

Aeroallergen sensitization correlates with PC₂₀ and exhaled nitric oxide in subjects with mild-to-moderate asthma

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Background: Aeroallergen sensitization in adult asthmatic patients from a wide geographic area has not been correlated with patients' characteristics, markers of airways inflammation, and lung function.

Objective: We assessed data obtained from the Asthma Clinical Research Network trials to determine the relationship of aeroallergen sensitization to age, sex, ethnicity, and markers of inflammation and airways function.

Methods: Skin testing (14 epicutaneous) was performed on 1338 subjects with objectively diagnosed mild-to-moderate asthma from 11 Asthma Clinical Research Network studies. Skin testing used identical techniques and a quality assurance program to ensure uniformity across centers.

Results: Ninety-five percent of the subjects had at least 1 positive skin test response. Of these, 14% had positive reactions to 1 or 2 allergens and 81% had positive reactions to 3 or more allergens, and 2% of subjects reacted only to seasonal allergens, 26% only to perennial allergens, and 67% to both. Increasing IgE and exhaled nitric oxide values, decreasing PC₂₀ values, and minority ethnicity significantly correlated with the number of positive skin test responses. Subjects with late-onset asthma were less likely to be sensitized; nonetheless, 89% of subjects older than 60 years had positive responses.

Conclusion: Ninety-five percent of patients with mild-to-moderate asthma might have an allergic component. Age does not significantly affect aeroallergen sensitization, but the pattern of allergic sensitization varies with ethnicity and geography. Measures used to characterize asthma, such as IgE, exhaled nitric oxide, and PC₂₀ values, are correlated with aeroallergen sensitization. (*J Allergy Clin Immunol* ■■■■;■■■;■■■-■■■.)

Key words: Asthma, allergy, skin testing, aeroallergens, exhaled nitric oxide, IgE, methacholine challenge

Asthma and other IgE-mediated diseases continue to increase in prevalence in the United States and throughout the world.¹ Allergens, both occupational and environmental, comprise one of the multiple triggers for asthma, along with others, including exposure to tobacco smoke, air pollution, viral infection, irritant exposure, exercise, cold dry air, sinusitis, and esophageal reflux. Skin testing, which is both sensitive and specific, has been used to objectively determine patient sensitization to allergens that can be a trigger for asthma and other allergic disorders.²⁻⁵ Allergic sensitization to aeroallergens, as defined by skin testing, has been shown to vary by economic status, location, ethnic identity, and other factors; however, correlations between aeroallergen sensitization and asthma characteristics in a large number of patients given objective diagnoses of mild-to-moderate asthma are lacking.⁶⁻⁸ A recent publication using patient recall of skin test reactivity in an observational study of those with severe asthma suggested that the vast majority of such asthmatic subjects were allergic to aeroallergens.⁹ We hypothesized that the vast majority of subjects of any age with well-characterized mild-to-moderate asthma will be sensitized to aeroallergens, as defined by having at least 1 directly observed positive skin test response, and that positive skin test responses will correlate with other measures used to assess asthma.

METHODS

We assessed data from subjects who provided written informed consent and were randomized into multiple studies performed by the National Heart,

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Supported by grants U10-HL51831, U10-HL51845, U10-HL51823, U10-HL51843, U10-HL56443, U10-HL51834, U10-HL51810, U10-HL74227, U10-HL74231, U10-HL74204, U10-HL74212, U10-HL74073, U10-HL74206, U10-HL74208, U10-HL74225, and U10-HL74218.

Disclosure of potential conflict of interest: T. J. Craig is on the advisory board for Aventis; has consulting arrangements with Genentech/Novartis, Glaxo, Schering-Plough, and AstraZeneca; and has received research support from Schering-Plough, Merck, Glaxo, ACAAI, Methapharm, Dyax, Lev, PDL, Centacore, Sanofi-Aventis, and Altana. R. F. Lemanske has consulting arrangements with Novartis, Merck, GlaxoSmithKline, Aventis, and AstraZeneca; has received research support from the National Heart, Lung, and Blood Institute; and is on the speakers' bureau for Merck and GlaxoSmithKline. M. E. Weshsler has consulting arrangements with Genentech, Novartis, Merck,

Aerocrine, Graceway, and Schering-Plough; has received research support from GlaxoSmithKline; and is on the speakers' bureau for Genentech, Novartis, Merck, and GlaxoSmithKline. S. Wasserman has consulting arrangements with AstraZeneca, Genentech, Novartis, Tanex, Icos, Vistakon, Tanabe, and Amylin; has received research support from GlaxoSmithKline, and Schering-Plough; is on the speakers' bureau for AstraZeneca; has served as an expert witness in medical malpractice cases about anaphylaxis, asthma, and drug allergies; and has served as an expert witness on the health effects of mold exposure. The rest of the authors have declared that they have no conflict of interest.

