

Sensitization to Dust Mites as a Dominant Risk Factor for Asthma among Adolescents Living in Central Virginia

Multiple Regression Analysis of a Population-based Study

SUSAN P. SQUILLACE, RICHARD B. SPORIK, GARY RAKES, NICOLLE COUTURE, ANDREW LAWRENCE, SUSAN MERRIAM, JUAN ZHANG, and THOMAS A. E. PLATTS-MILLS

Departments of Medicine, Pediatrics, Family Practice, and Statistics, University of Virginia, Charlottesville, Virginia

Factors influencing asthma were investigated in a population of school children in central Virginia. A survey of 1,054 children in two middle schools (one urban and one suburban) identified 135 students with symptoms suggestive of asthma. Eighty-eight symptomatic children and 123 control subjects were randomly selected for further evaluation by skin testing using common indoor and outdoor allergens; serum assays for total IgE and specific IgE; dust samples assayed for mite (*Der p 1* *Der f 1*), cat (*Fel d 1*), and cockroach (*Bla g 2*) allergens; and provocation with histamine to test for bronchial hyperreactivity. Forty-eight of the children with symptoms responded to ≤ 3.9 μmol of histamine and were considered to have asthma. Marginal analysis identified elevated total IgE and dust mite, cat, and cockroach sensitization as significant risk factors for asthma. Using multiple regression, only dust mite sensitization was independently associated with asthma (odds ratio = 6.6; $p < 0.0001$). Dust from 81% of the houses contained high levels of mite allergen (> 2 $\mu\text{g/g}$), while $\sim 40\%$ of the children were exposed to cat and 17% were exposed to cockroach allergen. In this population, there was no significant association between asthma and race, socioeconomic status, home smoking, sensitization to outdoor allergens, or allergen concentration in the child's home. In an area where there is a high prevalence of asthma and most houses contain high concentrations of dust mite allergen, sensitization to this allergen is the dominant risk factor for asthma defined as symptomatic bronchial hyperreactivity. Squillace SP, Sporik RB, Rakes G, Couture N, Lawrence A, Merriam S, Zhang J, Platts-Mills TAE. Sensitization to dust mites as a dominant risk factor for asthma among adolescents living in central Virginia: multiple regression analysis of a population-based study.

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The rise in asthma prevalence, morbidity, and mortality over the past three decades has been well documented. Of particular concern in the United States is the fact that asthma has become a disease of all sections of the population and indeed deaths are more common among young socioeconomically disadvantaged patients (1-3). Both case control and prospective studies of children and young adults have shown a strong relationship between sensitization to indoor allergens and asthma (4-7). Furthermore, studies from several countries have demonstrated a quantitative relationship between allergen in houses and sensitization of asthmatics (7-12). Many different factors, apart from changes in houses, have been proposed as contributing to asthma, e.g., diet, passive smoke, and air pollution. Taking studies from different parts of the world,

the role of outdoor air pollution appears to be modest (8, 13-15). In addition, in most studies, sensitization to outdoor pollens does not contribute significantly to the risk of developing asthma (4-8, 10, 11). Indeed, the only outdoor allergen that has been consistently associated with chronic bronchial hyperreactivity (BHR) is *Alternaria* (11, 16, 17). Population-based studies of school-age children in Australia and south-east Asia have demonstrated the association between hypersensitivity to dust mite allergens and asthma (11, 18, 19). In areas of the world where, because of high humidity dust mites flourish in houses, the association between asthma and sensitization to mites of the genus *Dermatophagoides* is so strong that it seems highly probable that there is a causal relationship (8, 20). Population-based studies in the United States have reached different conclusions. Burrows and colleagues in 1989 reported that there was a strong association between asthma and total serum IgE but not with specific skin tests (21). Further studies from the same group have identified *Alternaria* sensitization as relevant to asthma (16). By contrast, our studies on school children in New Mexico demonstrated that sensitization to cat or dog allergens was strongly associated with BHR (10). More recently, a major study in the northeastern United States has demonstrated that importance of cockroach sensitization and exposure to the severity of asthma among inner-city children

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Correspondence and requests for reprints should be addressed to Thomas A. E. Platts-Mills, M.D., Ph.D., University of Virginia Asthma and Allergic Diseases Center, Box 225 Health Sciences Center, Charlottesville, VA 22908.

