

Indoor allergens and longitudinal FEV₁ decline in older adults: The Normative Aging Study

Scott T. Weiss, MD,^a George T. O'Connor, MD,^b Deborah DeMolles, BA,^c
Thomas Platts-Mills, MD,^d and David Sparrow, DSc^c
Boston, Mass., and Charlottesville, Va.

We investigated the relationship between home allergen exposure and decline in FEV₁ in 10 asthmatic and 30 randomly selected, age-matched, nonasthmatic participants in the Normative Aging Study. We defined asthma as subject-reported wheezing apart from colds, with either a physician's diagnosis of asthma or a methacholine PD₂₀ FEV₁ of 8.6 μ mol or less. We examined the relationship between the annual decline in FEV₁ and the concentrations of the cockroach (*Blattella germanica*) allergens Bla g 1 and Bla g 2, the dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) allergens Der p 1 and Der f 1, and the cat (*Felis domesticus*) allergen Fel d 1 in house dust specimens. Bla g 1 (-79.8 ml/yr, $p = 0.0006$) and Bla g 2 (-40.81 ml/yr, $p = 0.0004$) were significant predictors of decline in FEV₁ after adjustment for age, smoking, and baseline FEV₁. These results were unchanged after elimination of the asthmatic subjects from the analysis. We conclude that cockroach allergen levels in homes is a risk factor for accelerated decline in FEV₁ independent of airway responsiveness. (J Allergy Clin Immunol 1998;101:720-5.)

Key words: Allergens, FEV₁, asthma, smoking

In 1961, Orie et al.¹ hypothesized that increased airway responsiveness and allergy might be endogenous factors predisposing individuals to the development of chronic bronchitis and emphysema. Subsequent data have indicated that increased airway responsiveness is a risk factor for accelerated decline in FEV₁ and hence a risk factor for the development of chronic obstructive pulmonary disease (COPD).²⁻⁵ To date, studies of population samples have used skin test reactivity^{4, 6-10} or serum total IgE concentration^{5, 9, 11-14} to assess the relation of allergy to decline or level of FEV₁, with conflicting results.

The acute asthmatic response to an inhaled allergen

Abbreviations used

COPD: Chronic obstructive pulmonary disease
NAS: Normative Aging Study

depends on three factors: the degree of nonspecific airway responsiveness, sensitization, and allergen dose.¹⁵ The late asthmatic response to inhaled allergen appears to result from the bronchial mucosal inflammation that follows mast cell degranulation. In perennial allergic asthma chronic allergen exposure results in persistent airway inflammation,¹⁶ which may in turn cause airway remodeling^{17, 18} and chronic (irreversible) airflow obstruction. Whether such a process occurs in persons without overt asthma is unknown. Thus far no data have been reported regarding this potential influence of long-term exposure to indoor allergens on longitudinal decline in lung function.

The purpose of this study was to evaluate the relationship between in-home exposure to five common aeroallergens and the rate of decline in pulmonary function. The population assessed in this analysis was a subset of individuals followed-up as part of the Normative Aging Study (NAS), an ongoing investigation of risk factors for the development of COPD.

METHODS

Population

The NAS is a longitudinal study of aging established by the Veterans Administration in 1961.¹⁹ The study cohort consists of 2280 community-dwelling men from the Greater Boston area who were 21 to 80 years of age at the time of enrollment. Volunteers were screened at entry according to specific health criteria¹⁹ and were free of known chronic medical conditions at the outset. In particular, volunteers with asthma, chronic bronchitis, or chronic sinusitis were excluded from the study.

Since entry into the study, the men have reported for periodic examinations, each including a uniform medical history and a physical examination along with blood and urine tests. Since 1984, additional tests have included methacholine inhalation challenge, allergy skin tests, and determination of serum total IgE concentration. Subjects are instructed to refrain from eating and drinking after midnight and to refrain from smoking after 8 pm the night before each examination. The protocol for this study was approved by the Human Studies Subcommittee, Department of Veterans Affairs Outpatient Clinic; written informed consent was obtained from all subjects.

