

Skin Test Reactivity to Common Aeroallergens and Decline of Lung Function

The Normative Aging Study

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It has been hypothesized that allergy is associated with an increased risk of developing chronic irreversible airflow obstruction. We have investigated the relation between immediate cutaneous hypersensitivity to common aeroallergens and the subsequent rate of decline of lung function in 1,025 men participating in the Normative Aging Study; subjects had a mean age of 61 ± 8 (SD) yr and denied any history of asthma. Subjects performed spirometry and underwent allergen skin testing at a baseline visit and performed repeat spirometry after a median of 3.1 yr. Skin prick tests were performed using four glycerin-preserved allergens (house dust, mixed grasses, mixed trees, and ragweed); wheal size was measured at 20 min. Multiple linear regression analysis was used to examine the annual rate of change of lung function in relation to skin test reactivity, defined as a mean wheal size to the 4 allergens ≥ 2 mm, after adjustment for age, height, smoking status, and initial lung function. Skin test reactivity was a significant predictor of the annual rates of decline of FEV₁ and FEV₁/FVC ratio. The regression model predicted an excess decline of FEV₁ of 9.45 ml/yr for subjects with mean wheal diameter ≥ 2 mm ($p < 0.05$); the excess rate of decline of FEV₁/FVC ratio was 0.29 percent/yr ($p = 0.001$). There was no significant relation between mean wheal diameter and rate of decline of FVC. The magnitude of the effects of a mean wheal diameter ≥ 2 mm on rates of decline of FEV₁ and FEV₁/FVC ratio are 34% and 49%, respectively, of the magnitude of the effects of current cigarette smoking in these models. We conclude that cutaneous hypersensitivity to common aeroallergens is a significant independent predictor of subsequent decline of lung function among middle-aged and older men with no history of asthma. **Gottlieb DJ, Sparrow D, O'Connor GT, Weiss ST. Skin test reactivity to common aeroallergens and decline of lung function: the Normative Aging Study.**

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The most important known risk factor for the development of chronic obstructive pulmonary disease (COPD) is cigarette smoking; however, fewer than 20% of cigarette smokers develop clinically important airflow obstruction (1). Therefore, host factors responsible for the susceptibility of some individuals to the adverse effects of cigarette smoke are of great interest. In 1961, Orie and coworkers observed that many patients with chronic bronchitis had an allergic background, and suggested that allergy might represent an endogenous factor predisposing individuals to the development not only of asthma, but of chronic bronchitis and emphysema as well (2). Subsequent studies in clinical,

occupational, and population samples, however, have failed to demonstrate a clear relation between atopy, defined by cutaneous hypersensitivity to common aeroallergens, and the development of airflow obstruction (3-12).

The purpose of the present study was to evaluate prospectively the relation between atopy, as determined by immediate cutaneous hypersensitivity to four common aeroallergens, and the rate of decline of spirometric measures of lung function, including both FEV₁ and the FEV₁/FVC ratio, in the well-defined cohort of men participating in the Normative Aging Study. The mean age of these subjects, 61 yr, was greater than that of most previous cohorts in which this relation has been examined. This study also differs from previous investigations in its use of a measure of mean cutaneous reactivity to all allergens tested.

METHODS

Subjects

The Normative Aging Study (NAS) is a longitudinal study of aging located at the Veterans Administration Outpatient Clinic in Boston. The NAS cohort has been described in detail elsewhere (13). Recruited in the 1960s, the cohort initially consisted of 2,280 male volunteers who were health-screened at entry; those with chronic medical conditions including asthma, chronic bronchitis, and chronic sinusitis were excluded.

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Members of this cohort have reported every 3 to 5 yr for a comprehensive evaluation, including medical history, physical examination, blood and urine tests, and spirometry. Beginning in 1984, allergy skin testing has also been performed.

Between 1984 and 1990, there were 1,085 subjects who performed spirometry and underwent allergy skin testing at a baseline clinic visit, and had spirometry measured at the following visit. Of these subjects, 59 who reported a history of asthma on at least one visit were excluded from analysis. One subject with a large wheal response to the glycerin control was also excluded from analysis. The remaining 1,025 subjects form the basis of this investigation.