Received for publication August 14, 2007; revised November 14, 2007; accepted for publication December 12, 2007.

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0091-6749/\$34.00

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doi:10.1016/j.jaci.2007.12.1153

Abbreviations used

ACRN: Asthma Clinical Research Network

eNO: Exhaled nitric oxide

FVC: Forced vital capacity

Lung, and Blood Institute's Asthma Clinical Research Network (ACRN). Subjects were recruited from pulmonary and allergy clinics and through advertisements to the general public. The vast majority of subjects were recruited from non-allergy clinic populations. The studies included SOCS,¹⁰ SLIC,¹¹ BARGE,¹² BAGS,¹³ CIMA,¹⁴ MICE,¹⁵ DICE,¹⁶ IMPACT,¹⁷ SMOG,¹⁸ SLIMSIT,¹⁹ and the Predicting Response to Inhaled Corticosteroid Efficacy trial.²⁰ We focused our primary analysis on correlations between aeroallergen sensitization and demographics, such as ethnicity, sex, and age. We secondarily assessed other measures used in the characterization of asthma, such as methacholine reactivity, exhaled nitric oxide (eNO) level, pulmonary function, peripheral blood and sputum eosinophil numbers, and total serum IgE levels, for correlation with allergic sensitization status.

All centers performed epicutaneous skin testing by using an identical technique, as specified by the ACRN "Manual of operations." Trained certified personnel and a quality assurance program ensured expertise before research personnel participated in the ACRN studies. Allergens used in the testing panel were the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*; the molds *Alternaria*, *Aspergillus*, and *Penicillium* species; and dog, cat, ragweed, grass mix, tree mix, weed mix, and cockroach. Appropriate negative (diluent) and positive (histamine) controls were included (Greer, Lenoir, NC). Skin testing was performed with the Multitest device (Lincoln Diagnostics, Decatur, Ill). The positive control was required to have a wheal of at least 3 mm in size with surrounding erythema to be considered a valid test. After 15 minutes of incubation, the skin test response was considered positive if the wheal exceeded that elicited by the negative control by 3 mm with documented erythema. Aeroallergen sensitization was defined as a positive response to at least 1 allergen.

Patients recruited into the studies were required to have evidence of asthma, as defined by either a positive methacholine challenge result (<8 mg/mL), defined as PC₂₀, an improvement of FEV₁, or both of 12% or greater with 2 to 8 puffs of albuterol. For safety, skin tests were not performed if the FEV₁ was less than 60% of predicted value or if the patient had a recent history of asthma instability. Demographics, peak flow measurement, spirometry, methacholine testing, eNO quantization, sputum induction, and screening laboratory tests were performed on entrance into and periodically during the studies and on termination. Spirometry, methacholine testing, eNO measurement, sputum test for eosinophils, and genotyping were performed as outlined in the ACRN manual of operations and as described in previous publications.¹⁰⁻²⁰

The total number of positive skin test responses was summarized into the categories of 0, 1 to 2, and 3 or more. The associations between this measure and the demographic information and measures of asthma severity were then evaluated by using the Cochran-Mantel-Haenszel nonparametric test of correlation adjusted for the ACRN trial. The adjustment for the ACRN trial accounted for the different types of run-in periods included in each trial. For significant associations, the mean, median, or geometric mean of each measure at each level of allergic sensitization was reported. Partial Kendall τ correlation coefficients were also calculated between allergic status and the demographic and asthma severity measures adjusted for the ACRN trial.

The categorization of allergic status into no allergic sensitization, seasonal only, perennial only, and at least one of each was evaluated by using the Cochran-Mantel-Haenszel nonparametric test of mean differences to determine whether associations existed between this variable and the demographic and asthma severity measures adjusted for ACRN trial. For significant associations, the mean, median, or geometric mean of each measure at each level of the seasonal/perennial categorization was reported.