From ^aChanning Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston; ^bPulmonary Center, Department of Medicine, Boston University School of Medicine, Boston; ^cNormative Aging Study, VA Outpatient Clinic, Boston; and ^dthe Division of Allergy, Department of Medicine, University of Virginia Medical Center, Charlottesville.

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Reprint requests: Scott T. Weiss, MD, MS, Channing Laboratory, 181 Longwood Ave., Boston, MA 02115.

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TABLE I. Characteristics of 40 male NAS subjects who provided indoor dust specimens for allergen analyses

Characteristic	Value*	
	Nonasthmatic subjects (n = 30)	Asthmatic subjects (n = 10)
Age (yrs)	59.60 ± 1.09	57.50 ± 2.58
Height (cm)	177.21 ± 1.26	174.42 ± 2.33
Smoking status		
Current (%)	1 (3.3)	3 (30.0)
Former (%)	19 (63.3)	6 (60.0)
Never (%)	10 (33.3)	1 (10.0)
Baseline lung function†		
FEV ₁ (% predicted)	101.33 ± 2.97	69.81 ± 5.52
FVC (% predicted)	103.89 ± 2.42	80.41 ± 4.43
FEV ₁ /FVC (% predicted)	96.90 ± 1.69	85.42 ± 4.06

FVC, Forced vital capacity.

*Values are expressed as means ± SEM except for smoking status, which is expressed as number (percentage) of subjects.

†Predicted values are from regression equations based on asymptomatic subjects who never smoked in the NAS cohort.

Questionnaire data

Standard questionnaires based on the American Thoracic Society²⁰ questionnaire were used to obtain information on respiratory symptoms and illnesses, as well as smoking habits. Current smokers were defined as those men who were smoking at least one cigarette per day within 1 month before the examination. Former smokers were defined as those men who had previously smoked at least one cigarette per day but who had ceased smoking more than 1 month before the examination. Never smokers were defined as those men who had never smoked cigarettes or who had smoked less than a total of 20 packs during their lifetime. Subjects who reported that they used to have or still had a doctor's diagnosis of asthma were considered former and current asthmatic subjects, respectively.

Home dust samples

In September to October 1993 and May 1995, each NAS subject collected dust samples from his home and filled out a questionnaire about his home environment. The questionnaire and a lightweight Eureka (Mighty Mite II) vacuum cleaner modified with a cellulose filter were sent to and picked up from subjects' homes by overnight courier. Specific instructions for dust collection were supplied with the vacuum. Subjects obtained dust samples separately from three rooms (living room, bedroom, and kitchen). The living room samples were obtained from the chair or sofa that subjects used most and from the floor surface, which was vacuumed for a minimum of 5 minutes underneath and around the chair or sofa. The bedroom samples were obtained from the surfaces of the mattress and bedding and from the floor surface, which was vacuumed for at least 5 minutes underneath and around the bed. The kitchen samples were obtained from floor areas adjacent to walls and cabinets and from the floor of the under-sink cabinet. The dust was weighed, sifted, and aliquoted for analysis by two-site monoclonal antibody-based ELISA.²¹⁻²³ Assays for the specific dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) allergens Der p 1 and Der f 1 and for the major cat (*Felis domesticus*) allergen Fel d 1 were performed by Vespa Laboratories (Spring Mills, Pa.), and the assays for the major

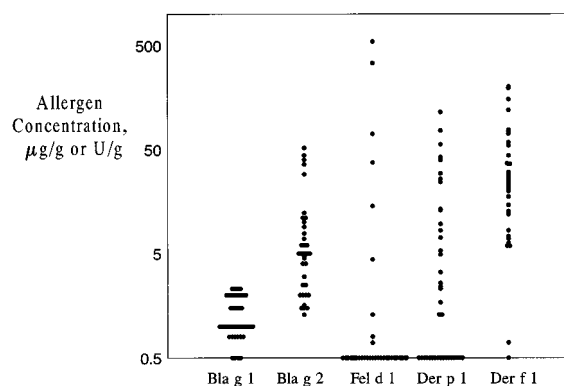


FIG. 1. Concentrations of five indoor allergens expressed in micrograms per gram (Der p 1, Der f 1, or Fel d 1) or units per gram (Bla g 1 or Bla g 2) of fine dust from homes of 40 men participating in Normative Aging Study.

