Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children

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Background: Wheezing illnesses cause major morbidity in infants and are frequent precursors to asthma.
Objective: We sought to examine environmental factors associated with recurrent wheezing in inner-city environments.
Methods: The Urban Environment and Childhood Asthma study examined a birth cohort at high risk for asthma (n = 560) in Baltimore, Boston, New York, and St Louis. Environmental assessments included allergen exposure and, in a nested case-control study of 104 children, the bacterial content of house dust collected in the first year of life. Associations were determined among environmental factors, aeroallergen sensitization, and recurrent wheezing at age 3 years.
Results: Cumulative allergen exposure over the first 3 years was associated with allergic sensitization, and sensitization at age 3 years was related to recurrent wheeze. In contrast, first-year exposure to cockroach, mouse, and cat allergens was negatively associated with recurrent wheeze (odds ratio, 0.60, 0.65, and 0.75, respectively; $P \leq .01$). Differences in house dust bacterial content in the first year, especially reduced exposure to specific Firmicutes and Bacteriodetes, was associated with atopy and atopic wheeze. Exposure to high levels of both allergens and this subset of bacteria in the first year of life was most common among children without atopy or wheeze.
Conclusions: In inner-city environments children with the highest exposure to specific allergens and bacteria during their first year were least likely to have recurrent wheeze and allergic sensitization. These findings suggest that concomitant exposure to high levels of certain allergens and bacteria in early life might be beneficial and suggest new preventive strategies for wheezing and allergic diseases. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Asthma, atopy, allergen exposure, microbial exposure, inner city*

Wheezing illnesses affect 35% to 50% of children by the age of 3 years[1,2] and are a leading cause for outpatient visits and hospitalizations.[3,4] Wheezing in nonatopic children is often transient, but recurrent wheezing in children with early allergic

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Abbreviation used
URECA: Urban Environment and Childhood Asthma

sensitization or other signs of atopy during the preschool years is a risk factor for asthma.[5] Because the prevalence and severity of asthma are high in inner cities in the United States, it is especially important to identify risk factors that contribute to the development of allergic sensitization and wheezing in this environment.

The indoor environment of poor urban neighborhoods can include adverse conditions that promote allergic sensitization and recurrent wheezing.[6] Examples include stress, lack of biodiversity, and exposure to indoor pollutants and perennial allergens, such as cockroach and mouse.[7-10] Conversely, farm-related microbial exposures in early life have been linked to protection against allergic diseases.[11,12] Whether relationships exist between microbial exposure and allergic disease outcomes in urban settings is unknown.

To examine the relationship between these conditions and development of allergic sensitization and recurrent wheezing, we studied children enrolled in an ongoing birth cohort study (Urban Environment and Childhood Asthma [URECA]). Per study design, the entire cohort was evaluated at age 3 years to test the hypothesis that high levels of exposure to sensitizing allergens, especially those associated with cockroach and mouse, is associated with the development of allergic sensitization and recurrent wheezing. In addition, a nested case-control study was designed to determine whether early-life exposure to certain microbes in house dust obtained from inner-city homes is associated with development of allergic sensitization and wheezing. The results of these 2 studies are presented in this report.

METHODS

Study design

URECA is a longitudinal birth cohort study in 4 urban areas: Baltimore, Boston, New York City, and St Louis.[13] Selection criteria included residence in an area with more than 20% of residents below the poverty level; mother or father with allergic rhinitis, eczema, and/or asthma; and birth at 34 weeks' gestation or later. Maternal questionnaires were administered prenatally, and participant questionnaires were administered every 3 months thereafter. Clinic visits occurred at 12, 24, 33, and 36 months, and homes were visited annually beginning at age 3 months for an environmental survey and house dust collection. Between February 2005 and March 2007, 1850 families were screened; 889 met the eligibility criteria, and 560 were enrolled. Informed consent was obtained from the parent or legal guardian of the infant.

