

Asthma in the Elderly*

Cockroach Sensitization and Severity of Airway Obstruction in Elderly Nonsmokers

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Study objectives: To test the hypothesis that the presence of sensitization to indoor allergens is associated with increased severity of airway obstruction in elderly subjects with asthma.

Design: Cohort study of subjects enrolled in a public hospital asthma clinic.

Setting: Asthma clinic in a municipal public hospital serving an indigent population in New York City.

Patients: Subjects aged ≥ 60 years with asthma who were enrolled in the Bellevue Hospital Asthma Clinic. Total serum IgE and allergen-specific IgE measurements were performed in a cohort of elderly never-smokers who had asthma (45 patients) who had undergone spirometry before and after bronchodilator (BD) therapy.

Measurements and results: The results of radioallergosorbent tests demonstrated that most subjects (ie, 60%) were sensitized to at least one allergen, with many sensitized to at least one indoor allergen. Cockroach (CR) was the most common allergen to which subjects were sensitized, with 47% displaying an elevated serum-specific IgE level. Fewer subjects were sensitized to dust mite, cat, dog, or ragweed. Subjects sensitized to CR (CR+) had greater reductions in airflow compared to subjects not sensitized to CR (CR-) [$64 \pm 4.4\%$ predicted vs $77.1 \pm 4.1\%$ predicted FEV₁, respectively; $p < 0.05$]. Following BD administration, only 29% of CR+ subjects achieved a normal post-BD FEV₁ compared to 58% of CR- subjects. Lung volume measurements differed between CR+ and CR- subjects, with a greater elevation of functional residual capacity in CR+ subjects.

Conclusion: In a population of elderly urban patients with asthma, the presence of CR-specific serum IgE is associated with more severe asthma, as reflected by an increase in airway obstruction and hyperinflation. (CHEST 2002; 122:1580-1586)

Key words: asthma; cockroach; elderly; FEV₁; IgE

Abbreviations: BD = bronchodilator; BHAC = Bellvue Hospital Asthma Clinic; CR = cockroach; CR- = not sensitized to cockroach; CR+ = sensitized to cockroach; ERV = expiratory reserve volume; FRC = functional residual capacity; kIU = kilo-international units; NHLBI = National Heart, Lung, and Blood Institute; NYC = New York City; RAST = radioallergosorbent test; RV = residual volume; TLC = total lung capacity; V₅₀ = expiratory flow rate at mid-lung volume

Morbidity from asthma has been increasing in recent years, with a severe impact in urban areas. Although asthma affects all age groups, morbidity and mortality is particularly high in the elderly. In New York City (NYC), asthma-attributable mortality rates in adults > 65 years of age are six times

higher than those in adults < 40 years of age.¹ Whereas many factors contribute to the urban asthma problem, sensitization to indoor allergens may play a particularly significant role. In NYC and other urban centers, cockroach (CR) sensitivity in children has been associated with greater symptom frequency and more emergency department visits due to asthma.²⁻⁵

Although asthma-related morbidity in children has been linked to indoor allergen exposure and sensitization, it is not known whether this relationship persists in older populations. Atopy has traditionally been considered to be uncommon in elderly persons with asthma.⁶ More recent studies have suggested that there may be a higher prevalence of allergen

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sensitization in the elderly than previously believed.^{7,8} We hypothesized that sensitization to specific allergens, particularly indoor allergens, would be associated with increased severity of pulmonary function abnormalities in elderly subjects. We now report that sensitization to indoor allergens is common in elderly urban subjects with asthma, with particularly high rates of sensitization to CR. Moreover, the presence of CR sensitization is associated with greater impairment in pulmonary function and persistent airflow limitation.

MATERIALS AND METHODS

Subjects

The Bellevue Hospital Asthma Clinic (BHAC) is a public hospital clinic serving an indigent population in NYC. All patients enrolled in the clinic are asked to complete a New York University institutional review board-approved questionnaire for entry into a database. Patients are routinely referred for clinically indicated pulmonary function testing, and the results of the testing are maintained in a New York University institutional review board-approved database. Patients who had been enrolled in the BHAC between 1991 and 1998 (2,112 patients) were evaluated for entry into the study. Patients in the database with physician-diagnosed asthma (National Institutes of Health/National Heart, Lung, and Blood Institute [NHLBI] guidelines),⁹ who were ≥ 60 years of age and had a < 1 pack-year history of cigarette use were identified (114 patients). Spirometry testing was completed by 92 of 114 eligible subjects before and after BD administration. Patients were referred for total serum IgE measurement and allergen-specific IgE analysis with a radioallergen sorbent test (RAST) for clinical assessment. Forty-five subjects completed the testing. Demographics, clinical characteristics, and baseline FEV₁ were similar in this group compared to the larger group of elderly nonsmokers.