Spirometry and Methacholine Challenge Protocol

All subjects performed spirometry between 7:30 and 9:30 A.M. Forced vital capacity (FVC) maneuvers were performed standing, wearing noseclips, under the guidance of an experienced technician, using a 10-L water-filled Warren-Collins survey spirometer which was calibrated daily. Acceptability of the spirometry was judged according to American Thoracic Society standards (14), and spirometry repeated, up to a maximum of 8 spirometrys, until at least 3 acceptable spirometrys, at least 2 of which were reproducible (FEV₁ and FVC within 5%), were obtained from each subject.

Methacholine challenge testing was performed as previously reported (15). Briefly, incremental doses of aerosolized methacholine were inhaled at 5-min intervals yielding the following cumulative doses of methacholine in micromoles: 0, 0.3, 2.0, 8.6, 16.8, and 49.8. Spirometry was performed 30, 90, and 180 s after each inhalation level. If the first two spirometrys were consistent (FEV₁ within 5%), then the higher of the two was chosen for analysis; otherwise, the higher FEV₁ from the two most consistent spirometrys was used. The test was terminated when a 20% decline in FEV₁ occurred or at the end of the dose schedule if such a decline did not occur. Methacholine responsiveness was expressed as a continuous variable using an estimate of the overall slope of the dose-response relationship as previously described (15). Of the 1,025 subjects included in the present analysis, 799 underwent methacholine challenge testing.

Allergy Skin Testing

Cutaneous hypersensitivity to common aeroallergens was determined by skin testing using the prick method of Pepys (16). The volar surface of each arm was cleaned and dried, and glycerin-preserved allergens and a glycerin control were placed at 5-cm intervals. The allergens were supplied by Hollister-Stier (Spokane, WA) and included house dust (1:10), ragweed (1:20), mixed trees (1:20), and mixed grasses (1:20). The allergens and glycerin control were in number-coded bottles in order to blind the research assistant performing the test. The skin was pricked with a Greer needle (Greer Laboratories, Winston-Salem, NC). The reaction was measured at 20 min by adding the largest diameter of the wheal to its perpendicular, and then halving the sum. When a wheal reaction occurred to the glycerin control, the wheal diameter of this reaction was subtracted from the wheal diameter of each allergen reaction prior to analysis. The mean wheal size was the arithmetic mean of the reactions to the four allergens (house dust, ragweed, mixed trees, and mixed grasses).

Analysis

All statistical analyses were performed using SAS software (SAS Institute, Cary, SC). The rate of change of lung function was determined for each subject as the difference between the follow-up and baseline values of each lung function measurement (FEV₁, FVC, and FEV₁/FVC ratio) divided by the time in years between examinations. Mean annual decline of lung function was examined in relation to cutaneous hypersensitivity, defined as a mean wheal size ≥ 2 mm, using analysis of covariance to adjust for age, height, smoking status, and initial lung function level (17). The relation between annual decline of lung function and skin test reactivity was also analyzed using multiple linear regression analysis. The rate of change of each of the three measures of lung function (FEV₁, FVC, and the ratio FEV₁/FVC) was evaluated separately as the dependent variable in regression analysis. The mean wheal size to the four allergens was the independent variable of interest; the wheal size resulting from each of the individual allergens was also analyzed separately. The covariates age, height, and smoking status (as dummy variables for current and former smoking) were entered in all models. Because ad-

TABLE 1
SUBJECT CHARACTERISTICS

Number of subjects	1,025
Age, yr*	60.6 $\pm$ 7.6
Smoking status†	
Current	134 (13.1)
Former	565 (55.1)
Never	326 (31.8)
Baseline lung function‡	
FEV ₁ , % predicted	94.2 $\pm$ 15.7
FVC, % predicted	96.4 $\pm$ 14.6
FEV ₁ /FVC ratio, % predicted	97.1 $\pm$ 8.8
Mean wheal size§	
< 2 mm	803 (78.3)
2–4.9 mm	177 (17.3)
≥ 5 mm	45 (4.4)

* Values are mean $\pm$ SD.

