Prematurity, atopy, and childhood asthma in Puerto Ricans

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Background: Puerto Rican children share a disproportionate burden of prematurity and asthma in the United States. Little is known about prematurity and childhood asthma in Puerto Rican subjects.
Objective: We sought to examine whether prematurity is associated with asthma in Puerto Rican children.
Methods: We performed a case-control study of 678 children aged 6 to 14 years with (n = 351) and without (n = 327) asthma living in San Juan, Puerto Rico. Prematurity was defined by parental report for our primary analysis. In a secondary analysis, we only included children whose parents reported prematurity that required admission to the neonatal intensive care unit. Asthma was defined as physician-diagnosed asthma and wheeze in the prior year. We used logistic regression for analysis. All multivariate models were adjusted for age, sex, household income, atopy (≥1 positive IgE level to common allergens), maternal history of asthma, and early-life exposure to environmental tobacco smoke.
Results: In a multivariate analysis there was a significant interaction between prematurity and atopy on asthma (P = .006). In an analysis stratified by atopy, prematurity was associated with a nearly 5-fold increased odds of asthma in atopic children (adjusted odds ratio, 4.7; 95% CI, 1.5-14.3; P = .007). In contrast, there was no significant association between prematurity and asthma in nonatopic children. Similar results were obtained in our analysis of prematurity requiring admission to the neonatal intensive care unit and asthma.
Conclusions: Our results suggest that atopy modifies the estimated effect of prematurity on asthma in Puerto Rican children. Prematurity might explain, in part, the high prevalence of atopic asthma in this ethnic group. (J Allergy Clin Immunol 2014;133:357-62.)

Key words: *Childhood asthma, prematurity, Puerto Rican, atopy*

Abbreviations used
ETS: Environmental tobacco smoke
FVC: Forced vital capacity
NICU: Neonatal intensive care unit
OR: Odds ratio

Asthma is the most common chronic disease of childhood in the United States.[1,2] In this country, the prevalence of childhood asthma is higher in Puerto Rican subjects (16.1%) and non-Hispanic black subjects (11.2%) than in non-Hispanic white subjects (7.7%) or Mexican American subjects (5.4%).[2] Puerto Rican children living on the island of Puerto Rico have an even higher prevalence of asthma than those living on the US mainland.[3] Poverty is a contributory factor but not the sole explanation for the high asthma prevalence in Puerto Rican children.[4]

Prematurity might explain, in part, the high prevalence of childhood asthma in Puerto Rican subjects. In the United States the preterm birth rate is higher among Puerto Rican (13.4%) or non-Hispanic black (17.1%) women than among non-Hispanic white (10.8%) or Mexican American (11.3%) women.[5] Furthermore, the proportion of children born prematurely is higher on the island of Puerto Rico (17.6%) than in any other state or territory of this country.[6] Whereas prematurity has been consistently associated with an increased risk of asthma in preschool-age children,[7-9] there is conflicting evidence of a link between prematurity and asthma in school-age children (in whom a diagnosis of asthma is more likely to be accurate). For example, a meta-analysis that included 19 observational studies (published between January 1966 and May 2005) showed that although prematurity was associated with a nearly 40% excess odds of asthma in children of all ages (pooled odds ratio [OR], 1.37; 95% CI, 1.30-1.43),[7] this association became weaker and nonsignificant (pooled OR, 1.19; 95% CI, 0.94-1.51) when the analysis was restricted to studies of older participants (ie, children ≥10 years old). Whether atopy modifies the effects of prematurity on asthma at school age is unknown.

Even though Puerto Rican subjects share a disproportionate burden of prematurity and asthma in the United States, no study has examined the relation between these 2 conditions in this ethnic group.

We hypothesized that prematurity would be associated with asthma in Puerto Rican children but that this association would differ depending on atopic status. To test this hypothesis, we examined the relation between prematurity and asthma in a case-control study of 678 school-age Puerto Rican children living in San Juan, Puerto Rico.

METHODS

Subject recruitment

From March 2009 to June 2010, children in San Juan were chosen from randomly selected households. As previously described,[10,11] households in

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the metropolitan area of San Juan were selected by using a multistage probability sampling design. Primary sampling units were randomly selected neighborhood clusters based on the 2000 US Census, and secondary sampling units were randomly selected households within each primary sampling unit. A household was eligible if 1 or more residents were children aged 6 to 14 years. In households with 1 or more eligible children, only 1 child was randomly selected for screening. On the basis of the sampling design, 7073 households were selected, and 6401 (approximately 91%) were contacted. Of these 6401 households, 1111 had 1 or more children within the age range of the study who met other inclusion criteria (see below). In an effort to reach a target sample size of approximately 700 children (which would give us ≥90% power to detect an OR of ≥2 for exposures with a prevalence of ≥25%), we attempted to enroll a random sample (n = 783) of these 1111 children. Parents of 105 of these 783 eligible households refused to participate or could not be reached. There were no significant differences in age, sex, or area of residence between eligible children who did (n = 678 [86.6%]) and did not (n = 105 [13.4%]) agree to participate. We selected as cases children who had physician-diagnosed asthma and wheeze in the previous year (n = 351). We selected as control subjects children who had neither physician-diagnosed asthma nor wheeze in the prior year (n = 327). All study participants had to have 4 Puerto Rican grandparents to ensure their Puerto Rican descent.