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(22). Thus, although there have been case control studies showing an association between dust mite sensitization and asthma, there has been very little population-based evidence that this applies to asthma in the United States. Equally important, there have been no studies that have used objective measures of bronchial reactivity which would allow estimates of the prevalence of asthma and comparison of different risk factors in a population that is representative of a large proportion of the United States. The current study applies a well-defined investigative protocol to a population of rural and urban, caucasian and African-American middle school children living in an area that is typical of the humid areas of the United States (10, 11). Information was obtained on a random sample of children about symptoms, BHR, sensitization to allergens, and the concentration of allergens in their houses. The results were analyzed using multiple regression to identify risk factors that separate subjects into three groups: asymptomatic, symptomatic but without objective evidence of asthma, and symptomatic with demonstrable BHR.

METHODS

A respiratory questionnaire based on Woolcock's modified ATS questionnaire for children was administered in all science classes in two middle schools (one suburban and one urban) in central Virginia during September of 1992 and 1993, respectively (10, 11). A similar questionnaire was mailed to parents prior to the school visit. Students were considered symptomatic if the child or parent answered three or more questions related to asthma symptoms positively. Control subjects were randomly selected using a random-number table from all students who were not judged to be symptomatic. All symptomatic patients and a similar number of control subjects were recruited for further evaluation. In the urban middle school, African-American children constituted 49% of the children answering questionnaires, 53% of the children reporting symptoms of asthma, and 56% of the symptomatic children studied in detail.

Evaluations included skin-prick testing (using a lancet technique), histamine provocation, and serum collection (10, 11). Subjects were tested to extracts of *Dermatophagoides farinae*, *D. pteronyssinus*, cat dander, mixed cockroach, grass pollen, Eastern tree pollen mix, mixed ragweed, and histamine (1 mg/ml) and diluent controls (kindly provided by Hollister-Stier/Bayer, Spokane, WA). Skin tests with a mean wheal diameter ≥ 4 mm after 15 min of observation were considered positive. Bronchoprovocation was performed with a DeVilbiss hand-held nebulizer using the method described by Yan (7, 10, 23). A PD_{20} of ≤ 3.9 μ mol cumulative dose of histamine was interpreted as indicating BHR. Twenty subjects underwent repeat bronchoprovocation within 2 mo of their initial evaluation to validate the reproducibility of the bronchoprovocation results. In 18 cases, the repeat result was within 1 doubling dilution and in no case was the classification changed. Serum was assayed for IgE antibody to dust mites (*D. pteronyssinus* and *D. farinae*), cat dander, German cockroach, and grass, tree, and ragweed pollen using the RAST technique. Total serum IgE was determined using a two-site ELISA and was classified as elevated (total IgE > 40 IU) or highly elevated (total IgE > 200 IU).

All subjects recruited for skin testing and bronchial provocation were offered a home visit. During home visits, dust was collected from the bedding, bedroom floor, living room (sofa and carpet/flooring), and kitchens using standard techniques. Dust was extracted in buffered saline using previously described methodology, and the resulting extracts were assayed for Group I mite allergens, *Fel d 1* and *Bla g 2*, using two-site monoclonal antibody-based assays (24–26). Results were expressed in micrograms of allergen per gram of sieved dust. Thresholds for clinical important exposure used for this analysis were 2 μ g/g for Group I mite allergen, 8 μ g/g for the cat allergen *Fel d 1*, and 2 U/g for the cockroach allergen *Bla g 2* (6–8, 27). Recent results have suggested that the Unit of *Bla g 2* is equivalent to 40 ng (27).

Incomplete questionnaires were addressed at the home visit. Information regarding home smoking was solicited in the initial questionnaire and confirmed at the home visit. Home value was determined from 1994 local government assessments through public records.

Statistical analysis was done using logistic multiple regression (28). Initially, a univariate analysis (i.e., analysis performed without adjusting for any of the covariates) was performed to see how each potential explanatory variable [e.g., race, sensitivity, exposure] effected the probability of each subject falling into one of three groups: control [C], symptomatic but without BHR [Sx], or symptomatic with BHR [i.e., asthma] [A]. Ordered categorical analysis was undertaken assuming the patient groups were in the order A, Sx, C. Variables declared statistically nonsignificant by the univariate analysis were dropped from future analyses. Variables found to be statistically significant in the univariate analysis were then tested in a combined analysis that served to control for the influence of each explanatory variable on the other variables studied. For each analysis performed, a test of uniform association was applied to determine if the three patient groups could be evaluated with a single odds ratio (28). This test compares the odds of control subjects versus all symptomatic subjects and the odds of non-asthmatics versus asthmatics. In cases where the analysis failed the test of uniform association, odds ratios were expressed separately for the symptomatic versus nonsymptomatic model (C versus Sx and A) and for the asthmatic versus nonasthmatic model (C and Sx versus A). Results are presented as odds ratios (OR) and 95% confidence interval (CI).

