

Exposure to cockroach allergen in the home is associated with incident doctor-diagnosed asthma and recurrent wheezing

Augusto A. Litonjua, MD, MPH, Vincent J. Carey, PhD, Harriet A. Burge, PhD, Scott T. Weiss, MD, MS, and Diane R. Gold, MD, MPH *Boston, Mass*

Background: Indoor inhaled allergens have been repeatedly demonstrated to worsen asthma in sensitized individuals, but their role in incident asthma is more controversial.

Objective: We investigated the relationship between exposure to allergens (dust mite, cat, and cockroach) measured in the home and incident doctor-diagnosed asthma and recurrent wheezing in children born to parents with asthma, allergies, or both.

Methods: From an ongoing longitudinal family and birth cohort study, we identified 222 siblings (median age, 2.87 years) of the index children. Allergen levels in the home were measured from dust samples obtained at the beginning of the study. Incident doctor-diagnosed asthma and recurrent wheezing were determined from questionnaires administered at 14 months and 22 months after the initial questionnaire.

Results: Thirteen (5.9%) children were reported to have incident asthma, twenty (9.0%) children had recurrent asthmatic wheezing, and 18 (8.1%) had recurrent wheezing without asthma. Compared with children living in homes with Bla g 1 or 2 levels of less than 0.05 U/g, children exposed to Bla g 1 or 2 levels of 0.05 to less than 2 U/g had a relative risk for incident asthma of 8.27 (95% confidence interval, 1.04-66.04), whereas children exposed to Bla g 1 or 2 levels of 2 U/g or greater had a relative risk for incident asthma of 35.87 (95% confidence interval, 4.49-286.62). Cockroach allergen exposure was likewise a significant predictor for recurrent asthmatic wheezing. Neither dust mite nor cat allergen levels were significantly associated with either outcome. These findings remained after control for several covariates.

Conclusion: Exposure to cockroach allergen early in life may contribute to the development of asthma in susceptible children. (*J Allergy Clin Immunol* 2001;107:41-7.)

Key words: Cockroach, indoor allergens, asthma, wheeze

Abbreviations used

CI: Confidence interval
LRI: Lower respiratory tract illness
RR: Relative risk

Although indoor inhaled allergens have been repeatedly demonstrated to worsen asthma in specifically sensitized individuals, the role of these allergens in incident asthma is controversial. The strongest evidence for the association between allergen exposure and prevalent asthma has come from studies on dust mite allergen exposure and dust mite sensitization.¹ Studies have shown a dose-response relationship between exposure to dust mite allergens and sensitization in areas with high levels of exposure.^{2,3} Furthermore, sensitization to dust mite has been found to be a major risk factor for prevalent asthma in these areas.³

In areas where dust mite is not the dominant allergen, similar evidence for the relationship between exposure to other allergens and prevalent asthma has been observed.^{4,5} It has recently been shown that among children who have asthma and who are sensitized to cockroach allergen, exposure to high levels of cockroach allergen (Bla g 1 > 8 U/g) is associated with greater asthma morbidity.⁶ However, to date, only one study has prospectively shown a relationship between exposure to allergens (dust mite) early in life and the development of asthma.⁷

As part of an ongoing longitudinal epidemiologic study on children born to parents with asthma, allergies, or both, we collected information on children who were 5 years old or younger. The aim of this analysis was to determine the relationship of exposure to indoor allergens and the development of doctor-diagnosed asthma in these children. In addition, we investigated the relationship between exposure to these allergens and recurrent wheezing.

METHODS

Population and study sample

The subjects for this analysis were drawn from the siblings of the index children participating in the Epidemiology of Home Allergens

From Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston.

Presented in part at the 1998 American Thoracic Society International Conference, April 28, 1998, Chicago, Illinois.

Supported by grants HL07427 and AI35786 from the National Institutes of Health.

Received for publication June 7, 2000; revised August 22, 2000; accepted for publication August 23, 2000.

Reprint requests: Augusto A. Litonjua, MD, MPH, Channing Laboratory, 181 Longwood Ave, Boston, MA 02115.

Copyright © 2001 by Mosby, Inc.

0091-6749/2001 \$35.00 + 0 1/1/111143

doi:10.1067/mai.2001.111143

and Asthma study, an ongoing longitudinal family and birth cohort study, the primary aim of which is to examine the role of indoor home allergen exposure in the development of asthma-wheeze and allergic sensitization during early childhood in children whose parents have asthma or allergy. Recruitment and exclusion criteria have been detailed previously.⁸ In brief, 499 families were recruited between 1994 and 1996 within 48 hours of the birth of the index child at a tertiary hospital in Boston. If either parent had a history of doctor-diagnosed asthma, hay fever, or allergies, a screening questionnaire was administered, and if either parent was allergic to house dust or house dust mites, cockroaches, pollens, animals, or mold, then they were eligible for inclusion in the cohort.