Information on demographics, clinical characteristics, and tobacco use were obtained from the previously validated BHAC questionnaire¹⁰ that had been completed at the first clinic visit. The age of onset of asthma was determined by subject reporting of symptoms or initial physician diagnosis, whichever had occurred earlier. Inhaled corticosteroids were prescribed according to NHLBI guidelines at the initial clinic visit. Long-acting β_2 -agonists were not prescribed prior to pulmonary function testing.

Laboratory Data

The measurement of total serum IgE levels and RAST analyses were performed in a commercial laboratory (Pharmacia ImmunoCAP assay; Quest Diagnostics; Teterboro, NJ). The RAST was used as a measure of sensitization because, in comparison to skin testing, it was convenient and posed no risk to subjects. All RAST testing was performed within 1.8 years of pulmonary function testing. Allergens analyzed included the following: cat epithelium; dog epithelium; mouse urine protein; dust mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*); CR (*Blattella germanica*); grasses (timothy and orchard cocksfoot); weeds (English plantain and common ragweed); trees (oak, sycamore, and maple); and molds (*Alternaria tenuis* and *Aspergillus fumigatus*). Specific IgE antibody levels of > 0.35 kilo-international units (kIU)/L were defined as positive.

Pulmonary Function Testing

Spirometry and plethysmography were performed after BHAC enrollment and the initiation of treatment. Studies were performed with appropriate equipment (PK Morgan; Andover, MA) in accordance with standard methods.^{11–14} Subjects did not receive therapy with short-acting inhaled β_2 -agonists prior to testing. Maximum expiratory flow-volume curves were obtained, and FVC, FEV₁, and expiratory flow rate at mid-lung volume (V₅₀) were determined. Functional residual capacity (FRC) was measured using body plethysmography. Slow vital capacity, inspiratory capacity, and expiratory reserve volume (ERV) were measured. Total lung capacity (TLC), and residual volume (RV) were calculated. Spirometry was repeated following the administration of 180 μ g albuterol.

Statistical Analysis

Demographic and clinical characteristics were compared using analysis of variance and χ^2 analysis. Logarithmic transformation was performed to normalize the distribution of total serum IgE.¹⁵ Linear regression analysis was used to assess the relationship between log₁₀ serum IgE levels and pulmonary function, age, and gender. To minimize the confounding influence of age, sex, and height, percent predicted values were used for analysis. Analysis of variance was used to assess the relationship between specific IgE levels and measures of pulmonary function. All results are reported as the mean $\pm$ SEM. To assess the contribution of duration of disease, comparisons between pulmonary function indexes in the groups of subjects sensitized to CR (CR+) and not sensitized to CR (CR–) were repeated using analysis of variance with duration of asthma as a covariate. Analyses were performed using the software package JMP version 3.1.5 (SAS Institute, Inc., Cary, NC, copyright 1995).

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical characteristics of the elderly cohort are shown in Table 1. The cohort consisted predominantly of women (78%) and mem-

Table 1—Demographic and Clinical Data*

Variables	Elderly Cohort (<i>n</i> = 45)	CR+ (<i>n</i> = 21)	CR– (<i>n</i> = 45)
Age, yr	69 (61–87)	69 (61–81)	69 (61–87)
Sex, %			
Male	22	19	25
Female	78	81	75
Race/ethnicity, %			
Hispanic	62	70	54
White	24	10	38
African American	5	10	0
Other	9	10	8
Insurance, %			
Medicaid	38	47	30
Medicare	36	27	43
None	21	26	18
Private	5	0	9
Duration of asthma, yr	28 (1–69)	32 (1–64)	23 (1–69)
Age of onset, yr	39 (1–72)	34 (2–69)	42 (1–72)

*Values in parentheses are ranges.

bers of racial/ethnic minority groups (62% Hispanic and 5% African-American descent). The gender distribution and race/ethnicity of the elderly cohort reflected that of the clinic population as a whole. The high proportion of Medicaid patients (38%) and patients without health insurance (21%) were consistent with the low socioeconomic status of the group. The mean age of onset of asthma for the elderly cohort was 39, ranging widely from early childhood to age 72. Surprisingly, only 22% of the cohort reported the onset of asthma before age 20. Clinical onset of asthma occurred at age 60 or later in 16% of subjects. The mean duration of disease was 28 years. Baseline per cent predicted FEV₁ for the cohort was 71.1%, consistent with the presence of moderate-severe persistent asthma as defined by the NIH/NHLBI EPR criteria.⁹ Moreover, a large proportion of the cohort (11%) reported a history of intubation.