RESULTS

Ninety-five percent of the students enrolled in the schools studied completed questionnaires ($n = 1,054$). The questionnaire identified 135 students with symptoms suggestive of asthma who were invited to take part in the second phase of the study. Eighty-eight of these (33 African-American and 55 caucasian) along with 123 control subjects (32 African-American and 91 caucasian) were recruited for skin tests, blood tests, and bronchial provocation with histamine. The response rate for these studies was 65% for symptomatic children and 52% for asymptomatic children. House visits were made to 194 (54 African-American and 140 caucasian) of the 211 subjects.

Histamine bronchoprovocation of the 88 symptomatic students studied identified 48 students with $PD_{20} \leq 3.9$ μ mol of histamine. The rate of BHR among tested symptomatic subjects was significantly different from the rate among tested asymptomatic control subjects (48 of 88 versus 14 of 123) ($p < 0.0001$). If it is assumed that the prevalence of BHR among the untested symptomatic subjects was similar to the rate among tested subjects, we would predict a total of 74 students with symptomatic BHR (6.7% of the total population).

Statistical Analysis

Race was not significantly associated with subject group ($p = 0.11$): African-American subjects were equally distributed among the three groups (26% of controls, 40% of symptomatic, and 35% of asthmatic subjects). In the univariate analysis, other explanatory variables that were not significantly associated with patient group included: sensitivity to grass mix and ragweed; the quantitative measurement of exposure to mite, cat, or cockroach in the patient's home; and home value. In this analysis, home smoking was not significantly associated with asthma or symptoms (Table 1). From parental questionnaires ($n = 441$), 28% of the symptomatic children and 26% of the control subjects were exposed to a smoker at home. Sensitivity to each of the three indoor allergens (i.e., dust mite, cat, and cockroach) as well as elevated levels of serum IgE (≥ 40 and ≥ 200 U) and sensitivity to tree mix were significantly associated with patient group (Table 1). All univariate analyses passed the test for uniform association.

The multivariate regression analysis that included all variables found to be statistically significant in the original analysis

TABLE 1
UNIVARIATE ORDINAL ANALYSIS OF POTENTIAL RISK FACTORS IN PATIENT GROUPS*

Risk Factor	n	Control Subjects (n = 123)	Symptomatic Subjects (n = 40)	Asthmatic Subjects (n = 48)	Odds Ratio† (95% CI)
Race, % African-American	211	26	40	35	1.57 (0.89–2.8) ^{ns}
Home value, \$	183				
< 60,000		24	20	28	0.8 (0.38–1.7) ^{ns}
60,000 to 150,000		35	54	35	
> 150,000		41	26	37	
Home smoking	153	19	24	33	1.9 (0.92–3.8) ^{ns}
Specific sensitization‡					
Mite	211	16	48	73	8.3 (4.6–15) ^a
Cat	211	7	8	31	5.1 (2.3–11) ^a
Cockroach	211	6	25	25	3.8 (1.8–8.1) ^b
Rye	211	17	38	25	1.7 (0.94–3.2) ^{ns}
Ragweed	211	8	20	17	1.9 (0.86–4.1) ^{ns}
Tree mix	211	7	20	20	2.7 (1.2–5.9) ^c
Total serum IgE					
IgE > 40 IU	175	50	90	90	8.6 (3.6–20) ^b
IgE > 200 IU	175	20	30	56	3.7 (1.9–6.9) ^b
Exposure to allergen§					
Mite					
2 µg	194	84	68	81	0.89 (0.39–2.1) ^{ns}
10 µg	194	64	41	37	0.6 (0.29–1.2) ^{ns}
Cat, 8 µg	194	42	35	33	0.7 (0.4–1.3) ^{ns}
Cockroach					
2 U	194	16	11	26	1.1 (0.42–3.1) ^{ns}
10 U	194	8	8	14	1.7 (0.68–4.3) ^{ns}

* Data are expressed as percentage of subjects with each risk factor.

† Odds ratio for the three groups with 95% confidence interval. Significance: ^ap < 0.0001; ^bp < 0.001; ^cp < 0.05; ^{ns}nonsignificant.

‡ Sensitivity to allergen as measured by skin-prick testing or RAST.