Study procedures

Study participants completed a protocol that included administration of questionnaires, spirometry, and collection of blood samples (for measurement of serum total and allergen-specific IgE levels). One of the child's parents (usually [for approximately 93% of subjects] the mother) completed a questionnaire that was slightly modified from one used in the Collaborative Study of the Genetics of Asthma.[12] This questionnaire was used to obtain information about the child's general and respiratory health; sociodemographic characteristics; family history of asthma, allergic rhinitis, or eczema; current exposure to environmental tobacco smoke (ETS); and early-life exposure to ETS (*in utero* or before 2 years of age).

Height and weight were measured to the nearest centimeter and pound, respectively. Spirometry was conducted with an EasyOne spirometer (NDD Medical Technologies, Andover, Mass). All participants had to be free of respiratory illnesses for 4 or more weeks, and they were also instructed to avoid (when possible) the use of inhaled short- and long-acting bronchodilators for 4 or more and 12 or more hours before testing, respectively. Forced expiratory maneuvers were judged to be acceptable if they met or exceeded American Thoracic Society criteria modified for children.[13] The best FEV_1 and forced vital capacity (FVC) values were selected for data analyses. Serum levels of total IgE and IgE specific to common allergens (dust mite [Der p 1], cockroach [Bla g 2], cat dander [Fel d 1], dog dander [Can f 1], and mouse urinary protein [Mus m 1]) were determined by using the UniCAP 100 system (Pharmacia & Upjohn, Kalamazoo, Mich). For each allergen, an IgE level of 0.35 IU/mL or greater was considered positive.

Written parental consent was obtained for participating children, from whom written assent was also obtained. The study was approved by the Institutional Review Boards of the University of Puerto Rico (San Juan, Puerto Rico), Brigham & Women's Hospital (Boston, Mass), and the University of Pittsburgh (Pittsburgh, Pa).

Statistical analysis

For our primary analysis, prematurity was treated as a binary variable based on parental response to the following question: "Was your child born prematurely?" For our secondary analysis, prematurity requiring neonatal intensive care unit (NICU) admission was treated as a binary variable based on a positive response to the question on prematurity, as well as to the following question: "Was your child kept in a neonatal intensive care unit?" Our outcome of interest was asthma (defined as physician-diagnosed asthma and wheeze in the previous year).

For each continuous variable, we used 2-sample *t* tests to compare 2 groups. For the comparison of each binary variable between 2 groups, we used Fisher exact tests. For the multivariate analysis, we used a stepwise approach to build the logistic regression models. Because of their well-established association with prematurity, asthma, or both, all models included age,[2] sex,[14] household income (<$15,000/y vs ≥$15,000/y [near the median income for households in Puerto Rico in 2008-2009]),[4,15,16] maternal history of asthma and early-life exposure to ETS.[17] The following covariates were also included in the initial multivariate models if they were associated with asthma at a *P* value of .20 or less in bivariate analyses: body mass index as a *z* score (based on 2000 Centers for Disease Control and Prevention growth charts),[18,19] low birth weight (<2500 g), mode of delivery (cesarean vs vaginal birth), total IgE level (transformed to a logarithmic [log_{10}] scale), atopy (≥1 positive allergen-specific IgE), current exposure to ETS, parental education (≥1 parent completed high school vs none), type of health insurance (private or employer-based health insurance vs others), maternal history of 1 or more atopic diseases (asthma, allergic rhinitis, or eczema), and lung function measures (FEV_1 and FEV_1/FVC ratio). These additional covariates remained in the final models if they were associated with asthma at a *P* value of less than .05 or if they changed the parameter estimate (β) by 10% or greater. After the final models were built, we tested for first-order interactions between prematurity and the other covariates in the models. We assessed the overall goodness of fit of each model using the Hosmer-Lemeshow test.

As a confirmatory step, we conducted a conditional logistic regression analysis of prematurity and asthma after matching cases and control subjects through propensity scoring (see the Methods section in this article's Online Repository at www.jacionline.org). Statistical significance was defined as a *P* value of less than .05. All statistical analyses were performed with SAS version 9.3 software (SAS Institute, Cary, NC).

RESULTS

Compared with control subjects, cases were significantly more likely to be younger, to be male, to be atopic (ie, to have ≥1 positive allergen-specific IgE), to be exposed to ETS (currently or in early life), and to have a history of prematurity or prematurity requiring NICU admission, a higher total IgE level, a maternal history of asthma or 1 or more atopic diseases, and a lower FEV_1 and FEV_1/FVC ratio (Table I).

Table II shows a comparison of participating children with and without a history of prematurity (jointly and separately in cases and control subjects). In this analysis low birth weight was significantly associated with prematurity in cases, control subjects, and all subjects combined. Current exposure to ETS was significantly associated with prematurity in control subjects only. There was no significant association between any other variable (eg, indicators of socioeconomic status or atopy) and prematurity in cases, control subjects, or all subjects combined.

A comparison of participating children with and without a history of prematurity requiring NICU admission (jointly and separately in cases and control subjects) is shown in Table E1 in this article's Online Repository at www.jacionline.org. In this analysis, low birth weight was significantly associated with prematurity requiring NICU admission in cases, control subjects, and all subjects combined. There was no significant association between any other variable and prematurity requiring NICU admission in cases, control subjects, and all subjects combined.

After excluding subjects without data on allergen-specific IgE levels, 287 (approximately 88%) of the 327 control subjects and 305 (approximately 87%) of the 351 cases remained in the multivariate analysis of prematurity and asthma. Compared with those not included in this analysis, control subjects and cases were more likely to have a household income of less than $15,000/y, and control subjects were less likely to have private/employer-based health insurance. There were no other significant differences between control subjects or cases that were and were not