RESULTS

One thousand three hundred thirty-eight subjects were included in this analysis, and Table I summarizes their

TABLE I. Sex, age, and ethnic origin of subjects with skin test data in ACRN trials

Category		No.	Percentage
Sex	Female	771	58
	Male	567	42
Ethnic origin	African American	279	21
	Asian and American Native	67	5
	Hispanic	111	8
	White	864	65
	Other	17	1
Age (y)		Mean = 32	Range = 12-65

baseline characteristics. Additional demographics are available in Table II. Patients ranged in age from 12 to 65 years, with 58% being female and 42% being male. Ethnicity distribution included 65% white, 21% African American, 8% Hispanic, and 6% "other." Skin test results to specific antigens and to positive and negative controls are noted in Table III.

Ninety-five percent of subjects had at least 1 positive skin test response and thus, for the purposes of this study, are considered to have aeroallergen sensitization. Fourteen percent of subjects had 1 to 2 positive test responses, and 81% had a positive response to 3 or more allergens. The average number of positive test responses was 5. Of those who reacted, 2% did so only to seasonal allergens, 26% only to perennial allergens, and 67% to both categories. The percentage of positive test responses decreased slightly, although not significantly, with increased decades of life (Fig 1), and those 60 to 70 years of age had a higher mean and median number of positive skin test responses than younger subjects (Fig 2), and 89% had at least 1 positive skin test response. Subjects with onset of asthma before 30 years of age were more likely to be sensitive to aeroallergens (96%) than those whose onset of asthma was later (88%, $P \leq .001$).

Skin tests also varied by ethnicity (Fig 3), and all nonwhite subjects, defined as all nonwhite minorities, had a higher frequency of 3 or more skin tests than white subjects ($P = .024$, Table IV). Ninety-six percent of male subjects and 94% of female subjects were aeroallergen sensitive. Although both FEV₁ (male subjects, 81.7%; female subjects, 87.1%; $P = .001$) and the FEV₁/forced vital capacity (FVC) ratio (male subjects, 69.9%; female subjects, 74.5%; $P = .001$) varied by sex, sex did not influence aeroallergen sensitization ($P = .276$), nor did FEV₁ percentage or FEV₁/FVC ratio for either sex vary by aeroallergen sensitivity. We also assessed skin tests by ACRN site geographic location (Table V) to determine regional distribution of positive skin test responses. Of note are the high prevalence of positive skin test responses to cat and dust mite and a relatively uniform distribution of positive test responses across the ACRN sites. Notable exceptions to this uniform distribution were the observed and expected low prevalence of dust mite and cockroach sensitization in Denver and the low prevalence of positive reactions to ragweed in San Francisco but also the unexpected low prevalence of positive reactions to tree mix and dog in San Francisco. In all regions of the country, sensitivity to *Aspergillus* and *Cladosporium* species was lower than that noted to essentially all other allergens tested.

When measures used to characterize asthma were compared with aeroallergen sensitization (Table IV) both eNO and IgE levels increased significantly with an increased number of

TABLE II. Summary of simple descriptive statistics for all subjects included in the analyses

Label	N	Mean	SD	Minimum	Lower quartile	Median	Upper quartile	Maximum
FEV ₁ % predicted	1342	84.8	14.0	43.0	75.0	84.0	94.0	137.0
FEV ₁ /FVC (%)	1342	72.6	9.8	32.9	66.2	72.7	79.6	100.0
PC ₂₀	1326	1.1*	1.6†	−6.2	−0.9	0.0	1.1	5.3
Median eNO (ppb)	757	18.3	12.5	0.5	9.7	15.2	23.5	125.5
Sputum eosinophils	603	2.0	4.4	0.0	0.0	0.4	1.6	58.4
Blood eosinophils (/mm ³)	535	248.4	201.7	0.0	111.0	200.0	310.0	1616.0
IgE	516	134*	1.4†	0.7	4.1	5.1	5.9	8.5

All hypothesis testing and inferential results reported in the article are adjusted for the different clinical trials.

*Geometric mean reported.

†Coefficient of variation reported.