Total Serum IgE and Allergen-Specific IgE

To determine whether there was an association between total serum IgE and lung function, total serum IgE was determined for the cohort. The median total serum IgE concentration was 50.0 U/mL (mean log₁₀ IgE, 1.67 ± 0.01). Log₁₀ IgE did not differ according to gender. There was no relationship between log₁₀ IgE and age, age of onset of asthma, or duration of disease (data not shown).

The presence of IgE specific to common indoor and outdoor allergens was tested by RAST. The majority of subjects had IgE antibodies specific to at least one allergen (60%). IgE antibodies specific to at least one indoor allergen were present in half the cohort (53%). Fewer subjects had a positive response to at least one outdoor allergen (20%). The frequency distribution of allergen sensitization is demonstrated in Figure 1. CR was the most common allergen to which subjects were sensitized (47%), with isolated CR sensitivity present in 20% of subjects. The median level of IgE specific to CR was 1.41 kIU/L (range, 0.36 to 800 kIU/L). Most subjects (75%) had a class 2 or greater response on a modified RAST scoring system. A positive response to dust mite (*D farinae* and/or *D pteronyssinus*) was present in 18% of subjects. Sensitization to household pets was less common, with a positive response to cat in 18% of subjects, and to dog in 13% of subjects. The most common outdoor allergen to which subjects were sensitized was ragweed (11%). Less than 10% of the cohort were sensitive to any other individual allergen.

Relationship Between Pulmonary Function and Allergen Sensitization

To determine whether there was an association between lung function and total IgE, regression analysis of measures of air flow and lung volumes on

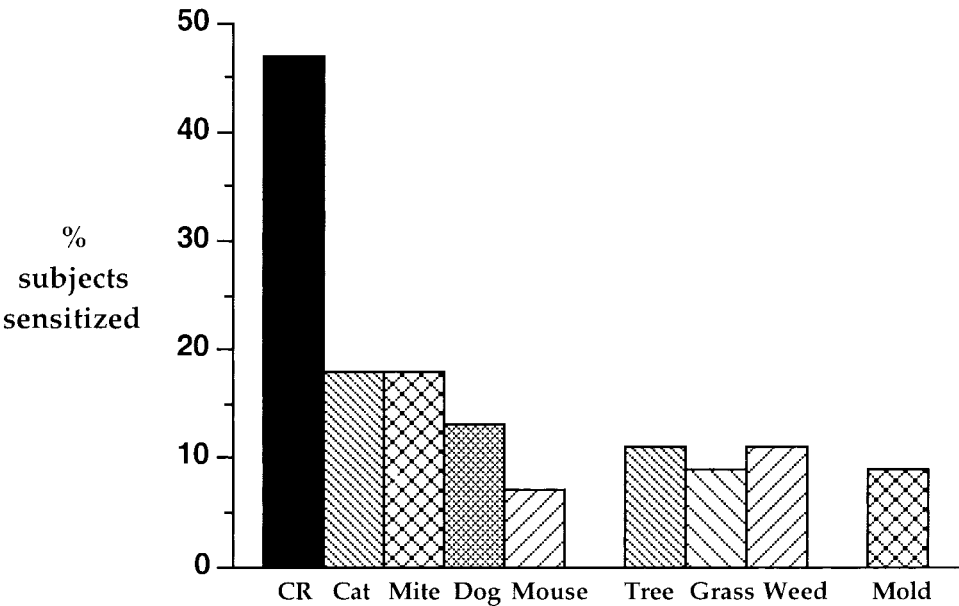


FIGURE 1. Frequency distribution of allergen sensitization in an elderly cohort of urban asthmatic subjects. Sensitization to specific allergens was determined by RAST. The allergens analyzed included CR (*B germanica*), cat epithelium, dust mite (*D farinae* and/or *D pteronyssinus*), dog epithelium, mouse urine protein, trees (oak, sycamore, and maple), grasses (timothy and/or orchard cocksfoot), weeds (English plantain and/or common ragweed), and molds (*A tenuis* and/or *A fumigatus*). A specific IgE level of > 0.35 kIU/L was considered to be positive.