† Values are n (%).

‡ Predicted values are from regression equations based upon asymptomatic never-smokers in the Normative Aging Study cohort.

§ Mean of wheal size to house dust, mixed grasses, mixed trees, and ragweed minus wheal size to negative control. Values are n (%).

justment for initial level of lung function in studies of the longitudinal change of lung function is controversial, regression analyses were performed both with and without the inclusion of baseline lung function (as a percentage of the predicted value) in the models. Regression diagnostics, including plots of residual versus predicted rates of change in lung function and inclusion of appropriate first-order multiplicative interaction terms, were used to assess the validity of the multivariate models.

RESULTS

Characteristics of the 1,025 subjects are given in Table 1. The mean time interval between initial and follow-up spirometry was 3.3 $\pm$ 0.8 (SD) yr. The low prevalence of current smoking (13.1%) is likely to reflect heightened health consciousness in this group of men who have participated in the NAS for more than 20 yr. The percentage of subjects with a mean wheal reaction of ≥ 2 mm was 21.7%; the percentage with a wheal reaction ≥ 2 mm to at least one of the four allergens was 49.4%, and was between 21% and 27% for each allergen. Although only 4.4% of subjects had a mean wheal diameter ≥ 5 mm, 22.1% of subjects had a wheal reaction of ≥ 5 mm to at least one of the four allergens tested (3.0% to house dust, 10.3% to mixed grasses, 7.5% to mixed trees, and 12.6% to ragweed).

Mean annual decline of lung function stratified by skin test reactivity is presented in Table 2. A larger mean wheal reaction was associated with a more rapid decline of both FEV₁ and FEV₁/FVC ratio. After adjustment for age, height, smoking status, and initial lung function level by analysis of covariance, subjects with mean wheal diameters ≥ 2 mm had a mean annual decline of FEV₁ that was 9.45 ml/yr more rapid than subjects with a mean wheal diameter of < 2 mm ($p < 0.05$). Subjects with mean wheal diameters ≥ 2 mm had an adjusted mean annual decline of FEV₁/FVC ratio that was 0.29 percent/yr more rapid than subjects with a mean wheal diameter of < 2 mm ($p = 0.001$). Larger mean wheal size was not associated with a more rapid rate of decline of FVC ($p = 0.98$).

In order to investigate possible modification of these relations by smoking status, mean annual decline of lung function was stratified by both smoking status and mean wheal size (Table 2). Annual rates of decline have been adjusted for age, height and initial lung function by analysis of covariance. Wheal size ≥ 2 mm was associated with a more rapid decline of FEV₁ in each smoking status group. The excess decline associated with wheal size ≥ 2 mm was similar among current (6.1 ml/yr), former

TABLE 2
ANNUAL RATE OF CHANGE OF LUNG FUNCTION*
BY WHEAL SIZE AND SMOKING STATUS

		Smoking Status		
	Total (1,025)	Never (326)	Former (565)	Current (134)
Wheal size [†]		FEV ₁		
< 2 mm	-35.5 (803)	-30.4 (250)	-35.4 (443)	-47.3 (110)
≥ 2 mm	-45.0 [‡] (222)	-38.9 (76)	-47.1 (122)	-53.4 (24)
Wheal size [†]		FVC		
< 2 mm	-28.8 (803)	-23.1 (250)	-30.2 (443)	-35.6 (110)
≥ 2 mm	-28.7 (222)	-12.8 (76)	-37.3 (122)	-36.1 (24)
Wheal size [†]		FEV ₁ /FVC		
< 2 mm	-0.34 (803)	-0.34 (250)	-0.32 (443)	-0.48 (110)
≥ 2 mm	-0.64 [§] (222)	-0.73 (76)	-0.53 (122)	-0.79 (24)

* Change in pulmonary function in ml/yr (FEV₁ or FVC) or percent/yr (FEV₁/FVC). For the total group, values are adjusted for age, height, current smoking, former smoking, and initial pulmonary function level by analysis of covariance. For the individual smoking status groups, values are adjusted for age, height, and initial pulmonary function level by analysis of covariance. For each category, the number of subjects is indicated in parentheses.