TABLE III. Skin tests results noted in the 1338 patients recruited into the ACRN studies

Skin test	No. positive	Percent positive
Negative control	22	1.7
Positive control	1330	99.4
Tree mix	562	42.1
Grass mix	680	50.9
Ragweed	695	52.0
Weed mix (nonragweed)	515	38.5
Dog	475	35.5
Cat	974	72.8
<i>Alternaria</i>	598	44.7
<i>Cladosporium</i>	242	18.1
<i>Aspergillus</i>	315	23.6
<i>Dermatophagoides farinae</i>	753	56.4
<i>Dermatophagoides pteronyssinus</i>	821	61.4
Cockroach	512	38.3

positive test responses ($P = .008$ and $P < .001$, respectively), whereas PC₂₀ decreased as the number of positive skin test responses increased ($P < .001$). The average values for all 3 (ie, eNO, IgE, and PC₂₀) were greatest in those subjects with either positive skin test responses to perennial allergens alone or to both seasonal and perennial allergens compared with those who responded only to seasonal allergens (Table VI). We did not find consistent correlations between sensitization to aeroallergens and percent predicted FEV₁, sputum eosinophils, peripheral blood eosinophils, FEV₁, or peak flow values in the morning or evening.

In the studies in which genotyping was available (SOCS, SLICS, and BARGE), we did not identify correlations between aeroallergen sensitization or the number or type of positive skin test responses for subjects with either the B16Arg/Arg or B16Gly/Gly form of the β -adrenergic receptor.

DISCUSSION

Our data demonstrate that as many as 95% of subjects with mild-to-moderate asthma have aeroallergen sensitization. Unfortunately, we are unable to determine by using our database whether allergy symptoms and skin test results correlated. Ideally, the term “allergic” should be reserved for patients with symptoms associated with exposure to the allergen identified by a positive skin test response. Therefore for the purpose of this article and consistent with the literature, we have used the term

“aeroallergen sensitive” to define those subjects with a positive skin test response to at least 1 aeroallergen. With this in mind, our data suggested that as many as 95% of subjects with mild-to-moderate asthma might have an allergic component to their asthma. The percentage of patients in our studies with positive skin test responses is higher than that noted in previously published studies. Previously published rates of aeroallergen sensitization in patients with asthma have ranged from 51%⁵ to 81.9%,²¹ with other studies reporting results between these extremes.²¹⁻²⁵ Our results cannot be attributed to a selective recruitment of allergic subjects because most subjects came from sources other than allergy clinics and allergic status was not a criterion for enrollment.

A recent study of patients with severe asthma, difficult-to-manage asthma, or both that used patient recall of unstandardized and unwitnessed allergy skin tests reports that 93.5% of those who recalled skin tests remembered being informed of a positive result.⁹ Because most of the ACRN studies have focused on the larger population of patients with mild-to-moderate asthma, we are unable to comment directly on skin test reactivity in severe asthma. This is important because some cohorts of those with severe asthma might be expected to be nonallergic. For example, the phenotypes of asthma with nasal polyps, chronic sinusitis, chronic rhinitis, and aspirin sensitivity and those with late-onset asthma lacking sputum eosinophilia often manifest as severe nonallergic asthma. Thus being sensitive to aeroallergens cannot be used to include or exclude the diagnosis of asthma but might be an additional factor important to understand the multiple phenotypes of this increasingly prevalent disorder.²⁶

An increased prevalence of allergen sensitization during the early decades of life followed by a decrease later in life has been described previously.²⁷⁻²⁹ As stated by Jayaratnam et al,³⁰ “random samples of patients with asthma identified by validated questionnaires, increased age, female gender, chronic rhinosinusitis, and more severe impairment of lung function are associated with an elevated chance of the patient being non-atopic.” Although our study is not longitudinal, our data suggested that aeroallergen sensitivity might not wane with time. This is of importance in 2 ways: (1) efforts to reduce the acquisition of allergic sensitization in childhood might have important benefits even later in life, and (2) age alone should not obviate the search for allergic triggers of asthma. Others have also demonstrated a high prevalence of skin test reactivity in the elderly, with 74.7% of participants having at least 1 positive test response to an airborne allergen.³¹

