
Cockroach exposure independent of sensitization status and association with hospitalizations for asthma in inner-city children

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Background: Children with asthma living in urban environments experience disproportionately high asthma hospitalization rates. Excessive exposure to perennial allergens, including cockroach and house dust mite (HDM), have been implicated, but data are limited.

Objective: To examine the relation between cockroach and HDM exposure and measures of asthma morbidity and health care utilization.

Methods: Participants included 86 atopic asthmatic children living in New Orleans, Louisiana. Sensitization status was determined by means of serum specific IgE testing, and vacuum dust samples were collected for allergen analysis. Logistic regression analysis was used to assess the odds of persistent wheezing, emergency department visits, and asthma hospitalization in those with high vs low levels of allergen exposure.

Results: Approximately 44% and 40% of children were exposed to Bla g 1 levels greater than 2 U/g and HDM levels greater than 2 $\mu\text{g/g}$, respectively, and 24% reported at least 1 hospitalization in the previous 4 months. The median Bla g 1 level was significantly higher in the homes of children hospitalized compared with those with no hospital admissions (7.2 vs 0.8 U/g). In multivariable models, the odds of hospitalization were significantly higher in children exposed to Bla g 1 levels greater than 2 U/g (adjusted odds ratio, 4.2; 95% confidence interval, 1.24–14.17), independent of sensitization status. Exposure to HDMs was not associated with any measure of morbidity.

Conclusions: Exposure to cockroach allergen was strongly associated with increased hospitalization in children with asthma. This effect cannot be explained entirely by IgE-mediated inflammation. Controlled interventional trials are needed to determine whether isolated cockroach abatement improves asthma control.

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INTRODUCTION

An estimated 7 million US children currently have asthma, with the highest burden borne by low-income black children living in urban environments.¹ The annual asthma hospitalization rate for black children is 33.5 per 10,000.² Inner-city children are exposed to high levels of indoor allergens in cities across the United States,^{3–6} and allergen avoidance is a major component of asthma control advocated by physicians.⁷ However, results of intervention trials^{8–12} assessing the effectiveness of allergen reduction techniques have been

mixed. There is strong evidence linking allergen exposure and sensitization to the diagnosis of asthma, but there is conflicting evidence as to whether current exposure is associated with asthma morbidity.

Allergens found in household dust that have been linked to asthma include those derived from pet dander, rodent excrement, mold spores, plant pollens, and arthropod feces, with the relative importance of particular allergens depending on the geographic location and socioeconomic condition of the study population. Abundant evidence^{4,6,13–16} confirms that exposure to house dust mites (HDMs) is independently associated with allergic sensitization; however, exposure to HDM antigen has not been found to be independently associated with clinical asthma endpoints, even in those sensitized.^{4,6,17,18} Numerous studies^{4,13–15,19,20} have also documented a relationship between exposure to cockroach allergen and sensitization in asthmatic children. In contrast to HDM allergy, there seems to be a positive relationship between cockroach exposure and asthma morbidity, although the number of studies are limited, with positive findings affected by the lack of adjustment for important covariates.^{4,6,21}

The apparent differences in clinical outcomes for asthmatic patients regarding HDMs and cockroach allergens are per-

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plexing because the major allergens of HDMs and cockroaches include environmentally stable enzymes that are passed in feces and incorporated into the household dust to which children are frequently exposed. Implementation of effective allergen avoidance strategies depends on an improved understanding of the underlying relationship between these exposures and clinical outcomes. The purpose of this study was to examine the relationship between exposure to HDMs and cockroaches, allergic sensitization, asthma morbidity, and health care utilization due to asthma by children in an inner-city environment. The results of this study will provide further data on which effective intervention strategies targeted to atopic asthmatic children in the inner city can be developed and tested.

METHODS

A cross-sectional study was conducted to assess the association between allergen exposure and asthma morbidity and health care utilization. Asthmatic children aged 4 to 17 years were recruited from allergy clinics serving low-income children throughout urban New Orleans. Eligibility criteria included medical record evidence of physician-diagnosed asthma and medical record evidence of a positive skin test reaction for any indoor allergen (eg, pet dander, HDM, cockroach, or mold). To reduce confounding due to adherence with asthma management, and to control confounding due to access to health care, inclusion was further restricted to children having kept their previous 2 appointments at the enrolling allergy clinic. Children were recruited between March 15, 2004, and June 30, 2005.