† Mean of wheal size to house dust, mixed grasses, mixed trees, and ragweed minus wheal size to negative control.

‡ $p < 0.05$ for difference from wheal size < 2 mm.

§ $p = 0.001$ for difference from wheal size < 2 mm.

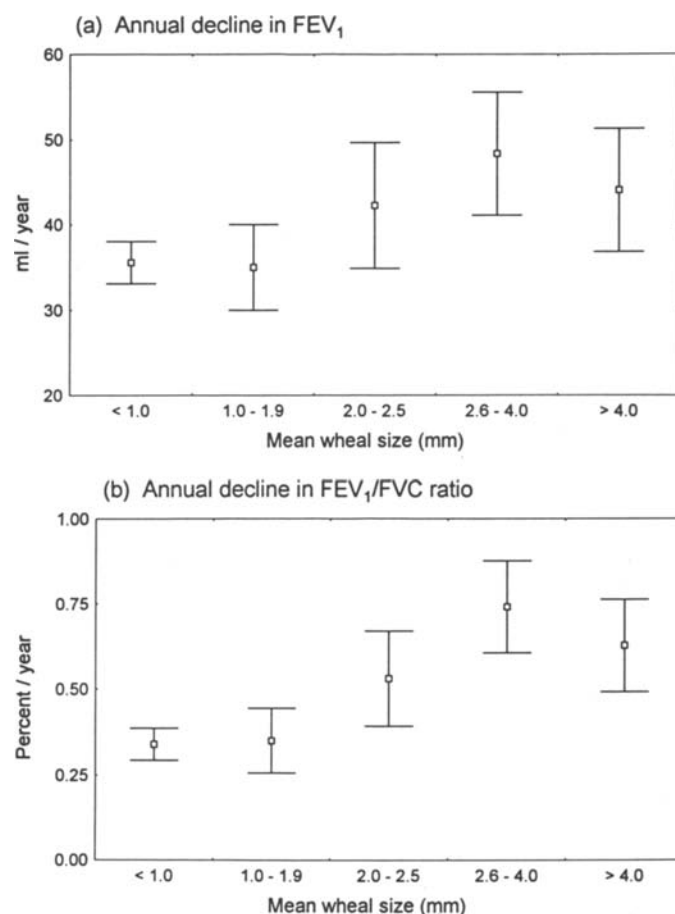


Figure 1. Annual decline in FEV₁ (A) and FEV₁/FVC (B) for subjects grouped by mean wheal diameter: < 1 mm ($n = 648$); ≥ 1 mm, < 2 mm ($n = 155$); 2–2.5 mm ($n = 72$); 2.6–4.0 mm ($n = 75$); > 4.0 mm ($n = 75$). Values are mean (□) and standard error (±) adjusted for age, height, smoking status, and initial lung function by analysis of covariance.

(12.3 ml/yr), and never smokers (8.5 ml/yr). Wheal size ≥ 2 mm was also associated with a more rapid decline of FEV₁/FVC ratio in each group. The excess decline associated with wheal size ≥ 2 mm was similar among current (0.31 percent/yr), former (0.21 percent/yr), and never smokers (0.39 percent/yr). Because of the small sample size within each smoking status stratum, these estimates are imprecise and generally not statistically significant.

The relation of mean wheal size to annual change in lung function, adjusted for age, height, smoking status, and initial lung function by analysis of covariance, is shown graphically in Figure 1. Among subjects with mean wheal size < 2 mm, there was no apparent difference in rate of decline of either FEV₁ or FEV₁/FVC ratio between subjects with mean wheal size < 1 mm and those with mean wheal size between 1 and 2 mm. Among subjects with mean wheal size ≥ 2 mm, those in the highest tertile (mean wheal > 4.0 mm) did not appear to have more rapid decline in lung function than those in the lowest tertile (mean wheal 2.0 to 2.5 mm). For this reason, skin test reactivity is treated as a dichotomous variable in the regression models which follow. Annual change in lung function was modeled as a function of age, height, smoking status (as dummy variables for current smoking and former smoking), initial lung function level (as percentage of predicted), and mean wheal size ≥ 2 mm, with separate models for FEV₁, FVC, and FEV₁/FVC ratio. Mean wheal size was evaluated in the main analysis; each of the four allergens was also evaluated in a separate model.