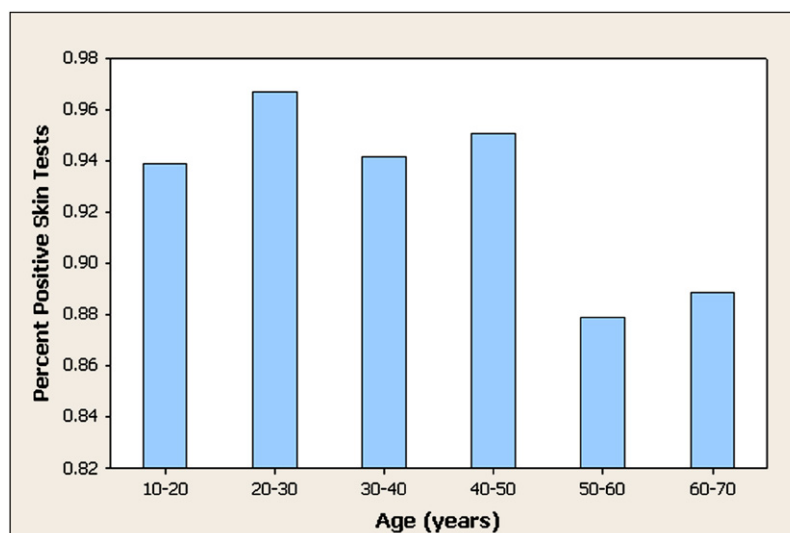


FIG 1. Associations between percentages of positive skin test responses versus age by decade of life.

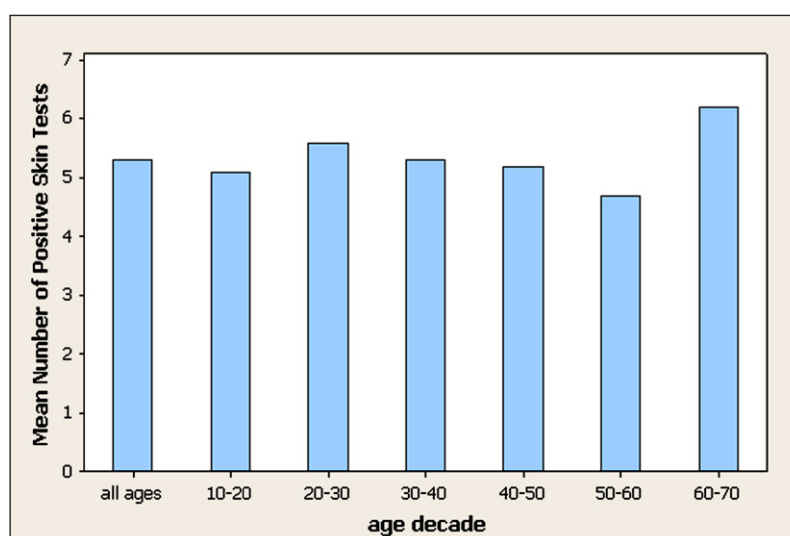


FIG 2. Association between skin test results and decade of life.

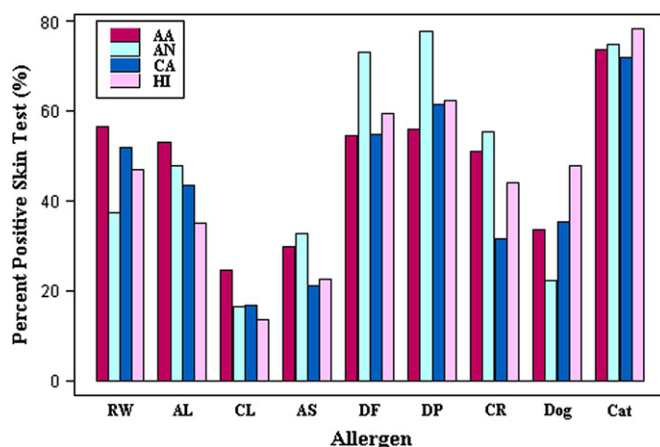


FIG 3. Prevalence of skin test responses by ethnic origin. AA, African American; AN, American Native/Asian American; CA, white; HI, Hispanic; RW, ragweed; AL, *Alternaria* species; CL, *Cladosporium* species; AS, *Aspergillus* species; DF, *Dermatophagoides farinae*; DP, *Dermatophagoides pteronyssinus*; CR, cockroach.

TABLE IV. Ethnicity (minority defined as all nonwhite subjects) and asthma parameters to include eNO, IgE, and PC₂₀ compared with 0, 1 to 2, or 3 or more positive skin test responses

	No. of positive test responses	1 or 2 positive test responses	≥3 positive test responses	CMH <i>P</i> value adjusted for study
Minority	27%	29%	37%	.024
eNO (ppb)*	10.3	14.0	15.6	.008
PC ₂₀ (mg/mL)†	2.6	1.63	1.04	<.001
IgE (IU/L)†	12.2	59.7	191	<.001

CMH, Cochran-Mantel-Haenszel.