The study was approved by the Tulane University biomedical institutional review board. After obtaining written informed consent, a trained interviewer administered a structured questionnaire on sociodemographic factors and home characteristics to the primary caretaker of the asthmatic child. Visual observation of the home was then conducted using a structured format. A revised version of the validated Childhood Respiratory Health Questionnaire was used to measure the frequency of health care utilization, asthma symptoms and activity limitation, and medication use during the previous 4 months.²² The time frame was modified from events occurring in the previous 12 month to those in the previous 4 months to reduce the possibility of misclassification bias and to increase the likelihood that complete medical records would be available for review in this highly mobile inner-city population. Health care utilization outcomes included 1 or more visits to the emergency department (ED) for asthma, 1 or more overnight stays at the hospital for asthma, and 1 or more urgent trips to a physician's office for asthma. Sixteen or more days with wheezing episodes during the previous 4 months was used as a measure of asthma morbidity. To avoid interviewer bias, the Childhood Respiratory Health Questionnaire and visual observation data were collected by different study personnel.

Environmental Sampling and Measurements

Methods used in the collection and analysis of indoor allergens in vacuum dust samples are described in detail elsewhere.⁵ Briefly, 5 vacuum dust samples were taken from each household. Five-minute samples were taken from the living room floor and upholstery, child's bedroom floor and bed, and kitchen floor using separate dust collection bags (DACI Laboratory, Baltimore, Maryland) attached to a Kenmore (12-amp, HEPA-filtered, canister) electric-powered, portable handheld vacuum cleaner. Samples were analyzed for allergen content including dust mite (Der p 1 and Der f 1) and German cockroach (Bla g 1). For the analysis presented herein, the highest concentration of either Der f 1 or Der p 1 from the bedroom was used as the primary exposure variable for HDMs. Kitchen floor samples were used as the exposure variable for cockroaches.

IgE Analysis

Blood samples were collected via venipuncture at the time of environmental and survey data collection for the analysis of serum allergen specific IgE levels. Samples were analyzed by Quest Diagnostics (Lyndhurst, New Jersey) for allergen specific IgE antibodies to the HDMs *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, cat dander, dog epithelium and dander, and German cockroach. All the tests were performed using the ImmunoCAP specific IgE test (Pharmacia Diagnostics, Uppsala, Sweden). Participants with an allergen specific IgE level greater than 0.35 ku/L were considered positive for that allergen.

Statistical Analysis

We assessed the relationships between allergen exposure, allergen sensitization, asthma morbidity, and health care utilization. The association between each dust allergen and the corresponding allergen specific IgE antibody level was evaluated using the Spearman correlation coefficient. Nonparametric Wilcoxon rank sum tests were used to compare median dust allergen levels and measures of asthma morbidity. The primary end points were number of asthma-related ED visits, hospital admissions, and 16 or more days with wheezing in the previous 4 months. To assess the combined effects of sensitization and exposure on asthma morbidity, participants were categorized into 4 groups based on allergen exposure and allergen-specific sensitization status: not sensitized and not exposed, sensitized and not exposed, not sensitized and exposed, and sensitized and exposed. The proportion of participants with each asthma outcome among those sensitized and exposed was compared with the proportion with each asthma outcome in the other 3 categories combined.

χ^2 tests and adjusted logistic regression models were used to evaluate whether exposure, sensitization, asthma severity, and demographic variables were associated with asthma morbidity (with each outcome modeled separately). Variables found to be significant in univariate analysis were included in multivariable models. Odds ratios and 95% confidence inter-

vals were calculated using traditional cutoff levels for sensitization and exposure. All analyses were performed using statistical software (SAS version 9.1; SAS Institute Inc, Cary, North Carolina).