At home visits conducted 2 to 3 months after the birth of the index child, a trained research assistant administered a detailed respiratory symptoms questionnaire for siblings of the index child who were 5 years of age or younger. The respiratory questionnaire was administered again by means of telephone when the index child was 16 months old. A revised sibling respiratory questionnaire was administered for a third time when the index child was 24 months old.

At the time of the first home visit, 246 siblings younger than 5 years were identified. Fourteen children had information from only one of the 3 questionnaires, and 11 children were not biologically related to the index child's mother, father, or both. This left 222 eligible children who had information from at least 2 of the 3 questionnaires. Of these eligible children, 171 did not have a doctor's diagnosis of asthma or recurrent wheezing during the period of follow-up, and these children comprised the reference group. Three subsets were created: (1) the incident asthma data set comprised the reference group and the children who did not have a doctor's diagnosis of asthma at the time of the first questionnaire but who did have this diagnosis at the time of either of the next 2 questionnaires; (2) the recurrent asthmatic wheezing data set comprised the reference group and the children who had ever had a doctor's diagnosis of asthma and who had recurrent wheezing during the period of follow-up; and (3) the recurrent nonasthmatic wheezing data set comprised the reference group and the children who had recurrent wheezing but who did not have a doctor's diagnosis of asthma.

Home visit, dust collection, and allergen analysis

At the home visit, questionnaires regarding home characteristics, home environmental exposures (including smoking), demographic and socioeconomic characteristics of the family, and detailed respiratory symptoms of the siblings were administered by trained research assistants. Methods for the collection of dust samples and the processing and assay of allergens have been detailed previously.⁹ In brief, 5 separate dust samples were collected in standardized fashion by vacuuming 5 areas in the home. For this analysis, only allergens assayed from the family-living room and the kitchen floor dust samples were used. Dust extract was assayed for allergens, including house dust mite (Der p 1 and Der f 1), cat (Fel d 1), and cockroach (Bla g 1 and Bla g 2) allergens.

Definitions of outcome variables

Respondents (usually the mothers) to the sibling respiratory questionnaire administered at the home visit were asked about a doctor's diagnosis of asthma ("Has a doctor ever said that [name] has asthma?") and about wheezing ("Has this child's chest ever sounded wheezy or whistling, including times when he or she had a cold?"). If the answer to the wheezing question was yes, the respondent was asked whether wheezing had occurred within the last 12 months. If wheezing had occurred within the last 12 months, then the child was labeled with "wheezing in the past year."

Incident asthma was defined as a report of a doctor's diagnosis of asthma on the second or the third questionnaire among children who did not have a report of a doctor's diagnosis of asthma at the time of the home visit (when the first sibling respiratory questionnaire was administered) but had a report of wheezing in the past year on any of the questionnaires. Recurrent wheezing was defined as a report of wheezing in the past year on 2 of the 3 questionnaires. Recurrent asthmatic wheezing was then defined as a diagnosis of asthma and recurrent wheeze. Conversely, recurrent nonasthmatic wheezing was defined as recurrent wheeze without a diagnosis of asthma.

Definition of predictor variables

Predictor variables that were examined included maternal and paternal asthma, the child's race-ethnicity, maternal smoking during the perinatal period, current smoking in the home by any adult, and socioeconomic factors (total family income before taxes, highest educational level attained by either parent, and area of residence on the basis of poverty levels). Details of the ascertainment of these predictor variables have been reported elsewhere.^{10,11} Lower respiratory tract illness (LRI) was defined as doctor-diagnosed croup, bronchitis, bronchiolitis, or pneumonia, and recurrent LRI was defined as reports of LRI in the past year on at least 2 questionnaires.

Allergen concentrations were grouped in categories with potential relevance to sensitization and development of allergy-related recurrent wheeze. Cockroach exposure was categorized as Bla g 1 or Bla g 2 at the following levels: (1) 2 U/g or greater (including concentrations exceeding detectable limits); (2) 0.05 to less than 2 U/g; and (3) less than 0.05 U/g (including concentrations below the limits of detection). Dust mite exposure was categorized as Der f 1 or Der p 1 at the following levels: (1) 10 µg/g or greater (including concentrations exceeding detectable limits); (2) 2 to less than 10 µg/g; and (3) less than 2 µg/g (including samples below the limits of detection). Cat exposure was categorized as Fel d 1 at the following levels: (1) 8 µg/g or greater (including concentrations exceeding detectable limits); (2) 1 or greater to less than 8 µg/g; and (3) less than 1 µg/g (including concentrations below the limits of detection). For all the allergens, if no dust was available or if the amount was too small to be assayed for a particular allergen, values were considered to be missing. For this analysis, allergen levels in the kitchen and family room were combined.