*Medium reported.

†Geometric mean reported.

Allergen sensitivity to perennial allergens has been associated with asthma severity. The Inner-City Asthma and Childhood Asthma Management Program studies of the National Heart, Lung, and Blood Institute have confirmed sensitization to and exposure to house dust mite, indoor molds, and animal dander as independent variables for poor outcomes associated with

TABLE V. Comparing skin tests to ACRN center

Center	Negative control		Positive control		Tree mix		Grass mix		Ragweed		Weed mix (nonragweed)		Dog	
	No. positive	Percentage positive	No. positive	Percentage positive	No. positive	Percentage positive	No. positive	Percentage positive	No. positive	Percentage positive	No. positive	Percentage positive	No. positive	Percentage positive
Boston	4	1.6%	248	98.8%	128	51.2%	117	46.8%	118	47.2%	76	30.3%	102	40.6%
Denver	0	0.0%	238	100%	81	34.0%	132	55.5%	110	46.2%	99	41.6%	97	40.8%
Madison	0	0.0%	282	100%	141	50.2%	146	51.8%	190	67.6%	122	43.3%	92	32.6%
Philadelphia	2	1.0%	209	100%	97	46.4%	116	55.5%	132	63.2%	96	45.9%	78	37.3%
San Francisco	13	5.0%	257	98.8%	70	26.9%	118	45.4%	90	34.6%	92	35.4%	70	26.9%
New York	3	3.1%	96	98.0%	45	45.9%	51	52.0%	55	56.1%	30	30.6%	36	36.7%
All centers	22	1.6%	1330	99.4%	562	42.1%	680	50.9%	695	52.0%	515	38.5%	475	35.5%

TABLE VI. Mean parameters in patients with no positive test responses, positive seasonal responses, positive perennial responses, or at least 1 of each

	None positive	Seasonal only	Perennial only	At least 1 of both	CMH <i>P</i> value adjusted for study
eNO*	10.3	10.0	15.3	15.7	.017
IgE†	12.2	57.4	110	192	<.001
PC ₂₀ †	2.6	2.7	1.1	1.1	<.001

CMH, Cochran-Mantel-Haenszel.

*Medium reported.

†Geometric mean reported.

asthma.^{7,32} Other studies have also found statistically significant associations between exposure to indoor allergens and asthma stability.³³⁻³⁷ Still others have demonstrated correlations between asthma severity and eNO levels, serum levels of total IgE, and specific IgE levels, as determined by means of skin testing.^{8,38} Our study demonstrated correlations of increased levels of eNO and decreased PC₂₀ values with positive test responses to perennial allergens that suggested a similar association between perennial aeroallergen sensitivity and asthma severity. Several studies have also demonstrated increased asthma symptoms and associated inflammation during specific seasonal allergen exposures.³⁹⁻⁴¹ Our inability to demonstrate such a statistical correlation between asthma severity measures and skin test responses to seasonal allergens might be a consequence of the fact that exposure to most seasonal allergens is limited to 2 months or less per year. In our studies recruitment occurred throughout the year, and only a small portion of the subjects with seasonal allergies would have had the appropriate evaluations preformed at the time their seasonal allergy was active.

Differences in skin test reactivity between ethnic groups might reflect socioeconomic status, urban versus nonurban living, region of the country in which they reside, country of origin, occupation, and other living conditions, such as air conditioning, crowding, and pet ownership.^{7,37,42} Our study suggested a correlation between minority ethnicity and sensitivity to multiple aeroallergens. Similarly, we confirmed that the most common allergen sensitizations across all sites were to dust mites and cat and that high-altitude locations with low humidity, such as Denver, have a lower prevalence of positive skin test responses to cockroach and dust mite. Additionally, areas west of the Rocky Mountains have a lower prevalence of ragweed and hence fewer positive responses to ragweed allergen.^{37,42,43}

These data are relevant, especially when avoidance is suggested as an asthma control measure without objective evidence of a patient's specific sensitivities. Empiric avoidance can be directed at expected exposures but is most relevant and effective when directed by knowledge of allergen sensitivity, as defined by specific testing.