RESULTS

Study Population

Eighty-six children were enrolled in the study. Characteristics of the study population are detailed in Table 1. Most children were black and aged 4 to 11 years, and 94.2% of caregivers had at least a high school education. Approximately 70% of

families had an annual household income less than \$10,000. On enrollment, 83.5% and 54.1% of children were skin prick test positive to HDM and cockroach allergens, respectively, and 76% had a positive reaction to multiple allergens. In the 4 months preceding administration of the questionnaire, 25.6% of children reported 16 or more days with wheezing, 55.8% had at least 1 ED visit, 24.4% had at least 1 hospital admission, and 72.1% had 1 or more urgent physician visits. Most children (79.1%) reported daily use of asthma and allergy medications in the preceding 4 months. Using standard cutoff points for exposure thresholds, 39.5% of children were exposed to either Der f 1 or Der p 1 greater than 2.0 $\mu\text{g/g}$, and 44.2% were exposed to cockroach allergen greater than 2 U/g.

Univariate Analysis

Allergen exposure and levels of IgE specific antibodies. The population exhibited a high rate of sensitivity to HDMs, even at low levels of allergen exposure. Of those exposed to HDMs at concentrations below 2 $\mu\text{g/g}$ of dust, 72.6% had *D farinae* specific IgE and 68.3% had *D pteronyssinus* specific IgE. There was a statistically significant, weak linear relationship between Der p 1 allergen levels in bedrooms and the level of HDM specific IgE in children (Spearman $r = 0.279$, $P = .01$). Use of alternative methods to define exposure did not substantially alter the findings. When considering cockroach exposure, there was a significant, moderately strong association ($r = 0.430$, $P = .001$) between cockroach allergen exposure measured in the kitchen floor sample and IgE antibody levels in children (data not shown).

Dust allergen exposure and asthma morbidity and health care utilization. The median Bla g 1 level was significantly higher in the homes of children who were admitted to the hospital for asthma compared with those with no admissions (7.2 vs 0.8 U/g; $P < .05$). Median Bla g 1 exposure was also higher, but not statistically significantly, in the homes of children who had 1 or more ED visits for asthma and in those who reported 16 or more days of wheezing. Analogous comparisons of median household dust mite allergen levels did not reveal any significant differences with respect to ED visits, hospitalizations, or days of wheezing (Table 2). Use of alternative methods to define exposure did not alter the findings. Results of unadjusted analyses showed that the odds of reporting previous hospitalization were 4.5 times greater in children exposed to greater than 2 U/g of cockroach allergen than in those exposed to 2 U/g or less, independent of sensitization status (95% CI, 1.43–13.8; $P < .05$). In models assessing the relationship between dust allergen exposure and asthma morbidity in children exposed and sensitized, the odds of hospitalization were 3.1 times greater for children exposed and sensitized to greater than 2 U/g of cockroach than for children either not exposed or not sensitized (95% CI, 1.04–9.41; $P < .05$). We found no association between exposure to HDM and any measure of asthma morbidity, even in those sensitized (Table 3).

Table 1. Characteristics of the 86 Study Patients

	Patients, No. (%)
Demographic Characteristics	
Age of child, y	
4–11	66 (76.7)
12–17	20 (23.3)
Male sex	55 (64.0)
Annual household income, \$	
<10,000	51 (59.3)
10,000–15,000	12 (14.0)
15,001–25,000	10 (11.6)
25,001–50,000	8 (9.3)
Refused to answer	5 (5.8)
Employed	60 (69.8)
Education of caregiver	
Did not graduate from high school	4 (4.7)
High school graduate and some college	63 (73.3)
College graduate	18 (20.9)
Refused to answer	1 (1.2)
Race/ethnicity	
Black	84 (97.7)
White	2 (2.3)
Allergies and Asthma	
Allergen sensitivity ≥ 0.35 kU/L	
Either house dust mite	66 (76.7)
Cat dander	36 (41.9)
Dog dander	19 (22.1)
Cockroach	35 (40.7)
Asthma-related health care	
≥ 1 routine asthma physician visits ^a	73 (84.9)
≥ 1 emergency department visits ^a	48 (55.8)
≥ 1 hospital admissions ^a	21 (24.4)
≥ 1 urgent physician visits ^a	62 (72.1)
Ever admitted to the ICU for asthma	21 (24.4)
Medication use	
Missed asthma medication in the past 2 wk	25 (29.1)
Allergy medications taken at least 1 $\times$ daily	68 (79.1)
β_2 -agonists taken at least 1 $\times$ daily	22 (25.6)
Inhaled corticosteroids taken at least 1 $\times$ daily	46 (53.5)
Oral corticosteroids taken at least 1 $\times$ daily	7 (8.2)
Allergen exposure	
Bla g 1 > 2.0 U/g	38 (44.2)
Der f 1 or Der p 1 > 2.0 $\mu\text{g/g}$	34 (39.5)

Abbreviation: ICU, intensive care unit.