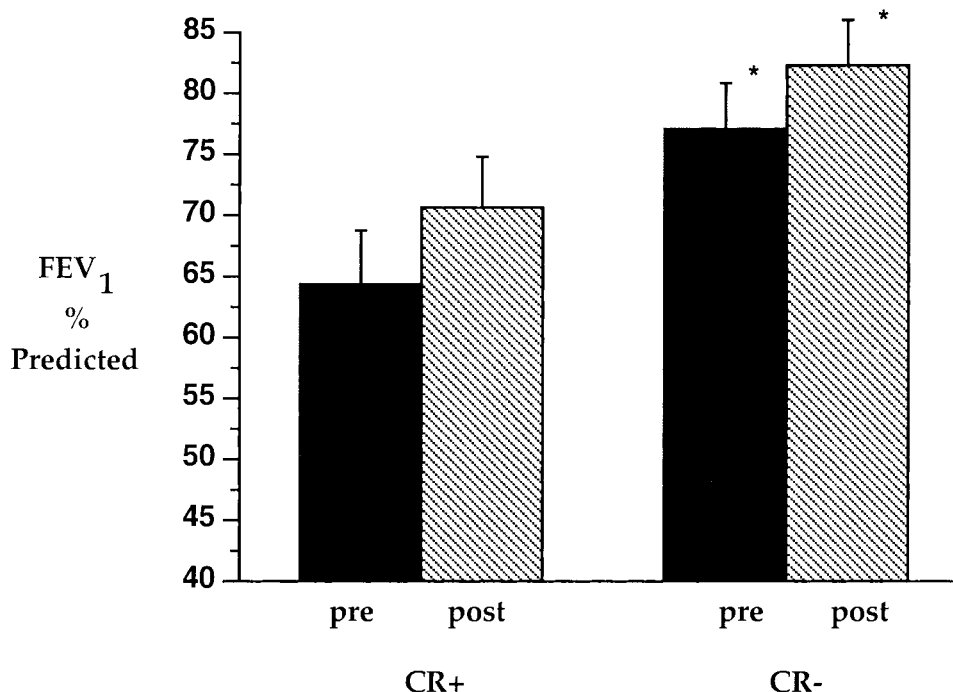


FIGURE 2. Baseline and post-BD therapy (post) FEV₁ levels in CR+ and CR- subjects. Spirometry was performed in CR+ and CR- subjects as described in the "Materials and Methods" section. The data are presented as the percent predicted. * = $p < 0.05$ for CR+ pre-BD therapy (pre) compared to CR- pre-BD therapy and CR+ post-BD therapy vs CR- post-BD therapy.

log₁₀ IgE were performed. No relationship was detected between log₁₀ IgE and any measure of pulmonary function (data not shown).

The question was raised as to whether there was an association between airflow abnormalities and the presence of specific allergen sensitization. We were unable to detect a relationship between measures of pulmonary function and the presence of sensitization to any outdoor allergen. However, there was a trend toward a lower FEV₁ in subjects sensitized to any indoor allergen compared to those without allergen sensitization ($65.8 \pm 4.2\%$ predicted vs $77.3 \pm 4.4\%$ predicted, respectively; $p < 0.06$). Since most (78%) of the subjects sensitized to at least one indoor allergen were sensitized to CR, we postulated that the trend toward greater impairment in pulmonary function in the indoor allergen group was driven predominantly by sensitization to CR.

Table 1 shows the demographics and clinical characteristics of CR+ and CR- subjects. Small variations in the distribution of race/ethnicity and gender between CR+ and CR- subjects were not statistically significant. To determine whether the presence of CR sensitization was associated with differences in lung function, we compared spirometry and plethysmography results in CR+ and CR- subjects (Table 2). Airflow, as measured by FEV₁, was significantly lower in CR+ subjects compared to CR- subjects ($64.3 \pm 4.4\%$ predicted vs

$77.1 \pm 4.1\%$ predicted, respectively; $p < 0.05$). There was a trend toward a greater reduction in V₅₀. The reduction in FEV₁ was accompanied by a reduction in the ratio of FEV₁/FVC in CR+ subjects compared to CR- subjects ($0.64 \pm 0.03\%$ vs $0.72 \pm 0.2\%$, respectively; $p < 0.05$). We were unable to detect differences in these parameters of pulmonary function in association with sensitization to any other specific indoor allergen (data not shown).