Statistical analysis

Univariate relationships between predictor variables and outcome variables were initially analyzed with contingency tables. Further analyses of the univariate and multivariable relationships between predictor and outcome variables by using Poisson regression were performed with the log link function in the GENMOD procedure in SAS software (SAS Institute Inc, Cary, NC). To account for correlations between children from the same household, methods developed by Zeger and Liang¹² using generalized estimating equations for the logistic case were performed with the REPEATED statement in the GENMOD procedure (SAS Institute, 1997).

Predictor variables that were significant at a *P* level of .05 or less in univariate models were selected for the multivariable models. In addition, bivariable models with cockroach allergen levels and each of the other predictor variables were created for incident asthma and recurrent asthmatic wheezing outcomes. Predictor variables that caused a 10% change in the parameter estimate for cockroach allergen were also included in multivariable models, even if the associated univariate *P* value did not reach the level of statistical significance. Multivariable models containing all the selected variables (*full* models) were then created for each outcome. Subsequently, reduced models were created by removing individual variables or groups of variables that were statistically nonsignificant in the full models.

RESULTS

Baseline characteristics

The baseline characteristics of the 222 children are presented in Table I. One hundred seventy-one (77.0%) children had neither a diagnosis of asthma nor recurrent wheezing, and 51 (23.0%) had either or both of these conditions. Thirty-three (14.9%) children had never had a doctor's diagnosis of asthma by the end of the follow-up period; thirteen (5.9%) children had incident asthma. Thirteen (5.9%) children had a report of wheezing in the past year on all 3 questionnaires, and 25 (11.3%) children had a report of wheezing in the past year on 2 of the 3 questionnaires; these 38 children were categorized as having recurrent wheeze. Of these 38 children with recurrent wheeze, 20 (52.6%) had a diagnosis of asthma and thus were categorized as having recurrent asthmatic wheeze, whereas 18 (47.4%) did not have a diagnosis of asthma and were categorized as having nonasthmatic recurrent wheeze.

Univariate analyses

Results of univariate analyses on the 3 outcomes are presented in Table II. Statistically significant associations with incident asthma were observed with young maternal age, current cigarette smoking in the home, recurrent LRI, total family income of less than \$30,000, and highest attained parental education of high school or less. Among the indoor allergens, only cockroach allergen levels were significantly associated with incident asthma. For recurrent asthmatic wheeze, prematurity, male sex, young maternal age, maternal cigarette smoking during the perinatal period, current adult smoking in the home, recurrent LRI, highest attained parental education of high school or less, and maternal asthma were significant predictors. As was the case for incident asthma, only cockroach allergen, among the indoor allergens, was a significant predictor for recurrent asthmatic wheezing. For recurrent nonasthmatic wheeze, prematurity, young maternal age, recurrent LRI, and Hispanic race were significant predictors. None of the allergens were significantly associated with recurrent wheeze among nonasthmatic children. No child who was exposed to 2 U/g or greater of cockroach allergen had nonasthmatic wheezing.

Multivariable models for incident asthma

In the full model containing all of the significant univariate predictors plus race (Table III), the associations of maternal age, current cigarette smoking in the home, race, total family income, and highest attained parental education level were all statistically nonsignificant. Cockroach allergen levels and recurrent LRI were significant predictors of incident asthma in the full model and the reduced models (Table III). In these models exposure to 0.05 to less than 2 U/g of cockroach allergen was associated with an 8- to 9-fold risk for incident asthma, whereas exposure to 2 U/g or greater was associated with a greater than 20-fold risk for developing asthma.

TABLE I. Baseline characteristics of 222 children

Characteristic	Value
Age, y (median [range])	2.87 (1.11-4.99)
Sex	
Male, n (%)	106 (47.7)
Female, n (%)	116 (52.3)
Birth weight, lb (mean $\pm$ SD)	7.58 $\pm$ 1.10
Prematurity, n (%)	32 (14.4)
Maternal smoking during perinatal period, n (%)	14 (6.3)
Current* smoking in the home by any adult, n (%)	25 (11.3)
Race-ethnicity, n (%)	
White	183 (82.4)
Black	18 (8.1)
Hispanic	12 (5.4)
Asian	9 (4.1)
Family income, n (%)	
<\$30,000	15 (6.8)
\$30,000-49,999	39 (17.6)
$\geq$ \$50,000	161 (72.5)
Area of residence based on poverty rates, n (%)	
<10%	163 (73.4)
10%-20%	46 (20.7)
$\geq$ 20%	13 (5.9)

*At the time of the first questionnaire.