^a In the previous 4 months.

Table 2. Dust Allergen Levels Stratified by Measures of Asthma Morbidity and Health Care Utilization

Exposure	Dust allergen levels, median (IQR)					
	No ED visits (n = 38)	≥1 ED visit (n = 48)	No hospital admissions (n = 65)	≥1 hospital admissions (n = 21)	<16 d with wheezing (n = 76)	≥16 d with wheezing (n = 10)
Bla g 1, U/g (kitchen floor)	0.8 (0.7–8.9)	2.1 (1.0–23.0)	0.8 (0.7–4.6)	7.2 (1.2–24.5) ^a	0.8 (0.7–16.4)	5.6 (0.6–8.8)
Dust mite allergen, μg/g ^b	2.1 (0.6–6.0)	2.2 (0.7–5.5)	1.8 (0.7–6.0)	2.5 (0.7–3.3)	2.0 (0.7–6.0)	2.7 (1.7–3.2)

Abbreviations: ED, emergency department; IQR, interquartile range.

^a $P < .05$ by Wilcoxon rank sum test.

^b Highest of either Der f 1 or Der p 1 from bedroom samples.

Multivariable Analyses

Multivariable analyses were performed to adjust for factors possibly confounding the relationship between cockroach exposure and asthma morbidity (Table 4). Only variables determined to be significant in the univariable analysis were considered for inclusion in the multivariable models. These variables included cockroach exposure, exposure and sensitization to cockroach allergen, oral corticosteroid use, and intensive care unit (ICU) admission. Hospital admission was the only outcome variable significantly associated with multiple exposure variables. Therefore, we examined factors

associated with hospitalization. In model 1, all the variables were entered. After simultaneously controlling for exposure and sensitization to cockroach allergen, oral corticosteroid use, and ICU admissions, the odds of reporting previous hospitalization were 5.4 times greater for children exposed to Bla g 1 greater than 2 U/g than for those exposed to 2 U/g or less (95% CI, 1.14–25.62 U/g). Stepwise regression techniques were used in model 2. After controlling for oral corticosteroid use and admission to the ICU, the odds of reporting previous hospitalization were 4.2 times higher in children exposure to Bla g 1 greater than 2 U/g than in those

Table 3. Association Between Measures of Asthma Morbidity and Health Care Utilization and Participant Characteristics