Differences in the measurements of lung volumes were also detected between CR+ and CR- subjects. There was a greater elevation in FRC ($145.0 \pm 7.0\%$ predicted vs $125.8 \pm 6.4\%$ predicted, respectively; $p < 0.05$) and RV ($188.8 \pm 10.7\%$ predicted vs $156.0 \pm 9.7\%$ predicted, respectively; $p < 0.05$). There was a trend toward a greater TLC in CR+ subjects ($127.1 \pm 4.8\%$ predicted vs $116.2 \pm 4.3\%$ predicted, respectively; $p < 0.09$). Interestingly, whereas both FRC and RV were greater in CR+ vs CR- subjects, ERV did not differ between the two groups.

Relationship Between Duration of Asthma and CR Sensitization

We have previously reported¹⁶ an association between the duration of asthma and the degree of impairment in pulmonary function. Although the

Table 2—Pulmonary Function in CR+ and CR− Subjects*

Variables	CR+		CR−	
	L	% Predicted	L	% Predicted
FEV ₁	1.4 ± 0.1	64.3 ± 4.4	1.7 ± 0.1	77.1 ± 4.1†
V ₅₀	1.2 ± 0.2	42.1 ± 6.6	1.8 ± 0.2	59.5 ± 6.1
FVC	2.2 ± 0.1	81.4 ± 3.7	2.4 ± 0.1	85.5 ± 3.5
FEV ₁ /FVC‡	0.64 ± 0.03		0.72 ± 0.02†	
TLC	5.8 ± 0.3	127.1 ± 4.8	5.3 ± 0.3	116.2 ± 4.3
RV	3.5 ± 0.2	188.8 ± 10.7	2.9 ± 0.2	156.0 ± 9.7†
FRC	4.0 ± 0.2	145.0 ± 7.0	3.5 ± 0.2	125.8 ± 6.4†
ERV	0.5 ± 0.1	53.9 ± 10.0	0.6 ± 0.1	60.0 ± 9.1

*Values given are mean ± SEM.

†p < 0.05 (percent predicted CR+ vs percent predicted CR−).

‡p < 0.05 (ratio of FEV₁/FVC for CR+ vs CR−).

duration of asthma did not differ significantly between the CR+ and CR− groups, we assessed whether duration was a covariate for the observed reduction in airflow in the CR+ group. Using an analysis of variance with duration of asthma as a covariate, we did not identify duration of asthma as a significant covariate for the differences in FEV₁ or FRC between CR+ and CR− subjects.

Reversible Airway Disease and CR Sensitization

Since CR+ subjects had more severe airflow limitation than did CR− subjects, we asked whether airflow obstruction would be reversed following BD administration. When evaluated as the percentage change in baseline FEV₁, CR+ and CR− subjects had a similar degree of improvement following BD administration (13% and 11% improvement in FEV₁, respectively). The absolute change in FEV₁ was also similar for the two groups (141.9 ± 31.4 vs 115.8 ± 31.4 mL, respectively as shown in Figure 2). Despite a similar degree of BD responsiveness, CR− subjects achieved a normal post-BD FEV₁ (82.2 ± 3.9% predicted), whereas CR+ subjects demonstrated persistent airway obstruction (70.6 ± 4.2% predicted FEV₁). After BD therapy, 58% of the CR− subjects achieved an FEV₁ ≥ 80% of predicted compared to only 29% of CR+ subjects (p < 0.05).

DISCUSSION

Although the importance of allergen sensitization in children with asthma has been well-described, the association between atopy and morbidity due to asthma in the elderly is not as clear. Our study investigated the relationship between allergen sensitization and pulmonary physiology in an elderly urban cohort with asthma. The data show that

elderly urban persons with asthma displayed a pattern of allergen sensitization that was similar to that reported in children and young adults in urban areas of the United States. Sensitization to indoor allergens was common, with many elderly subjects displaying sensitization to CR. Within this group of elderly subjects with asthma, the presence of IgE antibodies specific to CR was associated with a greater degree of airflow obstruction and hyperinflation. Moreover, the conditions of these subjects with a greater degree of airflow obstruction failed to reverse to normal after BD administration.

The pattern of allergen sensitization in our cohort was striking. In our elderly cohort, 47% of subjects were sensitized to CR. Indeed, 20% displayed isolated sensitization to this allergen. The distribution of sensitization was similar to that described for children in the National Cooperative Inner-City Asthma Study³ and in two studies^{17,18} of urban adults, including the Normative Aging Study. Our study of an elderly urban cohort extends these findings to an older age group and suggests a consistent pattern of allergen sensitization among urban persons with asthma of all ages in the United States. The pattern of sensitization reflected that reported in children even with our use of RAST rather than skin testing.

