10 ng/mL decrease in vitamin D level was associated with an 8% greater odds (OR, 1.08 [95% CI, 1.01-1.16]) of asthma. Compared with subjects with higher vitamin D levels (>30 ng/mL), those with intermediate levels (20-30 ng/mL) had a 16% greater odds of asthma (OR, 1.16; 95% CI, 0.96-1.42), and those with the lowest levels (<20 ng/mL) had a 19% greater odds of asthma (OR, 1.19 [95% CI, 0.98-1.45]).

Age was not a significant effect modifier of the vitamin D/asthma relationship ($P = .24$), but the effects of low vitamin D levels on asthma were strongest among younger rather than older subjects (Table E2). Lower vitamin D levels were only associated with asthma among those younger than 50 years (ORs of 1.16 [95% CI, 1.06-1.28] compared with 0.90 [95% CI, 0.75-1.07] in those ≥50 years). As was the case for current wheeze, vitamin D's relationship with asthma was strongest among nonatopic subjects, and those with lower total IgE levels ($P = .03$ and .08 for the respective interaction terms).

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TABLE E1. Demographic characteristics

	Percentage of noninstitutionalized US population*	Mean vitamin D level ± SE (ng/mL)
No. of subjects	6857	23.6 ± 0.5
Age (y), mean ± SE	39.7 ± 0.8	
<50	68%	23.8 ± 0.6
≥50	32%	23.0 ± 0.4
Sex		
Male	49%	23.7 ± 0.5
Female	51%	23.4 ± 0.6
Ethnicity (%)		
Non-Hispanic white	70%	25.8 ± 0.4
Hispanic	12%	20.2 ± 0.7
African American	12%	15.1 ± 0.5
Other	6%	21.0 ± 0.7
Income (ratio of poverty level)		
<1	13%	21.2 ± 0.8
1-2	20%	22.5 ± 0.5
2-3	16%	23.1 ± 0.6
3-4	17%	24.0 ± 0.6
>4	35%	25.0 ± 0.6
BMI *z* score†		
<1	48%	25.5 ± 0.5
1-2	39%	22.4 ± 0.5
≥2	13%	19.6 ± 0.6
Smoking		
Never smoker	51%	22.9 ± 0.6
Former smoker	25%	23.9 ± 0.6
Current smoker	24%	23.2 ± 0.6
COPD		
No	92%	22.3 ± 0.6
Yes	8%	23.3 ± 0.5
Asthma		
No	85%	23.6 ± 0.5
Yes	15%	23.2 ± 0.6
Wheeze in past year (%)		
No	84%	23.7 ± 0.5
Yes	16%	22.4 ± 0.6
Atopy		
Nonatopic	55%	23.9 ± 0.5
Atopic	45%	23.2 ± 0.6

*Greater than 6 years of age.
†The BMI *z* score was calculated compared with 20-year-old healthy subjects for those more than 20 years of age.

TABLE E2. History of asthma by vitamin D status and group

		History of asthma diagnosis				
			Age ≥50 y		Atopic	
	Category of vitamin D	Unstratified multivariate model	No (5049)	Yes (1808)	No (3530)	Yes (3327)
OR (95% CI), *P* value	≥30 ng/mL			1 by definition		
	20-30 ng/mL	1.16 (0.96-1.42), .12	1.25 (0.99-1.57), .06	0.950 (0.574-1.574), .83	1.14 (0.72-1.81), .55	1.15 (0.83-1.58), .38
	<20 ng/mL	1.19 (0.98-1.45), .07	1.32 (0.98-1.77), .07	0.930 (0.598-1.445), .73	1.21 (0.85-1.72), .27	1.15 (0.79-1.69), .41
	P value for trend	.08	.08	.74	.25	.45
	Each 10 ng/mL decrease in serum vitamin D level	**1.08 (1.01-1.16), .02**	**1.16 (1.06-1.28), .004**	0.90 (0.75-1.07), .22	**1.17 (1.03-1.32), .02**	1.02 (0.88-1.18), .83
	P value for interaction			.24		**.03**

TABLE E3. Asthma exacerbation and emergency department visit for asthma by vitamin D status

	Asthma exacerbation in past year	Emergency department visit for asthma in past year
OR (95% CI), *P* value		
≥30 ng/mL	1 by definition	
20-30 ng/mL	1.08 (0.62-1.88), .77	1.04 (0.41-2.62), .93
<20 ng/mL	**1.85 (1.05-3.25), .03**	1.69 (0.65-4.39), .26
Test for trend	**.03**	.22
Each 10 ng/mL decrease in serum vitamin D level	**1.38 (1.06-1.80), .02**	**1.53 (1.01-2.32), .04**

Data are for the 618 subjects who reported current asthma. Analyses were adjusted for age, sex, race/ethnicity, income, and BMI *z* score.

TABLE E4. Evaluation of potential confounders and mediators of the relationship between vitamin D level and respiratory status

	Wheeze			Asthma		
	OR for each 10 ng/mL decrease in vitamin D level	95% CI	*P* value	OR for each 10 ng/mL decrease in vitamin D level	95% CI	*P* value
Vitamin D only	1.19	1.06-1.34	.006	1.06	0.99-1.14	.11
Adjusted for demographic factors*	1.26	1.09-1.46	.004	1.08	1.01-1.16	.02
Adjusted for demographic factors and atopic status	1.26	1.09-1.46	.004	1.08	1.00-1.16	.06
Adjusted for demographic factors and total IgE level	1.24	1.07-1.44	.007	1.06	0.99-1.13	.10

*Analyses were adjusted for age, sex, race/ethnicity, income, and BMI z score. The total IgE level was log transformed.