Characteristic	OR (95% CI)		
	≥1 ED visit	≥1 hospital admission	≥16 d with wheezing
Exposure			
Bla g 1 exposure >2 U/g	1.80 (0.70–4.7)	4.53 (1.43–13.80) ^a	3.61 (0.65–19.99)
Der p 1 exposure >2 μg/g	0.70 (0.25–2.01)	1.13 (0.35–3.67)	1.60 (0.37–6.94)
Der f 1 exposure >2 μg/g	0.79 (0.29–2.14)	2.32 (0.79–6.78)	1.31 (0.31–5.60)
Sensitization			
German cockroach	1.99 (0.82–4.84)	1.45 (0.54–3.92)	1.53 (0.41–5.75)
House dust mite	0.84 (0.31–2.23)	0.60 (0.21–1.76)	3.44 (0.41–28.8)
Exposure and sensitization ^b			
Bla g 1 exposure >2 U/g and sensitized	1.54 (0.53–4.46)	3.12 (1.04–9.41) ^a	2.16 (0.44–10.66)
Der p 1 exposure >2 μg/g and sensitized	0.70 (0.25–2.01)	1.13 (0.35–3.67)	1.60 (0.37–6.94)
Der f 1 exposure >2 μg/g and sensitized	0.62 (0.21–1.80)	1.86 (0.58–5.85)	1.81 (0.41–7.88)
Medication use/morbidity			
Oral corticosteroid (≥1 × daily)	5.30 (0.6–45.9)	9.80 (1.80–55.5) ^a	7.74 (1.43–41.65) ^a
Daily β ₂ -agonist (≥1 × daily)	1.54 (0.57–4.19)	0.88 (0.28–2.77)	1.29 (0.30–5.47)
Daily ICU (≥1 × daily)	1.06 (0.45–2.49)	1.58 (0.58–4.31)	0.85 (0.23–3.19)
Missed asthma medication in the last 2 wk	1.75 (0.45–6.81)	0.97 (0.33–2.87)	1.75 (0.45–6.81)
Ever admitted to the ICU for asthma	2.42 (0.83–7.03)	3.31 (1.39–9.63) ^a	1.38 (0.32–5.90)
Home and demographic characteristics			
Sibling with asthma	0.96 (0.35–2.62)	1.44 (0.48–4.45)	2.50 (0.63–9.94)
Owens a dog or cat	0.99 (0.35–2.81)	0.86 (0.25–2.96)	0.94 (0.18–4.86)
≥1 smokers in the home	0.65 (0.24–1.74)	0.26 (0.05–1.20)	0.75 (0.15–3.84)
Annual income ≤\$15,000	2.03 (0.79–5.86)	1.29 (0.37–4.48)	^c
Age 12–17 y	0.74 (0.27–2.0)	1.04 (0.33–3.32)	0.33 (0.04–2.81)
Male sex	1.25 (0.51, 3.08)	1.53 (0.53–4.21)	2.00 (0.53–7.56)

Abbreviations: CI, confidence interval; ED, emergency department; ICU, intensive care unit; OR, odds ratio.

^a Statistically significant ($P < .05$).

^b Sensitized/exposed vs all other categories combined.

^c Undefined estimate due to reduced cell size.

Table 4. Multivariable Regression Analyses of Children Who Were Hospitalized for Asthma vs Those With No Hospitalization

	OR (95% CI)	
	Model 1 ^a	Model 2 ^b
Bla g 1 exposure >2 U/g	5.41 (1.14–25.62)	4.20 (1.24–14.17)
Bla g 1 exposure >2 U/g and sensitized	0.65 (0.13–3.32)	NA
Oral corticosteroid use (≥1 × daily)	17.65 (1.52–204.75)	15.42 (1.39–171.37)
Ever admitted to the ICU for asthma	4.69 (1.29–17.01)	5.56 (1.27–16.36)

Abbreviations: CI, confidence interval; ICU, intensive care unit; NA, not applicable; OR, odds ratio.

^a Model 1 includes all variables found to be significant in the univariate analysis (Table 3) ($c = 0.780$).

^b Model 2 includes variables selected using forward and backward selection techniques. ($c = 0.773$).

exposed to 2 U/g or less (95% CI, 1.24–14.17 U/g). The results of alternative models with further adjustment for sociodemographic and clinical factors (income, insurance status, education, smoking in the home, asthma severity, and medication adherence) did not alter the results.

DISCUSSION

In this study, cockroach exposure seems to be an important correlate of asthma morbidity for inner-city children. The rate of hospital admissions in children exposed to cockroach allergen levels greater than 2 U/g was 4 to 5 times that of unexposed children in unadjusted and adjusted models. To our knowledge, there are only 2 other studies that examined whether current exposure to cockroaches is associated with asthma morbidity and health care utilization in atopic children. In the National Cooperative Inner-City Asthma Study, sensitized children exposed to cockroach allergen at greater than 8 U/g had increased hospitalization and morbidity rates than did those unexposed; however, this model was not adjusted for medication use, smoking, or income.⁶ In the Inner-City Asthma Study, children sensitized and exposed at greater than 2 U/g had significantly greater asthma-related morbidity (but not hospitalizations) in unadjusted analyses.⁴ In a related study, Sarpong and Karrison²¹ found an association between cockroach sensitization and hospitalization; however, significance was lost after controlling for sociodemographic factors. An unexpected finding from this study was the strong association between cockroach exposure and hospitalization, independent of sensitization status. In univariable and multivariable analyses, exposure to greater than 2 U/g of allergen was associated with a 4- to 5-fold increase in hospital admissions. Previously, the National Cooperative Inner-City Asthma Study examined the effect of exposure independent of sensitization. In that study, no association between exposure and morbidity was observed using the much higher cutoff point of 8 U/g.⁶