§ Exposure to allergen as measured by sampling of dust in home expressed in µg/g or U/g.

failed the test for uniform association and, therefore, results are presented separately. In the combined analysis comparing the asthmatic subjects with nonasthmatic subjects (control and symptomatic children), sensitivity to house dust mite was the only risk factor independently associated with patient group (OR = 6.6, CI = 3.1–14) (Table 2A). Subjects sensitized to house dust mite were almost seven times more likely to be asthmatic than subjects not sensitized to mite. The multivariable analysis comparing control subjects to all symptomatic subjects (symptomatic with and without BHR) found that sensitivity to dust mite as well as elevated levels of serum IgE were significantly associated with subject group (sensitivity to mite: OR = 5.4, CI = 2.5–11; IgE ≥ 40: OR = 4.2, CI = 1.6–10.9) (Table 2B).

DISCUSSION

The study sought to investigate risk factors associated with asthma in a population of school children living in the Southeast of the United States. In keeping with our previous case control studies on children and adults presenting to emergency rooms, it is clear that sensitization to indoor allergens was very strongly associated with asthma (4, 6, 29, 30). In the combined analysis, where the influence of each variable on the other variables was examined, the only factor that was independently associated with asthma was sensitivity to house dust mite. This is in keeping with results from other humid areas of the world (7, 8, 11). The questionnaire identified 12.3% of subjects as having symptoms suggestive of asthma, while the

TABLE 2A
MULTIVARIABLE REGRESSION ANALYSIS OF CONTROL/ SYMPTOMATIC SUBJECTS VERSUS ASTHMATIC SUBJECTS

Variable	Model 1	Model 2
	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Specific sensitivity		
Mite	4.8 (1.7–13) ^b	6.6 (3.1–14) ^a
Cat	2.7 (0.97–7.7) ^c	2.5 (0.95–6.4) ^{ns}
Cockroach	1.0 (0.36–2.8) ^{ns}	
Tree mix	1.0 (0.32–3.2) ^{ns}	
Total serum IgE		
IgE ≥ 40	1.5 (0.37–5.8) ^{ns}	
IgE ≥ 200	1.9 (0.76–4.7) ^{ns}	

In the first model, regression analysis was carried out including all factors found to be significant in the marginal analyses (Table 1). Those factors found to be nonsignificant were eliminated from the second model. Significance: ^ap < 0.0001; ^bp < 0.001; ^cp ≤ 0.05; ^{ns}nonsignificant.

TABLE 2B
MULTIVARIABLE REGRESSION ANALYSIS OF CONTROL SUBJECTS VERSUS SYMPTOMATIC/ASTHMATIC SUBJECTS

	Model 1	Model 2
	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Specific sensitivity		
Mite	6.5 (2.6–17) ^b	5.4 (2.5–11) ^a
Cat	0.8 (0.26–2.5) ^{ns}	
Cockroach	2.3 (0.83–6.6) ^{ns}	
Tree mix	2.3 (0.71–7.6) ^{ns}	
Total serum IgE		
IgE ≥ 40	3.4 (1.2–9.4) ^c	4.2 (1.6–11) ^c
IgE ≥ 200	0.7 (0.28–1.7) ^{ns}	

In the first model, regression analysis was carried out including all factors found to be significant in the univariate analyses (Table 1). Those factors found to be nonsignificant were eliminated from the second model. Significance: ^ap < 0.0001; ^bp < 0.001; ^cp ≤ 0.05; ^{ns}nonsignificant.

bronchial provocation results solidified the diagnosis in 6.7% of the population. This figure is similar to values from New Zealand, Australia, Scandinavia, and England, i.e., areas where an increase in asthma has been clearly documented.

Home smoking was not significantly associated with either symptoms alone or with symptomatic BHR. There was a trend to increasing symptoms and BHR related to parental smoking (OR = 1.8; $p = 0.08$). However, from the parental questionnaires, only 28% of the symptomatic children came from a home with a smoker, which was not different for the control subjects (26%). Home value based on 1994 assessments was analyzed at three levels: < \$60,000, \$60,000 to \$150,000, and > \$150,000. On this basis, 24% of subjects were classified as low, 39% as medium, and 37% as high socioeconomic status (SES) (63% of African-American subjects were thus classified as low and 37% as medium SES, while 13% of the Caucasians were low, 39% medium, and 48% high SES). In this socioeconomically diverse population living in a single area where race was strongly associated with home value, neither race nor home value was significantly associated with disease status. This is in contrast with inner-city studies in which race and low economic status have been reported to be predictors of disease status. In many of those investigations, cockroach was a ubiquitous allergen in the dwellings of those of low SES and was much less common in homes of the more affluent. In the population we studied, exposure and sensitization to cockroach allergens was predominantly found among low and medium socioeconomic groups (data not shown). This result confirms that sensitization is restricted to communities where children have significant exposure (8). However, within the community, exposure in individual houses was not significantly associated with disease (31).