Unlike previous studies, we have not demonstrated a difference in atopic status between the sexes.^{24,34,35} Similar to previous data, we confirmed that male subjects have a lower FEV₁ percent predicted and lower FEV₁/FVC ratio than female subjects, but this difference seems to be independent of aeroallergen sensitivity.

As noted above, we were able to establish a correlation between an increased number of positive skin test responses and eNO, IgE, and PC₂₀ values. The correlation with IgE is to be expected; however, the failure to demonstrate a similar correlation with spirometric values, peak flow, and sputum eosinophils was unexpected. Spirometric values and peak flows might not reflect the degree of inflammation in the airways; however, correlations between sputum eosinophilia and inflammation have been repetitively noted and would be expected to move in tandem with eNO and PC₂₀ values.^{3,43-49} We suspect that if we included all severities of asthma instead of the inclusion of only mild-to-moderate asthma that a correlation between skin testing and sputum eosinophils would have been positive. Nonetheless, the strong statistical correlations between eNO, PC₂₀, and IgE values and positive skin test responses suggest that allergy is an important factor in inflammation in mild-to-moderate asthma and that allergen avoidance or other allergy-directed measures might reduce inflammation.

As noted earlier, because the vast majority of our subjects had mild-to-moderate asthma, these data do not permit the same generalization to be applied to those with severe asthma. In some phenotypes of severe asthma, especially in those with late-onset disease, aeroallergen sensitivity might not correlate with severity. These same individuals might have low geometric mean total IgE serum levels when the IgE level is age and sex adjusted. In turn, others with severe late-onset asthma might be nonallergic and still have a nonspecific increase in IgE levels.⁵⁰ Finally, another subset of patients with severe nonallergic asthma has predominately neutrophils on sputum induction.^{26,49} Despite these observations, the results of other studies support extension of the importance of allergen sensitization to patients with severe or difficult-to-treat asthma as well.⁹

As anticipated, we were unable to demonstrate associations between aeroallergen sensitivity and genotype differences at the 16th position of the β -receptor gene.

TABLE V. (Continued)

Cat		Alternaria		Cladosporium special		Aspergillus		Dermatophagoides farinae mite		Dermatophagoides pteronyssinus mite		Cockroach	
No. positive	Percentage positive	No. positive	Percentage positive	No. positive	Percentage positive	No. positive	Percentage positive	No. positive	Percentage positive	No. positive	Percentage positive	No. positive	Percentage positive
175	69.7%	88	35.2%	38	15.2%	52	20.8%	139	55.6%	157	62.5%	76	30.3%
183	76.9%	104	43.7%	29	12.2%	48	20.2%	68	28.6%	83	34.9%	66	27.7%
202	71.6%	158	56.0%	68	24.1%	76	27.0%	174	61.9%	183	65.1%	95	33.7%
162	77.5%	96	45.9%	48	23.0%	43	20.6%	130	62.2%	140	67.0%	95	45.5%
180	69.2%	115	44.2%	40	15.4%	78	30.0%	186	71.5%	205	78.8%	126	48.5%
72	73.5%	37	37.8%	19	19.4%	18	18.4%	56	57.1%	53	54.1%	54	55.1%
974	72.8%	598	44.7%	242	18.1%	315	23.6%	753	56.4%	821	61.4%	512	38.3%

In summary, there are unique differences in sensitivity in subpopulations in the United States, mainly caused by ethnicity and geography, but it does not appear that sex and age are important variables. In addition, sensitivity to perennial allergens correlated with inflammation in mild and moderate asthma, as evidenced by increased levels of eNO and augmented bronchial hyperreactivity manifested by PC₂₀. These data suggest that objective assessment to determine sensitivity to aeroallergens is needed to accurately educate patients on appropriate environmental avoidance and in the consideration of other allergen-directed therapies for asthma. If epicutaneous skin testing or *in vitro* allergen-specific IgE testing is not available, empiric environmental changes could be recommended based on sensitivities expected for ethnicity and regional location and should be applied, even to the elderly patient with asthma. These results suggested that nearly all patients with mild or moderate asthma have aeroallergen sensitivity as a component of their disease and might benefit from appropriate identification of their sensitivities.

Clinical implications: Aeroallergens appear to be an important trigger for mild and moderate asthma, even in the elderly, and correlate with markers used to assess asthma.

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