Multivariable models for recurrent asthmatic wheezing

Cockroach allergen levels and recurrent LRI were significant predictors of recurrent wheeze among asthmatic children (Table IV). As in the case for incident asthma, all other predictor variables were not significantly associated with recurrent wheeze among asthmatic children in the full model. In several reduced models, the association between cockroach allergen and recurrent asthmatic wheezing was stronger compared with the full model, particularly when socioeconomic variables were removed. This was likely because of the association of cockroach allergen levels with the socioeconomic variables.

Multivariable models for recurrent nonasthmatic wheezing

In multivariable models for recurrent nonasthmatic wheezing, recurrent LRIs remained the strongest predictor (relative risk [RR], 8.11; 95% confidence interval [CI], 2.95-22.89). Hispanic children were also more likely to have recurrent nonasthmatic wheezing than non-Hispanic children (RR, 4.64; 95% CI, 1.22-17.61). Prematurity (RR, 2.37; 95% CI, 0.90-6.26) and maternal age (RR, 3.01; 95% CI, 0.85-10.70) were marginally significant. Cockroach allergen remained nonsignificant in these models.

DISCUSSION

Indoor dust concentrations of cockroach allergen (combined Bla g 1 and Bla g 2) were significantly asso-

TABLE II. Univariate predictors of incident asthma and recurrent wheezing

Variable	Incident asthma (n = 184)		Recurrent wheeze, asthmatic children (n = 191)		Recurrent wheeze, nonasthmatic children (n = 189)	
	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)
Birth weight						
>6.8 lb	9 (6.5)	1.00	14 (9.7)	1.00	14 (9.9)	1.00
<6.8 lb	4 (8.9)	1.51 (0.48-4.74)	6 (12.8)	1.30 (0.54-3.14)	4 (8.5)	0.76 (0.28-2.06)
Prematurity						
No	10 (6.1)	1.00	15 (8.9)	1.00	13 (7.8)	1.00
Yes	3 (14.3)	2.40 (0.73-7.90)	5 (21.7)	2.49 (1.02-6.10)	5 (21.7)	2.90 (1.21-6.93)
Sex						
Female	5 (5.0)	1.00	6 (5.9)	1.00	8 (7.8)	1.00
Male	8 (9.5)	1.89 (0.66-5.40)	14 (15.6)	2.57 (1.07-6.18)	10 (11.6)	1.53 (0.72-3.28)
Maternal age at child's birth						
>25 y	10 (5.8)	1.00	16 (8.9)	1.00	15 (8.4)	1.00
≤25 y	3 (27.3)	4.81 (1.46-15.81)	4 (33.3)	3.82 (1.45-10.06)	3 (27.3)	3.64 (1.24-10.65)
Maternal cigarette smoking during perinatal period						
No	11 (6.3)	1.0	17 (9.4)	1.00	16 (8.9)	1.00
Yes	2 (22.2)	3.41 (0.88-13.23)	3 (30.0)	3.06 (1.06-8.80)	2 (22.2)	2.34 (0.64-8.52)
Current* cigarette smoking in the home by any adult						
No	8 (4.9)	1.0	15 (8.7)	1.00	15 (8.7)	1.00
Yes	5 (26.3)	5.29 (1.87-14.95)	5 (26.3)	2.95 (1.18-7.41)	3 (17.7)	2.17 (0.70-6.75)
Recurrent LRI						
No	11 (6.2)	1.00	15 (8.2)	1.00	13 (7.2)	1.00
Yes	2 (33.3)	5.25 (1.47-18.78)	5 (55.6)	6.52 (3.04-13.97)	5 (55.6)	7.43 (3.22-17.11)
Race						
White	8 (5.2)	1.00	13 (8.2)	1.00	15 (9.4)	1.00
Black	3 (17.6)	3.31 (0.96-11.43)	4 (22.2)	2.64 (0.96-7.32)	0 (0.0)	—
Hispanic	1 (16.7)	3.09 (0.45-21.16)	1 (16.7)	1.93 (0.30-12.36)	3 (37.5)	3.84 (1.39-10.66)
Asian	1 (12.5)	2.30 (0.32-16.45)	2 (22.2)	2.59 (0.68-9.90)	0 (0.0)	—
Total family income						
≥\$50,000	9 (6.6)	1.00	15 (10.6)	1.00	12 (8.6)	1.00
\$30,000-\$49,999	1 (3.5)	0.56 (0.07-4.23)	3 (9.7)	0.98 (0.30-3.19)	6 (17.7)	2.04 (0.78-5.30)
<\$30,000	3 (25.0)	3.71 (1.15-11.99)	2 (18.2)	1.67 (0.43-6.41)	0 (0.0)	—
Area of residence by percentage of households below poverty						
<10%	9 (6.7)	1.00	14 (10.1)	1.00	15 (10.7)	1.00
10%-<20%	2 (5.1)	0.77 (0.17-3.44)	5 (11.9)	1.19 (0.45-3.14)	3 (7.5)	0.74 (0.23-2.44)
≥20%	2 (18.2)	2.60 (0.64-10.63)	1 (10.0)	0.94 (0.14-6.42)	0 (0.0)	—
Parental education						
College or beyond	9 (5.4)	1.0	15 (8.7)	1.00	17 (9.7)	1.00
High school or less	4 (23.5)	4.25 (1.46-12.38)	5 (27.8)	3.10 (1.27-7.56)	1 (7.1)	0.71 (0.10-4.94)
Maternal asthma						
No	8 (5.9)	1.0	9 (6.6)	1.00	11 (7.9)	1.00
Yes	5 (10.4)	1.78 (0.61-5.21)	11 (20.4)	3.11 (1.36-7.14)	7 (14.0)	1.65 (0.65-4.20)
Paternal asthma						
No	11 (7.9)	1.0	17 (11.7)	1.00	11 (7.9)	1.00
Yes	2 (4.6)	0.58 (0.13-2.53)	3 (6.8)	0.58 (0.18-1.89)	7 (14.6)	2.04 (0.82-5.04)
Cockroach allergen						
<0.05 U/g	1 (1.1)	1.0	6 (6.1)	1.00	7 (7.0)	1.00
0.05-<2 U/g	7 (9.1)	8.27 (1.04-66.04)	10 (12.5)	1.98 (0.75-5.25)	11 (13.6)	1.73 (0.69-4.32)
≥2 U/g	5 (38.5)	35.87 (4.49-286.62)	4 (33.3)	5.43 (1.76-16.80)	0 (0.0)	—
Dust mite allergen						
<2 µg/g	7 (9.0)	1.00	10 (12.4)	1.00	9 (11.3)	1.00
2-<10 µg/g	3 (6.5)	0.71 (0.19-2.63)	4 (8.5)	0.67 (0.22-2.03)	2 (4.4)	0.38 (0.09-1.66)
≥10 µg/g	3 (5.0)	0.55 (0.15-2.05)	6 (9.5)	0.76 (0.29-1.99)	7 (10.9)	0.85 (0.32-2.24)
Cat allergen						
<1 µg/g	12 (13.8)	1.0	15 (16.7)	1.00	8 (9.6)	1.00
1-<8 µg/g	0 (0.0)	—	0 (0.0)	—	7 (10.3)	1.16 (0.43-3.13)
≥8 µg/g	1 (2.9)	0.20 (0.03-1.48)	5 (12.8)	0.74 (0.29-1.89)	3 (8.1)	0.87 (0.24-3.15)