Mean wheal size was significantly related to the annual change in FEV₁ (Table 3). The excess rate of decline of FEV₁ associated with a mean wheal size ≥ 2 mm was 9.45 ml/yr ($p < 0.05$). In this model, the excess decline of FEV₁ associated with current smoking was 28.15 ml/yr. Thus, in this model, the effect of a mean wheal diameter ≥ 2 mm on the rate of decline of lung function is 34% as great as the effect of current smoking. Using first-order multiplicative interaction terms, there was no significant

interaction between mean wheal size and either current or former smoking or age ($p > 0.10$ for each interaction term).

Mean wheal size was also significantly related to the annual change in FEV₁/FVC ratio (Table 3). The excess rate of decline of FEV₁/FVC ratio associated with a mean wheal diameter ≥ 2 mm was 0.29 percent/yr. In this model, the excess decline of FEV₁/FVC ratio associated with current smoking was 0.60 percent/yr. Thus, in this model, the effect of a mean wheal diameter ≥ 2 mm on the rate of decline of lung function is 49% as great as the effect of current smoking. There was no significant interaction between mean wheal size and either smoking status or age ($p > 0.10$ for each interaction term).

There was no significant effect of mean wheal diameter ≥ 2 mm on the rate of decline of FVC (partial regression coefficient 0.13 ml/yr, $p = 0.98$; model not shown).

When the initial level of lung function was not included in the above models, the relation between mean wheal diameter and rate of change of lung function was essentially unchanged.

To determine whether the relation of skin test reactivity to rapid decline of lung function was explained by the association of both of these traits with airway hyperresponsiveness, we repeated the above models in the 799 subjects for whom methacholine airway responsiveness had been measured. In these models, the partial regression coefficients for mean wheal diameter ≥ 2

TABLE 3

REGRESSION MODELS PREDICTING RATE OF CHANGE OF LUNG FUNCTION IN RELATION TO SKIN TEST REACTIVITY

	$\beta^{\dagger}$	SEE ‡	p Value
ΔFEV_1^*			
Independent variable			
Intercept	77.57	62.75	0.22
Age, yr	-0.48	0.27	0.08
Height, cm	-0.03	0.31	0.92
Current smoking	-28.15	6.81	< 0.01
Former smoking	-9.59	4.39	0.03
Initial FEV_1 , % predicted	-0.64	0.13	< 0.01
Mean wheal size ≥ 2 mm	-9.45	4.77	< 0.05
$\Delta FEV_1/FVC^*$			
Independent variable			
Intercept	2.569	1.197	0.03
Age, yr	0.004	0.005	0.38
Height, cm	0.016	0.006	0.01
Current smoking	-0.603	0.128	< 0.01
Former smoking	-0.069	0.082	0.40
Initial FEV_1/FVC , % predicted	-0.056	0.004	< 0.01
Mean wheal size ≥ 2 mm	-0.292	0.089	< 0.01

* ΔFEV_1 = annual change in FEV_1 (ml/yr); $\Delta FEV_1/FVC$ = annual change in FEV_1/FVC (percent/yr).

† Partial regression coefficient.

‡ Standard error of the estimate of the partial regression coefficient.

mm as a predictor of decline of FEV_1 (-9.77 ml/yr) and FEV_1/FVC ratio (-0.27 percent/yr) were very similar to those obtained from the entire group of 1,025 subjects. When methacholine airway responsiveness, expressed as the log-transformed dose-response slope, was included in the models, the relation between skin test reactivity and rate of decline of lung function was essentially unchanged (for FEV_1 , $\beta = -8.88$ ml/yr; for FEV_1/FVC , $\beta = -0.24$ percent/yr). Using first-order multiplicative interaction terms, there was no significant interaction between skin test reactivity and methacholine airway responsiveness in either model ($p > 0.10$).

