Endotoxin in inner-city homes: Associations with wheeze and eczema in early childhood

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Background: An inverse association between domestic exposure to endotoxin and atopy in childhood has been observed. The relevance of this aspect of the hygiene hypothesis to US inner-city communities that have disproportionately high asthma prevalence has not been determined.

Objectives: To measure endotoxin in the dust from inner-city homes, evaluate associations between endotoxin and housing/lifestyle characteristics, and determine whether endotoxin exposure predicted wheeze, allergic rhinitis, and eczema over the first 3 years of life.

Methods: As part of an ongoing prospective birth cohort study, children of Dominican and African-American mothers living in New York City underwent repeated questionnaire measures. Dust samples collected from bedroom floors at age 12 or 36 months were assayed for endotoxin.

Results: Among the samples collected from 301 participants' homes, the geometric mean endotoxin concentration (95% CI) was 75.9 EU/mg (66-87), and load was 3892 EU/m^2 (3351-4522). Lower endotoxin concentrations were associated with wet mop cleaning and certain neighborhoods. Endotoxin concentration correlated weakly with cockroach (Bla g 2: $r = 0.22$, $P < .001$) and mouse (mouse urinary protein: $r = 0.28$; $P < .001$) allergens in the dust. Children in homes with higher endotoxin concentration were less likely to have eczema at age 1 year (odds ratio, 0.70 [0.53-0.93]) and more likely to wheeze at age 2 years (odds ratio, 1.34 [1.01-1.78]). These associations were stronger among children with a maternal history of asthma.

Conclusion: Endotoxin levels in this inner-city community are similar to those in nonfarm homes elsewhere. In this community, domestic endotoxin exposure was inversely associated with eczema at age 1 year, but positively associated with wheeze at age 2 years.

Clinical implications: Endotoxin exposure in the inner-city community may be related to wheeze in the early life; however, given the inverse association seen with eczema, the long-term development of allergic disease is still in question. (J Allergy Clin Immunol 2006;117:1082-9.)

Key words: *Endotoxin, asthma, allergy, hygiene hypothesis, wheeze, inner-city, eczema*

The hygiene hypothesis asserts that the increase in the prevalence of allergic disease documented in Western society in the 20th century can be attributed, at least in part, to lifestyle changes that have led to cleaner living conditions and reduced exposure to viruses and bacteria in the first years of life.[1,2] Inverse associations between bacterial endotoxin in house dust and atopic disease have been observed in cross-sectional studies.[3,4] Endotoxin, a LPS found in the outer membrane of Gram-negative bacteria, can downregulate T_H2 cytokine production and class switching to IgE isotype in mouse models.[5] Hence, several authors have postulated that ambient exposure to high amounts of endotoxin in the home or farm environment could modulate the risk for atopy by suppressing molecular pathways responsible for IgE-mediated atopic disease.[6-8]

It has been suggested that the hygiene hypothesis may explain intercommunity differences reported in the prevalence of atopic asthma.[9] The prevalence of asthma generally is greater among industrialized countries, where living conditions appear to be cleaner and fewer bacterial infections seem to occur, than among developing nations.[10,11] However, it is unclear where inner-city homes in the United States, generally afflicted by a disproportionately high prevalence of asthma, fall in the spectrum of environmental endotoxin exposure.[4,12] One unanswered question is whether a greater level of hygiene associated with an inner-city lifestyle can explain the higher asthma prevalence

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Abbreviations used:
EU: Endotoxin unit
GEE: Generalized estimating equation
GM: Geometric mean
MUP: Mouse urinary protein
NYC: New York City
OR: Odds ratio

relative to that observed in rural and suburban areas.[12,13] Another is the extent to which endotoxin exposure modulates the risk for developing atopic disease or wheeze in this community during childhood.

Our study examined endotoxin exposure and asthma-related health outcomes in the first 3 years of life in a birth cohort of children living in New York City (NYC) neighborhoods that have reported a disproportionately high asthma prevalence.[12] We hypothesized that differences in endotoxin exposure would be associated with asthma-like symptoms, allergic rhinitis, and eczema. Our strategy was to (1) measure endotoxin in the dust from homes, (2) determine whether allergen levels, housing, and/or lifestyle characteristics were associated with endotoxin exposure in the inner city, and (3) determine whether endotoxin exposure in this inner-city birth cohort predicted wheeze, allergic rhinitis, and eczema over the first 3 years of life.