*At the time of the first questionnaire.

TABLE III. Multivariable models for incident asthma

Variable	Full model	Reduced model A	Reduced model B	Reduced model C
Cockroach allergen				
<0.05 U/g	1.00	1.00	1.00	1.00
0.05-<2 U/g	9.22 (1.24-68.49)	8.99 (1.17-69.05)	8.81 (1.23-62.98)	8.42 (1.15-61.82)
≥2 U/g	26.47 (2.06-339.46)	21.87 (1.68-284.18)	25.84 (1.96-341.46)	26.47 (2.24-312.20)
Recurrent LRI				
No	1.00	1.00	1.00	1.00
Yes	9.12 (2.83-29.40)	9.41 (2.97-29.84)	9.85 (3.06-31.71)	10.04 (3.16-31.89)
Maternal age at child's birth				
>25 y	1.00	1.00	1.00	—
≤25 y	2.13 (0.80-5.69)	1.93 (0.77-4.86)	2.34 (0.73-7.47)	—
Current* cigarette smoking in the home				
No	1.00	1.00	1.00	1.00
Yes	3.64 (0.91-14.54)	3.36 (0.75-15.00)	4.15 (1.19-14.45)	3.94 (1.02-15.16)
Race				
White	1.00	—	1.00	—
Nonwhite	0.69 (0.13-3.65)	—	0.64 (0.12-3.57)	—
Total family income				
≥\$30,000	1.00	1.00	—	—
<\$30,000	0.88 (0.36-2.16)	0.89 (0.37-2.11)	—	—
Parental education				
College or beyond	1.00	1.00	—	—
High school or less	1.22 (0.31-4.70)	1.18 (0.33-4.19)	—	—

Values are given as RR (95% CI).