Cutaneous hypersensitivity to each of the four allergens studied was associated with a more rapid decline of lung function (Table 4). The relation between skin test reactivity and the rate of decline of lung function did not differ consistently across the four allergens: response to ragweed was most strongly associated with the rate of decline of FEV_1 , whereas response to mixed trees and house dust was most strongly associated with the rate of decline of FEV_1/FVC ratio. The mean response to all four allergens was superior to any individual allergen skin test reaction in predicting the rate of decline of lung function. Moreover, the effects of isolated house dust responsiveness (in the absence of response to outdoor allergens) and isolated outdoor allergen responsiveness (in the absence of response to house dust) on the rate of decline of lung function were nearly identical (data not shown).

DISCUSSION

Orie and coworkers suggested as early as 1961 that "allergy" was a host factor influencing the development of nonasthmatic obstructive lung disease (2). Since that time, there has been considerable interest in allergy as a factor that may modify the effects of smoking on the development of lung disease. Studies of the relation of allergy to the level and rate of decline of lung function have yielded conflicting, although generally negative, results (18). Our finding of a strong relation between skin test reactivity and the longitudinal rate of decline of lung function stands in contrast to most previous reports.

TABLE 4

COMPARISON OF THE EFFECT OF SKIN TEST REACTIVITY TO DIFFERENT ALLERGENS ON THE RATE OF DECLINE OF LUNG FUNCTION

	$\beta^{\ddagger}$	SEE §	p Value
ΔFEV_1^*			
Allergen †			
House dust	-3.06	4.58	0.50
Mixed grasses	-2.53	4.71	0.59
Mixed trees	-1.17	4.81	0.81
Ragweed	-6.81	4.43	0.12
Mean wheal	-9.45	4.77	< 0.05
$\Delta FEV_1/FVC^*$			
Allergen †			
House dust	-0.22	0.09	0.01
Mixed grasses	-0.08	0.09	0.37
Mixed trees	-0.26	0.09	< 0.01
Ragweed	-0.12	0.08	0.15
Mean wheal	-0.29	0.09	< 0.01

* ΔFEV_1 = annual change in FEV_1 (ml/yr); $\Delta FEV_1/FVC$ = annual change in FEV_1/FVC (percent/yr).

† Wheal size in response to each allergen entered in a separate linear regression model as a dichotomous variable (< 2 mm, ≥ 2 mm), along with age, height, initial FEV_1 (or FEV_1/FVC) as percentage of predicted, and smoking status as dummy variables for current or former smoking.

‡ Partial regression coefficient.

§ Standard error of the estimate of the partial regression coefficient.

The cross-sectional relation of lung function to atopy has been previously investigated in the NAS and in two other cohorts. In a previous report from the NAS, O'Connor and colleagues found that the level of FEV_1 was not significantly related to atopy (defined as a wheal size ≥ 5 mm to any of the four allergens used in the current investigation) when asthmatics were excluded from analysis (4). In a population-based study in the Netherlands, atopy, defined as a dichotomous variable based on the magnitude of the response to intradermal testing with four allergens (house dust, mixed pollens, epidermal products, and mixed molds) were associated with a lower cross-sectional level of FEV_1 only in the presence of eosinophilia (3). Burrows and coworkers have examined the cross-sectional relation of lung function to skin test reactivity in the Tucson Epidemiological Study of Obstructive Lung Diseases (TES). Using a 3-point ordinal scale to quantitate skin test reactivity to five common aeroallergens (house dust, dermatiacea mold mix, Bermuda grass, tree mix, and weed mix), they found that atopy was associated with low FEV_1/FVC ratio in current and former smokers, but not nonsmokers, among subjects 15 to 54 yr of age (5). In another analysis, which included subjects age 6 to 54 yr, a low FEV_1 was associated with atopy only in the presence of eosinophilia, whereas among subjects 55 yr and older no relation was observed between atopy and FEV_1 (6). The relations of skin test reactivity and eosinophilia to cross-sectional lung function were subsequently reanalyzed among TES subjects 40 to 74 yr of age to assess the possibility that inclusion of asthmatic subjects may have led to the observed associations between allergy and reduced lung function. Although FEV_1 was significantly inversely related to atopy in the total population, these relations became insignificant after exclusion of the 12% of subjects responding affirmatively to the question "Have you ever had asthma?" on a self-completion questionnaire (7). The authors conclude that "the 'Dutch hypothesis' appears relevant primarily to a syndrome that has been called 'chronic asthmatic bronchitis' but does not appear to apply to the more emphysematous forms of COPD that are characteristic of smokers without a known asthmatic background" (7).