The present results are in keeping with several recent studies in showing that sensitization to outdoor pollens is of much less importance than sensitization to allergens found indoors (5, 10, 11, 21). It has not been proved that increased exposure to indoor allergens is the cause of the increase in asthma. However, it is clear that most Americans spend the great bulk of their time indoors (32). Given the strength of the association between indoor allergen sensitization and chronic asthma, it is likely that the exposure inside houses has played a role in the epidemic of asthma. More than 80% of our subjects were exposed to elevated levels of mite allergen and 35% of those studied had developed immediate hypersensitivity to house dust mite. In contrast, less than 40% were exposed to cat allergen in their homes and only 17% were exposed to cockroach allergen. In areas where the allergen exposure pattern is different, other allergens are significantly and independently associated with disease (10, 16, 22, 33). In Los Alamos, New Mexico, and Sweden, sensitization to allergens derived from domestic animals has been associated with asthma (10, 33). In inner-city populations of the United States, sensitization to cockroach allergens is an important risk factor for asthma (6, 22, 30). A recent report from Tucson, Arizona found a high prevalence of positive skin tests to the airborne fungus *Alternaria* among school-age children with asthma (16). Although it is usually assumed that exposure to this fungus occurs outdoors, the distinctive spores are also found indoors and have been reported in homes from Arizona (34). The use of evaporative coolers in this arid region is known to produce high levels of fungal contamination. Thus, it is possible that significant exposure to fungal antigens occurs indoors in the Southwest.

Interestingly, in the regression analysis, elevated levels of serum IgE (i.e., IgE > 40) separated the control group from the symptomatic subjects (Table 2B) but did not separate the asthmatic from the nonasthmatic group (Table 2A). This re-

sult confirms the strong association between asthma and elevated total serum IgE that has been reported in cross-sectional and prospective studies (4, 7, 11, 21). The regression results suggest that elevated IgE is a consequence of specific sensitization and that it is sensitization to indoor allergens that is the primary risk factor for asthma. Our present results taken with those from other parts of the world and this country suggest that asthma is not a nonspecific response in persons genetically programmed to develop IgE antibody but is a specific response in those who are genetically at risk and who have become sensitized to common allergens in their environment.

Our results demonstrate among a diverse population living in a humid climate that dust mite sensitization is the dominant risk factor for asthma. At the same time, the study establishes using an objective test that there is a high prevalence (i.e., 6.7%) of symptomatic BHR in this community. We already know that asthma is associated with sensitization to other indoor allergens in different areas of the United States, i.e., cat or dog in New Mexico and German cockroach in the large cities of the Northeast (10, 22). Given that a large proportion of children with asthma are sensitized to indoor allergens and that moving children out of their houses produces improvement in symptoms and BHR, it is logical to assume that exposure to indoor allergens has played a role in the increased prevalence of perennial asthma (8). However, results obtained over the last few years create major conceptual problems for the hypothesis that increased exposure to indoor allergens is the cause of the increased prevalence. Changes in houses between 1960 and 1975 in some areas of Europe and in Australasia could have increased dust mite growth. However, it seems unlikely that concentrations of dust mite allergen have increased since 1975, either in those areas or the Southeast of the United States. Indeed, the concentrations of dust mite allergen found in the present study are not higher than those that we found in the United Kingdom in 1979 (7). It seems unlikely that dust mite, cockroach, and animal dander allergens have increased steadily over a 30-yr period in a wide range of countries. Thus, paradoxically the present results showing a strong association between dust mite sensitization and asthma do not support the hypothesis that increases the indoor allergens are the cause of the increase in asthma over the period of 1960 to 1990. Collectively, the evidence from different parts of the United States suggests that some ubiquitous aspect of Western society has either increased the response of the lungs to allergen exposure or increased the symptoms of allergic individuals. This issue has been discussed in detail elsewhere; however, it is clear that many different aspects of Western society could have enhanced the response to inhaled allergens (35). The changes that should be considered include those in: diet, outdoor air pollution, passive smoke, the complex changes associated with progressive increase in indoor entertainment, and the simple effects of spending more time indoors.

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