cockroach (*Blattella germanica*) allergens Bla g 1 and Bla g 2 were performed by one of the authors (T.P.-M.). The lower detection limits for the assays were 0.5 µg/g for mite allergens, 0.5 µg/g for cat allergen, 0.1 U/g for Bla g 1, and 0.5 U/g for Bla g 2. Recent evidence suggests that 1 U of the cockroach allergen Bla g 2 is approximately 40 ng of protein.²⁴ Allergen concentrations were analyzed in units or micrograms per gram of fine dust. In analyses of the results, the highest level of each allergen (of the three samples) in a house was taken as an index of exposure to that allergen.²⁵

Pulmonary function testing

Subjects performed forced vital capacity maneuvers in the standing position with a noseclip using a water-filled recording spirometer (Warren E. Collins, Braintree, Mass.). Each subject performed three acceptable maneuvers, and the maneuver with the highest forced vital capacity was chosen for all spirometric determinations. FEV₁ was measured by standard techniques²⁰ and corrected to body temperature and pressure saturated with water vapor. Spirometric data had been collected for each participant every 3 to 5 years since the establishment of the NAS in 1961. The two most recent spirometric examinations before the collection of home dust samples were considered for analysis. The mean interval between the first and second spirometric examinations was 3.79 ± 2.46 years, and the minimal interval was 2.7 years. The mean annual decline in FEV₁ was calculated as the first value subtracted from the second value divided by the number of years between observations.

Methacholine challenge testing

Methacholine challenge was performed as previously reported.^{26,27} Subjects underwent a methacholine challenge protocol adapted from that of Chatham et al.²⁸ Saline and methacholine solutions were aerosolized with a DeVilbiss 646 nebulizer attached to a DeVilbiss air compressor (DeVilbiss, Somerset, Pa.). All inhalations were 6-second vital-capacity inhalations followed by 2 seconds of breath-holding. Incremental doses of methacholine were inhaled at 5-minute intervals according to the following schedule: five inhalations of 0 mg/ml (phenol-buffered saline alone), 1 inhalation of 1 mg/ml, 1 inhalation of 5 mg/ml, 4 inhalations of 5 mg/ml, 1 inhalation of 25 mg/ml, and 4 inhalations of 25 mg/ml. Determination of nebulizer output by weight²⁷ indicated that the methacholine inhalation schedule corresponded to the following cumulative

TABLE II. Relation of antigen level ($\log_{10}$ U/gm or $\log_{10}$ μ g/gm) to decline in FEV₁ (ml/yr)

Antigen	Total sample (n = 40)			Nonasthmatic subjects (n = 30)		
	Regression coefficient*	SEM	p Value	Regression coefficient*	SEM	p Value
Bla g 1	-194.14	47.35	0.0002	-144.81	52.65	0.01
Bla g 2	-94.83	25.33	0.0007	-80.64	21.91	0.001
Der p 1	14.38	11.45	0.2	11.71	12.11	0.3
Der f 1	-3.86	19.36	0.8	10.30	17.55	0.6
Fel d 1	-9.22	11.09	0.4	-17.80	11.08	0.1

*Regression coefficients are from multiple linear regression models of the form FEV₁ decline (ml/yr) = $a + b_1 \times \text{age (yr)} + b_2 \times \text{initial FEV}_1 \text{ (ml)} + b_3 \times \text{ever smoking (0,1)} + b_4 \times \text{allergen concentration (}\log_{10} \text{ U/gm for Bla g 1 and Bla g 2, } \log_{10} \mu\text{g/gm for other allergens)}$.

doses of methacholine (in micromoles): 0, 0.330, 1.98, 8.58, 16.8, and 49.8. Spirometry was performed 30, 90, and 180 seconds after inhalation of each dose. If the first two spirometers at each level were consistent (FEV₁ within 5%), then the higher FEV₁ of these two was chosen for the analysis. Otherwise, the higher FEV₁ from the two most consistent acceptable spirometers was used. The test was terminated when a 20% decline in FEV₁ from the postsaline value occurred or at the end of the dose schedule if such a decline did not occur.