The relation of atopy to longitudinal rate of decline of lung function has been investigated in several cohorts. Campbell and

coworkers reported that, among 57 subjects with mild chronic bronchitis, the rate of decline of FEV₁ was unrelated to atopic status at the beginning of the follow-up interval. Atopy was defined as a wheal size of > 3 mm to any of 10 allergens including mixed grasses, animal danders, house dust, and aspergillus (8). Taylor and colleagues, reporting on 227 men without a history of asthma, found no relation between cutaneous hypersensitivity to nine "common inhalant allergens" at the beginning of follow-up and the rate of decline of lung function over a 7.5-yr period (9). Frew and coworkers have examined the relation of decline of FEV₁ to atopy, defined as a wheal size of $\geq$ 3 mm to grass pollen, cat fur, or house-dust mite *Dermatophagoides farinae*, in a prospective study of 703 nonasthmatic men in three occupational cohorts (office, sawmill, and grain workers). They found that, after adjustment for age, methacholine airway responsiveness, and initial FEV₁, atopy was a significant predictor of decline of FEV₁ only in current smokers, but not in former smokers or nonsmokers. Moreover, this effect was restricted to currently smoking grain workers, and was not present in office or sawmill workers (10). Annesi and coworkers found no association between the 5-yr decline of FEV₁ and atopy, defined as a wheal size of $\geq$ 5 mm to mixed grass pollen, dust or house dust mite, in a cohort of 308 working men who were skin tested at the end of follow-up (11). In a previous report on 790 men participating in the NAS, the annual decline of FEV₁ during a mean follow-up period of 19 yr was not associated with atopy, defined as a wheal size $\geq$ 5 mm to any of the four allergens used in the current investigation, assessed at the end of follow-up (12).

In the current prospective, longitudinal study of a cohort of nonasthmatic middle-aged and elderly men, we found that skin test reactivity to common aeroallergens was significantly related to the rates of decline of FEV₁ and FEV₁/FVC ratio. The effect of skin test reactivity on decline of lung function was independent of the effects of cigarette smoking and methacholine airway responsiveness, and there was no significant effect modification by either smoking status or airway responsiveness. Hypersensitivity to each of the four allergens studied (house dust, mixed grasses, mixed trees, ragweed) was associated with accelerated decline of lung function, and no individual allergen was clearly superior to the others in predicting the rate of decline of lung function.

The present study has certain advantages over previous studies, including its prospective longitudinal design, large sample size, and the exclusion of asthmatic subjects. Among previously reported longitudinal studies of atopy and lung function, only the relatively large ($n = 703$), prospective study of Frew and coworkers (10) found an association of atopy with more rapid decline of lung function, albeit restricted to the subset of current smokers in one of three occupational groups. Other prospective longitudinal studies (8, 9) have failed to identify any significant relation between skin test reactivity and decline of lung function, although each had a small sample size ($n = 57$ and $n = 227$), and one was comprised of subjects with established chronic lung disease (8). A large retrospective longitudinal study from the NAS also failed to demonstrate a significant relation between skin test reactivity and decline of lung function (12). In addition to its retrospective nature, the single assessment of skin test reactivity at the end of follow-up may have been a poor reflection of atopic status over the very long period (19 yr mean) over which decline of lung function was measured.