METHODS

Study cohort

Participants included 301 children recruited as part of an ongoing birth cohort, described previously, conducted by Columbia's Center for Children's Environmental Health.[14-17] Nonsmoking mothers not selected on allergic/asthmatic status of African-American and Dominican ethnicity living in Northern Manhattan and the South Bronx were recruited during the second or third trimester of pregnancy from prenatal clinics. This study was approved by Columbia University's Institutional Review Board.

Endotoxin measurement

As a proxy for early life domestic endotoxin exposure, endotoxin was measured in bedroom floor dust collected when the child was age 12 months. For 47 of the children, because of difficulties associated with scheduling home visits, samples were not available at age 12 months, but bedroom floor dust that had been collected at age 36 months was available and tested. Samples were collected in a 2-m^2 area for 5 minutes onto 70-mm cellulose filters (Whatman International, Maidstone, United Kingdom) with a canister vacuum cleaner (Eureka Mighty Mite, Bloomington, Ind) and a modified collection nozzle (ALK, Horshølm, Denmark). For endotoxin analysis, dust was extracted in pyrogen-free water with 0.05% Tween for 1 hour shaking and centrifuged, and the supernatant was removed and assayed without freezing. Endotoxin was analyzed by the kinetic chromogenic *Limulus* Amebocyte Lysate assay (Cambrex Corp, East Rutherford, NJ), described previously.[18,19] Results are reported both as the concentration of endotoxin per milligram of dust (endotoxin units [EU]/mg) and as the load of endotoxin collected per square meter (EU/m^2).

Dust samples also were collected from various locations in the home and were analyzed for cockroach (Bla g 2, bed, n = 255), mouse (mouse urinary protein [MUP], bed, n = 243), dust mite (Der f 1, bed, n = 209), cat (Fel d 1, bedroom floor, n = 292), and dog (Can f 1, bedroom floor, n = 289) allergens. The procedures for dust collection, allergen extraction, and ELISA have been described previously.[15,20-22]

Questionnaire

After a prenatal questionnaire, a detailed questionnaire including queries about wheezing; runny nose, sneezing, or itchy eyes without a cold (allergic rhinitis symptoms); and report of doctor's diagnosed eczema was administered to the parents about their offspring at ages 12, 24, and 36 months with additional, less detailed health follow-ups at 3, 6, 9, and 30 months. A child was considered to have wheezed if wheeze was reported during at least 1 of the interviews pertaining to that year of life. Other symptoms were recorded similarly.

Statistics

Because of the nonnormal distribution, geometric mean (GM) values (95% CIs) were calculated for endotoxin and means were compared by using ANOVA. Pearson correlations with logarithmically transformed values were used to compare endotoxin and allergen concentrations, and regression analysis was used to evaluate the associations between endotoxin and multiple allergens. Allergen concentrations below the limit of detection were assigned a value of half the limit of detection. Analyses for wheeze and other allergic symptoms were performed by using logistic multiple regression, adjusting for ethnicity, gender, maternal asthma, and smoking in the home. Generalized estimating equations (GEEs) were used to correct variance estimates for analyses of repeated measures. Data were analyzed by using SPSS version 12.0 (Chicago, Ill). GEE was performed by using SAS version 9.0 (Cary, NC).

To test the variability between samples collected at different time points in this cohort, 128 children who had endotoxin measured in a 12-month sample also had endotoxin measured in a 36-month sample. These latter 36-month samples are only included in (1) the correlation between 12-month and 36-month samples from the same home and (2) the analysis for the last sentence of the first health outcome paragraph in the results section.

RESULTS

Study population

Among the 301 mothers, 64% and 36% were of Dominican and African-American ethnicity, respectively, and 19% reported having a doctor diagnosis of asthma. The homes sampled were in East Harlem (18%), the South Bronx (36%), Washington Heights (15%), and West Harlem (32%). Seventy-three percent of the mothers reported an annual household income of $20,000 or less, and 75% reported that they currently received Medicaid at the time the dust sample was collected.

Endotoxin levels

The GM (95% CI) endotoxin concentration in the dust from the bedroom floor samples was 75.9 EU/mg (66-87). Calculated as the endotoxin load per square meter, the GM was 3892 EU/m^2 (3351-4522). There was a significant correlation between endotoxin concentration and load ($r = 0.60$; $P < .001$). There was a modest correlation

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