Skin testing

After completion of the methacholine challenge test, skin testing was performed as previously described²⁶ by the prick method of Pepys.²⁹ Subjects were tested in a double-blind fashion with the following aeroallergen preparations preserved in glycerin (supplied by Hollister-Stier/Miles, Spokane, Wash.): ragweed (1:20, wt/vol), mixed trees (1:20), mixed grasses (1:20), house dust (1:10), mixed cockroach (German, American; 1:10), standardized *D. farinae* (30,000 AU/ml), standardized *D. pteronyssinus* (30,000 AU/ml), and standardized cat hair (10,000 BAU/ml), along with a glycerin control. Wheal reactions were measured at 20 minutes as the sum of the largest wheal diameter plus the perpendicular diameter divided by 2. A positive skin test reaction was defined as a mean wheal diameter of 2 mm or more after subtraction of any wheal reaction to the glycerin control.

Study sample

The subjects were 10 asthmatic and 30 randomly selected, age-matched, nonasthmatic men who had reported for their regularly scheduled NAS examination during the 2 years preceding the collection of dust. Each subject had lived in the same home throughout the period between the first spirometric examination and home dust collection. Subjects were considered to have asthma if they reported wheezing apart from colds in combination with either a physician's diagnosis of asthma or a methacholine PD₂₀ FEV₁ of 8.6 μ mol or less. Subjects were considered to be nonasthmatic if they had no history of wheezing or asthma and had a methacholine PD₂₀ FEV₁ of greater than 49.8 μ mol. Nonasthmatic subjects were selected by stratified random sampling across decline in FEV₁ (quintiles) to ensure that a range of declines in FEV₁ was represented.

RESULTS

The characteristics of the 40 subjects are shown in Table I. The subjects' mean age was 59.1 years. The relatively low prevalence of current cigarette smoking (10%) reflects both age-related trends and heightened health consciousness in this group of men, who have

been participating in the NAS for more than 20 years. Baseline lung function was within normal limits. Only four subjects (one patient and three control subjects) reported having a cat in the home. The prevalences of positive results in allergy skin tests were as follows: cockroach extract, 54% (20 of 37); Der f extract, 34% (13 of 38); house dust extract, 21% (eight of 38); and cat hair extract, 12% (three of 25).

The allergen levels in the 40 homes sampled ranged widely (Fig. 1). Of the five allergens measured, Fel d 1 was the most likely to be below detectable limits (31 of 40 subjects, 78%).

Multiple linear regression was used to examine the relation of current dust allergen levels (the highest level among the three rooms sampled) to FEV₁ decline between the last two NAS examinations. After adjustment for initial FEV₁, smoking status, and age, the decline of FEV₁ was not related to the concentration of Der p 1, Der f 1, or Fel d 1. However, there was a significant association between the concentration of Bla g 1 and the decline in FEV₁ after adjustment for other covariates (Table II). Results nearly identical to those for Bla g 1 were obtained for Bla g 2. When subjects with asthma were excluded from analysis, the results were very similar. There were statistically significant associations between the decline in FEV₁ and concentrations of both Bla g 1 and Bla g 2 (Table II). These relations for all 40 subjects are shown in Figs. 2 and 3.

The relation of each allergen concentration to the rate of FEV₁ decline was examined separately for subjects with and without a positive skin test reaction to the allergen (Table III). Among subjects with a positive skin test reaction to cockroach extract, the rate of FEV₁ decline was significantly related to the concentration of both Bla g 1 and Bla g 2. Among subjects with a negative skin test reaction to cockroach extract, these relations were weaker. Regardless of skin test reactivity, the concentration of Fel d 1 and Der f 1 did not appear to be related to the rate of FEV₁ decline. The relation of Fel d 1 concentration to the rate of FEV₁ decline could not be assessed in subjects with a positive skin test reaction to cat extract because of small numbers ($n = 3$). Among subjects with negative skin test reactions, the concentration of Fel d 1 was not significantly related to the rate of FEV₁ decline.