Study assessments

Allergen-specific IgE (ImmunoCAP; Phadia, Uppsala, Sweden) levels were measured annually for milk, egg, peanut, and German cockroach. At 2 and 3 years of age, specific IgE levels for dust mites, dog, cat, mouse, and *Alternaria* species were also measured. Skin prick testing was performed at age 33 months for 14 common indoor and outdoor allergens.[13]

Household dust samples from the living room (chair or sofa and floor) and child's bedroom (mattress and floor) were collected, as described in the Methods section in this article's Online Repository at www.jacionline.org, and assayed for allergenic proteins, including Bla g 1 (cockroach), Can f 1 (dog), Fel d 1 (cat), Der f 1 and Der p 1 (house dust mites), and Mus m 1 (mouse), by using ELISA (Indoor Biotechnologies, Charlottesville, Va). A subsample (n = 104) of living room dust specimens collected at 3 months of age underwent culture-independent microbiome profiling with a 16S rRNA-based phylogenetic microarray (G3 PhyloChip; Second Genome, San Bruno, Calif; see the Methods section in this article's Online Repository for details) to generate a high-resolution profile of both dominant and rare microbiota members in each sample for comparative and correlative analyses. An approximately equal number of dust samples was randomly selected from each of 4 categories defined by clinical outcomes at age 3 years: (1) recurrent wheeze and aeroallergen sensitivity, (2) recurrent wheeze alone, (3) aeroallergen sensitivity alone, and (4) neither outcome (see Table E1 in this article's Online Repository at www.jacionline.org). This substudy population did not differ from the remainder of the cohort with respect to demographic characteristics or environmental exposures in the first year (see Table E2 in this article's Online Repository at www.jacionline.org).

Definitions

Aeroallergen sensitization was defined by a wheal 3 mm or more larger than that elicited by the saline control on skin prick testing or a specific IgE level of 0.35 kU/L or greater. Recurrent wheeze was defined as parental report of at least 2 wheezing episodes, with at least 1 episode occurring in the third year. Eczema was defined as a score of 1.0 or greater on the Eczema Area and Severity Index[14] at age 3 years. Children at higher risk for asthma were identified by using the modified Asthma Predictive Index.[15]

Statistical analysis

Demographic comparisons between recurrent wheezers and nonwheezers were tested by using Wilcoxon tests for continuous data and χ^2 tests for binary data. Univariate and multivariate analyses to determine association of exposures with sensitivity and recurrent wheeze were performed by using logistic regression. On the basis of this and previous analyses,[16] multivariate models were adjusted for race/ethnicity (strongly correlated with site), sex, mean perceived stress of the mother in the year after birth,[17] and number of smokers in the home.

The 3 allergen exposures showing a strong inverse relationship to recurrent wheeze (cockroach, mouse, and cat; see below) were combined into a single allergen exposure index based on tertiles of exposure to individual allergens (see the Methods section in this article's Online Repository). In addition, a dichotomous variable was created for exposure to each allergen (cockroach, mouse, and cat) to indicate whether the levels were greater than standard cutoffs (Bla g 1, 2 U/g; Mus m 1, 0.5 μg/g; and Fel d 1, 2 μg/g).[18]

Methods used to filter and analyze microbiome data are described in the Methods section in this article's Online Repository.

RESULTS

Factors related to recurrent wheeze in urban children

Of the 560 children in the URECA cohort, 478 (86%) remained in the study at age 3 years; 467 (83%) had sufficient data to assess recurrent wheeze, and 383 (68%) had serum IgE data available at age 3 years. Children included in the primary analysis (with complete follow-up data on wheeze, sensitization, and home allergen exposure data) differed from those not included in terms of study site and race/ethnicity but not allergen exposure (see Table E3 in this article's Online Repository at www.jacionline.org). Of these, 44% were sensitized to at least 1 aeroallergen, 36% had recurrent wheeze, and 9% had eczema (see Fig E1 in this article's Online Repository at www.jacionline.org). Furthermore, 12% of the cohort met the criteria for the modified Asthma Predictive Index, indicating a high risk for subsequent asthma. Factors related to recurrent wheeze were an annual family income of less than $15,000, lower birth weight and gestational age, and the number of smokers in the household