The major cockroach allergens are environmentally stable digestive enzymes passed in fecal pellets. The retention of protease activity may account for their tendency to provoke an immune response, even when a patient does not have allergic sensitization, as is seen with the major HDM allergens. Our failure to detect a clinical effect from HDM antigen exposure argues against a clinically significant irritant effect from cockroach proteins in asthma. Alternatively, the clinical effects of cockroach allergens may be caused by T cells. Thus far, epidemiologic studies of asthma have limited their sensitization assessments to IgE-mediated sensitization owing to the great difficulty in evaluating T-cell sensitization. From clinical studies on humans and animals looking at the process of sensitization to a variety of arthropods via skin exposure,²³ T-cell-mediated reactions precede the development of detectable IgE, suggesting that cockroach-specific T cells may instigate allergic inflammation in patients who lack detectable IgE.

Another hypothesis to explain these findings is that cockroach exposure is a surrogate for uncontrolled social exposures that lead to increased stress and subsequent vulnerability to asthma morbidity. These stressors could be working independently or in combination with elevated allergen levels to increase asthma morbidity through immune dysregulation.^{24–27} Studies show that black children are at higher risk for asthma than are white children only in the very poor, giving rise to the hypothesis that differential social and environmental conditions, leading to increased disorder and stress, may be driving factors.^{28–30} We addressed the potential confounding effects of medication adherence and disordered social environments in the design and analysis phases. First, participation was restricted to low-income families using public health clinics who resided in the inner city, received regular care by an asthma specialist, were given an asthma management plan, and kept their last 2 regularly scheduled clinic appointments. Second, we included several measures of poverty and medication adherence in the analysis (income, insurance status, education, smoking in the home, asthma severity, and medication adherence). Despite these efforts, residual confounding may still exist.

As with cockroach exposure and cockroach specific IgE levels, this study found that the concentration of HDM allergen in the bedrooms of asthmatic children was correlated with HDM specific IgE levels. In contrast to cockroaches, current exposure and sensitization to HDMs was not associated with any measure of asthma morbidity in unadjusted or adjusted models. These negative findings are consistent with other observational studies^{4,6,17,31} assessing asthma symptoms, medication use, and hospital visits and are supported by experimental studies^{32–35} in which reductions in HDM allergen levels did not affect clinical outcomes. The striking differences between HDM and cockroach may be explained by the effects of immunologic tolerance. As demonstrated by immunotherapy trials using HDM extracts, consistent exposure to high doses of allergen promotes clinical improvement by mechanisms that are independent of allergen specific IgE

levels.³⁶ Long-term nightly exposure to high doses of HDM allergens in bedrooms is expected to promote immunologic tolerance, in contrast to the comparatively more sporadic daytime exposure to cockroach allergens found in kitchens. As with HDM, administration of high-dose immunotherapy with cockroach extracts to cockroach-sensitive asthmatic patients results in reduced asthma morbidity.³⁷

This study is limited by the small sample size, which may have reduced our ability to detect an HDM effect. Although the allergen profile of the study sample is similar to that of other inner-city cohorts, regional variation in indoor allergen levels have been found.^{4,5,38} Although the present study and others showed a strong association between exposure to cockroach allergen and asthma morbidity, controlled trials of isolated cockroach abatement in urban homes using clinical outcomes are needed to determine whether reduction in cockroach exposure will result in improved asthma control and clarify the benefit expected for inner-city asthmatic children.

In conclusion, exposure to cockroach allergens is strongly associated with hospital admissions for asthmatic children and may be the factor driving high rates of asthma morbidity seen in inner-city children. This effect cannot be explained entirely by IgE-mediated inflammation. Exposure to HDM allergen is not associated with asthma morbidity, although this negative finding may be the result of a small sample size. The differences in response to these 2 arthropods may be due to patterns of exposure, with the consistent exposure to HDM in bedrooms resulting in high prevalence of sensitization and subsequent immune tolerance. Controlled interventional trials are needed to determine whether isolated cockroach abatement improves asthma control.

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