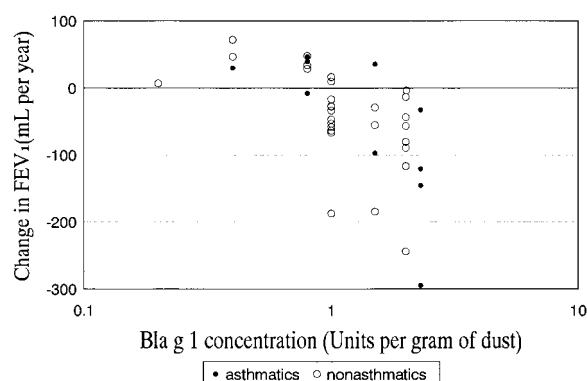


FIG. 2. Scatterplot of relation between longitudinal change in FEV₁ and concentration of Bla g 1 in indoor dust among 40 men participating in Normative Aging Study.

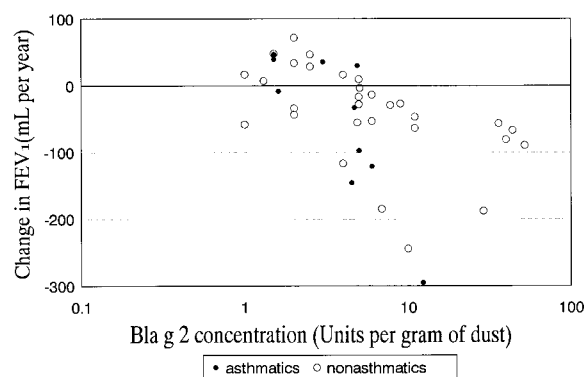


FIG. 3. Scatterplot of relation between longitudinal change in FEV₁ and concentration of Bla g 2 in indoor dust among 40 men participating in Normative Aging Study.

TABLE III. Relation of antigen level (log₁₀ U/gm or log₁₀ µg/gm) to decline in FEV₁ (ml/yr) stratified by skin test reactivity to the antigen

Antigen	n	Negative skin test reaction			n	Positive skin test reaction		
		Regression coefficient*	SEM	p Value		Regression coefficient*	SEM	p Value
Bla g 1†	17	-88.63	73.71	0.3	20	-312.67	75.90	0.0009
Bla g 2†	17	-81.51	30.44	0.02	20	-149.95	55.53	0.02
Der p 1‡	30	23.82	14.29	0.1	8	-29.71	26.12	0.3
Der f 1	25	-5.47	24.83	0.8	13	88.13	63.19	0.2
Fel d 1§	22	-32.02	19.40	0.1	3			

*Regression coefficients are from multiple linear regression models of the form FEV₁ decline (ml/yr) = a + b₁ × age (yr) + b₂ × initial FEV₁ (ml) + b₃ × ever smoking (0,1) + b₄ × allergen concentration (log₁₀ U/gm for Bla g 1 and Bla g 2, log₁₀ µg/gm for other allergens).

†Skin test reactivity with mixed cockroach (American, German) extract.

‡Skin test reactivity with house dust extract.

§Skin testing with cat hair extract was introduced later. Therefore only 25 subjects have data for this variable. A regression analysis was not performed for the three subjects with a positive skin test reaction to cat hair extract.

To address the possibility that an apparent association between cockroach allergen concentration and FEV₁ decline could be confounded by socioeconomic status, we repeated the multiple regression analysis using models that included variables for the Duncan Socioeconomic Index³⁰ and the level of educational attainment. Adjustment for socioeconomic status and level of education in this manner did not alter the relation of FEV₁ decline to allergen level (data not shown).

We repeated the analysis using pack-years of smoking as a continuous variable instead of using a dichotomous variable for ever smoking. There was no difference in results (data not shown).