*At the time of the first questionnaire.

ciated with incident doctor-diagnosed asthma and recurrent wheeze among asthmatic children over a 22-month period in this cohort of children of allergic or asthmatic parents. The risk estimates increased across exposure categories, suggesting a dose-response relationship. These associations remained after controlling for other covariates, including race and socioeconomic status. No significant association was found, however, between measured cockroach allergen levels and recurrent wheezing among nonasthmatic children in this same cohort.

It is now widely known that wheezing in early life does not necessarily lead to a diagnosis of asthma. In most children symptoms of wheezing remit after the first 3 years of life, and low lung function appears to be the main risk factor for these transient episodes.¹³ Children who go on to have the clinical syndrome known as asthma, on the other hand, usually have a family history of asthma and allergies and present with allergic symptoms early in life.^{13,14} In our cohort of children with a parental history of asthma or allergies, we identified 2 groups of children who had recurrent wheezing symptoms: one group with the presence of doctor-diagnosed asthma and the other group without asthma. Because we did not measure lung function in these children and have no objective markers of allergy, it is not clear whether children with recurrent nonasthmatic wheeze will eventually have asthma. Only follow-up of this cohort over time will tell.

Among urban asthmatic subjects, hypersensitivity to cockroach allergen is common.¹⁵ Recently, Rosenstreich et al⁶ showed that among children with asthma who are sensitized to cockroach allergen, exposure to high levels of cockroach allergen in the home was strongly associated with increased hospitalizations and other measures of

asthma morbidity. Our data are consistent with these findings in that exposure to cockroach allergen was associated with recurrent wheeze among children with asthma. A recently published analysis on the index children in this study also demonstrated that cockroach allergen was associated with recurrent wheeze in the first year of life.⁸ No previously published data, however, relate cockroach allergen exposure to incident asthma.

Presumably, an allergic mechanism underlies the effect of exposure to cockroach allergen in sensitized persons: asthmatic subjects sensitized to cockroach allergen exhibit immediate bronchoconstriction accompanied by early and late asthmatic symptoms and increases in peripheral eosinophil counts after bronchial provocation testing with cockroach antigen, whereas unsensitized asthmatic subjects do not exhibit these reactions.¹⁶ A limitation of our study is that we lack sensitization data on the children. Thus we do not know whether those with incident asthma or with recurrent asthmatic wheeze are sensitized to cockroach allergen. Although there may be a direct proinflammatory effect on the lung by cockroach allergen,⁸ neither lung function data nor markers of inflammation were collected for this analysis.

We found a relationship between both incident asthma and recurrent wheezing and low levels of cockroach allergen. Proposed thresholds for induction of disease⁶ are considerably higher than those used for this analysis. However, our results suggest that in susceptible children of parents with asthma, allergy, or both, levels well below these currently proposed thresholds may cause symptoms and even contribute to disease.

Although we found no statistically significant relationships between our outcomes and either dust mite or

TABLE IV. Multivariable models for recurrent wheeze among asthmatic children

Variable	Full model	Reduced model A	Reduced model B	Reduced model C
Cockroach allergen				
<0.05 U/g	1.00	1.00	1.00	1.00
0.05-<2 U/g	2.45 (1.01-6.00)	2.81 (1.17-6.71)	2.51 (1.02-6.16)	2.12 (0.88-5.11)
≥2 U/g	2.47 (0.34-18.13)	3.69 (0.81-16.87)	2.13 (0.29-15.83)	5.26 (1.42-19.53)
Recurrent LRI				
No	1.00	1.00	1.00	1.00
Yes	6.32 (2.23-17.90)	5.49 (2.02-14.88)	6.97 (2.53-19.21)	9.90 (4.36-22.49)
Maternal age at child's birth				
>25 y	1.00	1.00	1.00	—
≤25 y	1.53 (0.60-3.93)	1.76 (0.74-4.18)	1.85 (0.67-5.12)	—
Prematurity				
No	1.00	1.00	1.00	—
Yes	1.58 (0.72-3.47)	1.62 (0.68-3.83)	1.33 (0.61-2.90)	—
Current* cigarette smoking in the home				
No	1.00	1.00	1.00	1.00
Yes	2.58 (0.61-10.96)	2.67 (0.67-10.68)	2.81 (0.70-11.28)	3.27 (1.08-9.91)
Sex				
Female	1.00	1.00	1.00	—
Male	1.86 (0.76-4.56)	1.70 (0.68-4.29)	1.83 (0.72-4.66)	—
Race				
White	1.00	—	1.00	—
Nonwhite	2.11 (0.58-7.62)	—	1.99 (0.54-7.28)	—
Area of residence by percentage of households below poverty				
<20%	1.00	1.00	—	—
≥20%	0.36 (0.10-1.28)	0.41 (0.11-1.49)	—	—
Parental education				
College or beyond	1.00	1.00	—	—
High school or less	1.30 (0.46-3.64)	1.48 (0.47-4.64)	—	—
Maternal asthma				
No	1.00	1.00	1.00	—
Yes	1.81 (0.75-4.36)	1.94 (0.80-4.70)	1.84 (0.76-4.46)	—

Values are given as RR (95% CI).