The retrospective longitudinal study of Annesi and coworkers found no significant relation between atopy and rate of decline of lung function in 457 subjects recruited on the basis of a history of respiratory symptoms and diagnoses, including asthma (11). In cross-sectional analyses, persons with asthma have a lower level of lung function and a higher prevalence of atopy than the

general population (4, 7). Inclusion of asthmatics will thus increase the likelihood that atopy will be associated with a lower level of lung function in cross-sectional studies; however, the effect of including asthmatic subjects in longitudinal studies of lung function is less clear. As spirometric lung function is more variable in asthmatics than in nonasthmatics, estimates of long-term trends in lung function based on measurements made at only two time points are likely to be imprecise. The inclusion of asthmatics may thereby reduce statistical power.

Subjects in the present study had a mean age at the start of follow-up of 61 yr. This is substantially older than subjects studied by Frew and coworkers (10) (mean age approximately 40), who found a relation between skin test reactivity and decline in lung function only among current smokers in one of three occupational groups studied. Our subjects were also older than those of Annesi and coworkers (11) and Taylor and colleagues (9), who found no significant relation between atopy and decline of lung function. Barbee and coinvestigators have reported that among subjects participating in the TES, skin test reaction rates were highest in the third decade of life and fell thereafter, with a rapid decline during the sixth decade (19). It is plausible that subjects whose atopy persists into later life are at greater risk of developing irreversible airflow obstruction, as seen in the current study.

A potentially important methodologic difference between this and previous studies is the scale on which atopy is measured. Most previous studies of atopy and lung function decline have used dichotomous measures of skin test reactivity in which atopy is defined as a skin test response greater than a specified size to any of the several allergens tested. We have found that when skin test reactivity is dichotomized in this way, the apparent magnitude of the relation between skin test reactivity and decline of lung function is strongly influenced by the threshold selected for distinguishing atopic from nonatopic individuals (data not shown). In the present study, we have used a measure of the mean wheal size to all four allergens tested. This may yield a better estimate of a subject's overall level of cutaneous allergen reactivity.

The various studies of atopy and decline of lung function have employed different numbers and types of allergens to assess atopy. Although we found no clear difference among the four allergens used at the NAS in their relation to decline of lung function, differences in the choice of allergens cannot be excluded as a cause of the differences in the results of these studies. One limitation of this study is the lack of data on sensitivity to other potentially important indoor allergens, such as cockroaches and molds. Moreover, both this and previous studies lack data on allergen exposure, which may be an important modifier of the relationship between atopy and decline in lung function.

The findings of the present investigation lend support to the hypothesis that allergy is a host factor which predisposes individuals to the development of chronic airflow obstruction. The exclusion of subjects who reported ever having asthma suggests that the observed effect of atopy on longitudinal change in lung function reflects the development of chronic, rather than reversible, airflow obstruction; however, that cannot be directly demonstrated in this study. The magnitude of the observed effect of atopy on the rate of decline of lung function is potentially important. The excess decline of lung function associated with a mean wheal size $\geq$ 2 mm, a level of skin test reactivity with a prevalence of 22% in this cohort, was more than one-third as great as the effect of current cigarette smoking, the most important known risk factor for COPD. The effect of atopy on the rate of decline of lung function was additive with the effect of cigarette smoking.

The mechanisms by which atopy is associated with excess decline of lung function are unknown. Airway deposition of in-

haled aeroallergens is widely accepted as a cause of asthma (20); it is possible that airway deposition of allergens, in a susceptible individual, could elicit inflammatory processes leading to irreversible airflow obstruction. For example, mediators released by degranulation of mast cells in response to specific antigen are capable of recruiting monocytes and granulocytes (21), cells that are implicated in the pathogenesis of chronic airflow obstruction (1). Such mechanisms may be important in the development of emphysema in nonsmokers with severe asthma, who often have emphysema demonstrable on high-resolution computed tomography of the lungs (22), and may contribute to the development of chronic airflow obstruction in nonasthmatics as well.

In summary, we have found that skin test reactivity to four common aeroallergens is significantly related to the subsequent rate of decline of lung function in a cohort of middle-aged and older men without a history of asthma. The discrepancy between this finding and previous reports which found no such association may be related to the prospective design and larger sample size of this study, the exclusion of subjects with asthma, the older age of the subjects in this study, and the measure of skin test reactivity employed. The magnitude of the observed effect suggests that atopy may be an important contributing cause of COPD in some individuals.

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