DISCUSSION

Indoor dust concentrations of cockroach allergens (Bla g 1 and Bla g 2) were significantly related to decline in FEV₁ among 10 asthmatic and 30 nonasthmatic middle-aged and older men participating in the NAS. No significant relation was demonstrated for Der p 1, Der f 1, or Fel d 1. The relation between allergen exposure and decline in FEV₁ was not limited to asthmatic

subjects. Restriction of the analysis to the 30 nonasthmatic subjects revealed substantially similar relationships. The relation between Bla g 1 concentration and the rate of FEV₁ decline was significant among subjects with a positive skin test reaction to cockroach extract but not among subjects with a negative skin test reaction. The relation of Bla g 2 concentration to FEV₁ decline was significant regardless of skin test reactivity but was stronger among participants with a positive skin test reaction to cockroach extract.

Although exposure to indoor aeroallergens has been shown to aggravate asthma and possibly even to cause it,^{31,32} the potential role of such exposure as a cause of accelerated longitudinal decline in lung function during adulthood has not previously been studied. Asthma,³³⁻³⁵ allergy to common aeroallergens,⁶ and airway hyperresponsiveness²⁻⁵ have all been linked to accelerated lung-function decline, and the latter two associations are evident even among subjects without asthma.^{3,4,6} It is hypothesized that allergic airway inflammation after inhalation of an allergen by a sensitized person may result in ongoing airway damage and remodeling, leading ultimately to accelerated longitudinal deterioration

of lung function and the development of chronic airflow obstruction. Whether the observed relation of allergen exposure to longitudinal FEV₁ decline reflects reversible airway inflammation, irreversible airway remodeling, or other mechanisms can not be determined from the present data.

It is well recognized that hypersensitivity to cockroach antigen is common among urban asthmatic populations. In asthmatic subjects, cockroach sensitization is associated with higher IgE levels and greater steroid dependency.^{36,37} High indoor levels of cockroach allergen have been reported to correlate significantly with asthma morbidity in inner-city children.³⁸ No data are available regarding the impact of cockroach hypersensitivity and exposure on the natural history of disease and longitudinal pulmonary-function decline.

The greater impact of cockroach allergen than of other allergens on FEV₁ decline has a likely explanation: there was a higher prevalence of skin test reaction positivity to cockroach allergen (54%) than to cat allergen (12%), Der f (34%), or house dust (21%). One would expect allergen-induced airway inflammation and subsequent airway remodeling and lung-function decline to be limited to persons with hypersensitivity to the allergen. The small number of subjects with skin test reactivity to cat and mite allergen limits the power of this study to assess with confidence whether exposure to these allergens may have a similar impact on FEV₁ decline.

It is important to recognize certain limitations of this study. First, aeroallergen exposure in home house dust was assessed at the end of the study period. As noted in the Methods section, however, each participant resided in the same residence for the 3 years of observation. In addition, recall bias is not of concern in that exposure was assessed objectively by blinded investigators. The second major limitation of our investigation is the small sample size. We believe that a larger sample size would have provided a better test of the hypothesis that cat and house dust mite allergens contribute to accelerated decline in FEV₁. Finally, despite our best effort to adjust for socioeconomic status, in any observational study there remains the possibility of residual confounding because of incomplete adjustment for covariates such as socioeconomic status.

Our data do not permit discrimination between reversible and irreversible obstruction. It is possible that allergen avoidance and treatment with corticosteroids would result in improvement of FEV₁ in some subjects with excess FEV₁ decline. It is equally possible, however, that such FEV₁ loss is irreversible. Recent evidence suggests that chronic airway inflammation in persons with asthma may result in airway remodeling,^{17,18} with the consequent irreversible airflow obstruction seen in some patients with chronic asthma. Our data suggest that such a process may also take place in hypersensitive persons who are chronically exposed to high levels of allergen but who are not clinically asthmatic.

In conclusion, exposure to high concentrations of cockroach allergen is associated with accelerated pulmo-

nary-function decline in asthmatic as well as nonasthmatic subjects. In our study this relation was stronger among subjects with immediate cutaneous hypersensitivity to cockroach extract. Larger studies measuring exposure to indoor allergens would be of value in precisely quantifying exposure and its relationship to FEV₁ decline. Such studies would also be helpful in determining the relations among exposure levels, sensitization, and airway responsiveness and the roles of these variables in the development of COPD.

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