*At the time of the first questionnaire.

cat allergens, sensitization to these indoor allergens has been shown to be a risk factor for asthma, either in cross-sectional population-based studies^{3,4} or in emergency department studies.¹⁷ For dust mites in particular, prospective studies have shown that exposure in infancy is related to sensitization¹⁸ and to development of asthma by age 11 years.⁷ It may well be that for both dust mite and cat allergens, more time must elapse before a statistically significant association can be observed in our cohort. Furthermore, it may be difficult to define cat allergen exposure because this allergen has been shown to be ubiquitous, even in homes without a cat,⁹ and because of the high frequency of exposure outside the home.

A number of risk factors for asthma and childhood wheezing have been confirmed in this analysis. LRI was a strong predictor for both asthma and recurrent wheezing in our cohort. Most wheezing in early life is associated with viral infections, especially infection with respiratory syncytial virus.¹³ We can only assume that the wheezing episodes in the children in our cohort occurred in the setting of these LRIs because we could determine the timing of these wheezing episodes to no closer than 1

year preceding questionnaire administration. Furthermore, no specimens for determination of the cause of these LRIs were collected. Although debate continues about whether viral respiratory illnesses early in life are protective against or are risk factors for asthma and allergies,^{19,20} it appears that—at least in this cohort of susceptible children of parents with asthma, allergy, or both—LRIs are strongly associated with incident asthma and recurrent wheezing. An alternative explanation is that these children are predisposed to both severe LRIs and asthma.

Young maternal age,²¹ maternal cigarette smoking during pregnancy,²² environmental tobacco smoke exposure,²³ prematurity,²⁴ maternal asthma,¹⁴ and low socioeconomic status^{11,25} have all been shown to be risk factors for both childhood asthma and wheezing. These variables were related to either or both incident asthma and recurrent wheeze among asthmatic and nonasthmatic subjects in our univariate analyses. However, in the multivariable models these variables were not statistically related to the respective outcomes, probably because relatively few children ultimately experienced the outcomes and were exposed to the risk factors during this

short observation period. Further follow-up is expected to minimize this limitation in future analyses.

In the United States asthma appears to affect underprivileged populations disproportionately.²⁶ Compared with white children in our cohort, nonwhite children were more likely to have incident asthma and recurrent asthmatic wheezing in univariate models. Hispanic children, in particular, appeared more likely to have recurrent nonasthmatic wheezing than the other children in our cohort. Although the situation for minority children in the United States is complex, exposures related to low socioeconomic status are thought to play a role in the risk for asthma and wheezing respiratory illnesses^{26,27} in addition to some inherent biologic differences among races.^{28,29}

In summary, we have presented data that relate exposure to cockroach allergens with incident asthma. To our knowledge, this is the first time this relationship has been shown. We have also confirmed that exposure to cockroach allergen predisposes asthmatic subjects to recurrent episodes of wheezing, although sensitization data are lacking. Furthermore, it appears that levels of cockroach allergen lower than those previously associated with symptoms and disease may be important in susceptible cohorts like ours. It is not yet clear whether cockroach allergen is more potent than other allergens in eliciting an allergic response and whether mechanisms or pathways other than sensitization are important.