This study was not designed to test the overall prevalence of allergen-specific IgE to common allergens in the elderly population. However, because sensitization to CR was common within this population of elderly subjects with asthma, we evaluated whether we could detect an association between the presence of CR sensitization and decrements in pulmonary function testing within this population. Indeed, in comparison to CR− subjects, CR+ subjects demonstrated more severe airway obstruction, as measured by FEV₁. These findings are consistent with and extend the observations of the Normative

Aging Study, in which an accelerated rate of decline in FEV₁ was demonstrated in healthy and asthmatic elderly subjects with elevated CR allergen levels in the home.¹⁹ Moreover, our findings are consistent with and extend those of Kang et al,¹⁸ who demonstrated increased asthma severity in CR+ subjects in Chicago. Interestingly, a higher number of CR+ subjects in our study were initially prescribed inhaled corticosteroids compared to CR− subjects (90% vs 42%, respectively) based on the initial clinical assessment prior to obtaining pulmonary function test results. The observed differences in the severity of pulmonary function abnormalities were demonstrated despite the more aggressive treatment of CR+ subjects.

CR+ subjects displayed a reduced FEV₁ level that failed to improve to normal despite the administration of BD. This finding suggests the possibility that CR+ subjects were more likely to have fixed airway obstructions compared to CR− subjects. In addition, our study demonstrated a higher FRC and a trend toward an elevation in TLC in CR+ subjects. However, we failed to detect a difference in ERV between CR+ and CR− subjects. This compilation of findings suggests that CR+ subjects were more hyperinflated than the CR− subjects. The absence of a difference in ERV raises the question of whether the hyperinflation was associated with altered elastic properties in the lung rather than with differences in the degree of airtrapping.

The question can be raised as to whether the decreased lung function observed in the CR+ group was specific for CR sensitization. It is possible that our sample size may have limited our ability to detect a difference for other indoor allergens with lower rates of sensitization. A large body of data has linked asthma prevalence, asthma severity, and airway hyperresponsiveness to sensitization and exposure to indoor allergens, with a focus on the house dust mite.² The Childhood Asthma Management Program,²⁰ a study of children with mild asthma, did not detect a decline in FEV₁ in association with sensitization to any specific allergen. In contrast, the National Health and Nutrition Examination Survey II²¹ found decrements in FEV₁ in children in association with dust mite and dog sensitization. Our data suggest the importance of one specific indoor allergen to which our population was sensitized. We cannot rule out that exposure and sensitization to other indoor allergens also might be associated with important physiologic effects.

The mechanism by which CR sensitization might induce the described physiologic changes includes several possibilities. CR allergen exposure is perennial, and, thus, subjects may have a greater duration of exposure to this allergen compared to seasonal

allergens. Moreover, there may be specific properties of CR allergens that make them potent allergens. Recently cloned allergenic proteins of the common urban CR *B germanica* display sequence homology to aspartic proteases, ligand-binding proteins, and members of the glutathione S-transferase superfamily.^{22,23} The possibility that these proteins might be particularly effective proinflammatory stimuli in the airway is tantalizing. Indeed, Kang et al¹⁸ have demonstrated that asthma patients with CR sensitivity have higher total IgE levels. In addition, genetic influences may participate in the CR response since human leukocyte antigen alleles have been identified that predispose subjects of ethnically diverse populations to CR sensitization. Moreover, a possible quantitative-trait locus, D4S1647 has been identified as being associated with skin reactivity to the CR.^{24,25}

An association between total IgE levels and pulmonary function was not detected in our cohort. Serum IgE levels have been associated with increasing degrees of airway responsiveness and have been inversely related to FEV₁ and FEV₁/FVC ratio.^{26–28} Although serum IgE levels are known to decline in the elderly, levels were elevated in our elderly cohort when compared to the published age-adjusted and sex-adjusted standards.¹⁵ The possibility exists that the measurement of IgE lacks the sensitivity to reflect the physiologic severity of disease in a group of elderly subjects. Alternatively, the size of our population may have been too small to detect such a relationship.

In summary, our data demonstrated that elderly subjects with asthma in a city in the northeastern United States often were sensitized to common indoor allergens, with a striking rate of CR sensitization. Moreover, the presence of CR allergen sensitization in these asthmatic subjects was associated with a greater degree of airway obstruction and hyperinflation. These findings suggest that, as is the case in children, in urban elderly persons with asthma, CR sensitization is associated with increased asthma morbidity.

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