REFERENCES

- Platts-Mills TAE, Vervloet D, Thomas WR, Aalberse RC, Chapman MD. Indoor allergens and asthma: report of the third international workshop. *J Allergy Clin Immunol* 1997;100:s1-24.
- Kuehr J, Frischer T, Meinert R, Barth R, Forster J, Schraub S, et al. Mite allergen exposure is a risk factor for the incidence of specific sensitization. *J Allergy Clin Immunol* 1994;94:44-52.
- Peat JK, Tovey E, Toelle BG, Haby MM, Gray EJ, Mahmic A, et al. House-dust mite allergens: a major risk factor for childhood asthma in Australia. *Am J Respir Crit Care Med* 1996;153:141-6.
- Sporik R, Ingram JM, Price W, Sussman JH, Honsinger RW, Platts-Mills TAE. Association of asthma with serum IgE and skin-test reactivity to allergens among children living at high altitude: tickling the dragon's breath. *Am J Respir Crit Care Med* 1995;151:1388-92.
- Ingram JM, Sporik R, Rose G, Honsinger R, Chapman MD, Platts-Mills TAE. Quantitative assessment of exposure to dog (Can f 1) and cat (Fel d 1) allergens: relationship to sensitization and asthma among children living in Los Alamos, New Mexico. *J Allergy Clin Immunol* 1995;96:449-56.
- Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 1997;336:1356-63.
- Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house-dust mite allergen (Der p 1) and the development of asthma in childhood. *N Engl J Med* 1990;323:502-7.
- Gold DR, Burge HA, Carey V, Milton DK, Platts-Mills T, Weiss ST. Predictors of repeated wheeze in the first year of life. The relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. *Am J Respir Crit Care Med* 1999;160:227-36.
- Chew GL, Burge HA, Dockery DW, Muilenberg ML, Weiss ST, Gold DR. Limitations of a home characteristics questionnaire as a predictor of indoor allergen levels: clinical and epidemiologic implications. *Am J Respir Crit Care Med* 1998;157:1536-41.
- Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? *Am J Respir Crit Care Med* 1998;158:176-81.
- Litonjua AA, Carey VJ, Weiss ST, Gold DR. Race, socioeconomic factors, and area of residence are associated with asthma prevalence. *Pediatr Pulmonol* 1999;28:394-401.
- Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121-30.
- Martinez FD, Helms PJ. Types of asthma and wheezing. *Eur Respir J* 1998;12(Suppl 27):3s-8s.
- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;352:133-8.
- Kattan M, Mitchell H, Eggleston P, Gergen P, Crain E, Redline S, et al. Characteristics of inner-city children with asthma: The National Cooperative Inner-City Asthma Study. *Pediatr Pulmonol* 1997;24:253-62.
- Kang B. Study on cockroach antigen as a probable causative agent in bronchial asthma. *J Allergy Clin Immunol* 1976;58:357-65.
- Gelber LE, Seltzer LH, Bouzoukis JK, Pollart SM, Chapman MD, Platts-Mills TAE. Sensitization and exposure to indoor allergens as risk factors for asthma among patients presenting to the hospital. *Am Rev Respir Dis* 1993;147:573-8.
- Rowntree S, Platts-Mills TAE, Cogswell JJ, Mitchell EB. A subclass IgG4-specific antigen-binding radioimmunoassay (RIA): comparison between IgG and IgG4 antibodies to food and inhaled antigens in adult atopic dermatitis after desensitization treatment and during development of antibody responses in children. *J Allergy Clin Immunol* 1987;80:622-30.
- Martinez FD. Role of viral infections in the inception of asthma and allergies during childhood: could they be protective? *Thorax* 1994;49:1189-91.
- Openshaw PJM, O'Donnell DR. Asthma and the common cold: can viruses imitate worms? *Thorax* 1994;49:101-3.
- Infante-Rivard C. Young maternal age: a risk factor for childhood asthma? *Epidemiology* 1995;6:178-80.
- Tager IB, Hanrahan JP, Tosteson TD, Castile RG, Brown RW, Weiss ST, et al. Lung function, pre- and post-natal smoke exposure, and wheezing in the first year of life. *Am Rev Respir Dis* 1993;147:811-7.
- Martinez FD, Antognoni G, Macri F, Bonci E, Midulla F, De Castro G, et al. Parental smoking enhances bronchial responsiveness in nine-year-old children. *Am Rev Respir Dis* 1988;138:518-23.
- Björkstén B, Kjellman N-IM. Perinatal factors influencing the development of allergy. *Clin Rev Allergy* 1987;5:339-47.
- Schwartz J, Gold D, Dockery DW, Weiss ST, Speizer FE. Predictors of asthma and persistent wheeze in a national sample of children in the United States. *Am Rev Respir Dis* 1990;142:555-62.
- Weiss KB, Gergen PJ, Crain EF. Inner-city asthma: the epidemiology of an emerging US public health concern. *Chest* 1992;101:362s-7s.
- Gold DR, Rotnitzky A, Damokosh AI, Ware JH, Speizer FE, Ferris BG Jr, et al. Race and gender differences in respiratory illness prevalence and their relationship to environmental exposures in children 7 to 14 years of age. *Am Rev Respir Dis* 1993;148:10-8.
- Sherman CB, Tollerud DJ, Heffner LJ, Speizer FE, Weiss ST. Airway responsiveness in young black and white women. *Am Rev Respir Dis* 1993;148:98-102.
- Tollerud DJ, Brown LM, Blattner WA, Weiss ST, Maloney EM, Kurman CC, et al. Racial differences in serum immunoglobulin levels: relationship to cigarette smoking, T-cell subsets, and soluble interleukin-2 receptors. *J Clin Lab Anal* 1995;9:37-41.