



Combined effects of multiple risk factors on asthma in school-aged children

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ABSTRACT

Background: Little is known about synergistic effects of several risk factors on asthma. We developed a risk score in Puerto Rican children, and then used this score to estimate the combined effects of multiple risk factors on asthma at school age in Puerto Rican and Swedish children.

Methods: Case-control study in 609 Puerto Rican children (aged 6–14 years) and longitudinal birth cohort study of 2290 Swedish children followed up to age 12 years (The Children, Allergy, Milieu, Stockholm, Epidemiological Survey [BAMSE] Study). In both cohorts, there was data on parental asthma, sex, obesity, allergic rhinitis, and early-life second-hand smoke (SHS); data on diet and (in children ≥ 9 years) lifetime exposure to gun violence were also available in the Puerto Rico study. Asthma was defined as physician-diagnosed asthma and ≥ 1 episode of wheeze in the previous year.

Results: In a multivariable analysis in Puerto Rican children, male sex, parental asthma, allergic rhinitis, early-life SHS, an unhealthy diet and (in children ≥ 9 years) gun violence were each significantly associated with asthma. We next created a risk score using these variables (range, 0 to 5-6 in Puerto Rico and 0 to 4 in BAMSE). Compared with Puerto Rican children without any risk factors (i.e. a score of 0), Puerto Rican children with 2, 3, and at least 4 risk factors had 3.6 times (95% CI = 1.4–9.2), 10.4 times (95% CI = 4.0–27.0), and 21.6 times (95% CI = 7.2–64.9) significantly higher odds of asthma, respectively. In BAMSE, the presence of 2, 3, and at least 4 risk factors was significantly associated with 4.1 times (95% CI = 2.3–7.4), 6.3 times (95% CI = 3.0–13.3), and 17.2 times (95% CI = 4.1–73.2) increased odds of asthma at age 12 years.

Conclusions: Our findings emphasize the multifactorial etiology of asthma, and suggest that concurrent eradication or reduction of several modifiable risk factors may better prevent or reduce the burden of childhood asthma.

1. Introduction

Asthma is the most common chronic respiratory disease and a major public health problem among children worldwide, including those living in the United States (U.S.) and Sweden [1]. In the U.S., the prevalence of asthma at school age is higher in Puerto Ricans (16.1%) than in non-Hispanic (NH) blacks (11.2%), NH whites (7.7%) or Mexicans (5.4%) [2]. Among Swedish children aged 7 to 8 years, estimates

of the prevalence of physician-diagnosed asthma and current wheeze were 7.4% and 13% in 2006 [3].

A growing body of literature supports a multifactorial etiology for childhood asthma, including combined or interacting effects of non-modifiable (i.e. heredity and sex) and modifiable (i.e. environment and behavior) risk factors. Indeed, current evidence suggests causal roles for potentially modifiable exposures or behaviors on asthma, including but not limited to second-hand smoke (SHS), overweight or obesity,

Abbreviations: OR, odds ratio; CI, confidence interval; SHS, second-hand smoke

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unhealthy dietary patterns, changes in the gut microbiome, chronic pre- and perinatal stress, and indoor and outdoor pollutants [4]. Although children in high-risk populations are often concurrently exposed to several of these risk factors, most published studies have focused on a single risk factor (adjusting for the presence of other risk factors) or on the interaction between two risk factors for asthma [5,6].

In this study, we aimed to estimate the combined effects of risk factors for asthma in two studies of school-aged children. We first identified risk factors for asthma in a cross-sectional case-control study of Puerto Rican children ages 6 to 14 years, and built a risk score based on this information. We then tried to replicate our findings for the risk score in a longitudinal birth cohort study of Swedish children, in whom risk factors were identified at ages 1 to 4 years, and asthma was then assessed at the ages of 8 and 12 years. Using the risk score, we then estimated the combined effects of several risk factors on childhood asthma in two studies that differ with regard to overall design, geographic location, and population characteristics (e.g., racial ancestry, environment, and socioeconomic factors).

2. Methods

2.1. Subject recruitment and study procedures

2.1.1. Puerto Rico

Details on subject recruitment and study design have been previously described [7]. In brief, from March 2009 to June 2010, children were recruited from randomly selected households in San Juan, using a multistage probabilistic sampling design. A household was eligible if ≥ 1 resident was a child aged 6 to 14 years who had four Puerto Rican grandparents and had lived in the household for at least one year. Of 1111 eligible households, 438 (~39%) had ≥ 1 child with asthma (defined as physician-diagnosed asthma and at least one episode of wheeze in the prior year). From those 438 households, one child with asthma was selected (at random, if there was more than one such child). Similarly, one child without asthma was randomly selected from the remaining 673 households. In an effort to reach a target sample size of ~700 children (which would give us $\geq 90\%$ power to detect an odds ratio (OR) ≥ 2 for exposures with a prevalence $\geq 25\%$), 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, gender, or area of residence between eligible children who did ($n = 678$ [86.6%]) and did not ($n = 105$ [13.4%]) agree to participate. Of the 678 study participants, 609 (89.8%) had complete data on body mass index (BMI), and are thus included in the current analysis.

The caretaker of study participants (usually [$\geq 93\%$] the mother) completed two questionnaires, the first on the child's general and respiratory health (which was used to obtain information on demographics, socioeconomic status, family history and SHS), and the second on the child's food consumption in the prior week. The Exposure to Violence (ETV) survey [8] was also administered to participants 9 years and older. Internal consistency, test-retest reliability and validity have been established for both the English and Spanish versions of the ETV survey [9]. Height and weight were measured in all participants to the nearest centimeter and pound, respectively.

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, PR) and the University of Pittsburgh (Pittsburgh, PA).

2.1.2. The Children, Allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE) study

Subject recruitment and baseline characteristics of participants in the BAMSE Swedish birth cohort study have been previously described [10,11]. In brief, between 1994 and 1996, 4089 newborn infants were recruited and questionnaire data were obtained. Subjects were

recruited from central and northwestern parts of Stockholm, including both urban and suburban districts. Questionnaires on environment and lifestyle, as well as symptoms related to asthma and other allergic diseases were administered to the parents of participants when they were 1, 2, 4, 8 and 12 years of age. The response rates at ages 1, 2, 4, 8 and 12 years were 96%, 94%, 91%, 84%, and 82%, respectively. In this study, we included children with complete data up to 8 ($n = 2339$) and 12 ($n = 2290$) years.

The study was approved by the ethics committee at the Karolinska Institute, and parental consent was obtained for all children included in this report.

2.2. Statistical analysis

The primary outcome of interest was asthma, defined in both the Puerto Rico study and in BAMSE as physician-diagnosed asthma and at least one episode of wheeze in the previous year.

On the basis of their prior association with childhood asthma in our study in Puerto Rico, we examined the following variables: age, sex, low household income (defined as $< \$15,000/\text{year}$, the median household income for Puerto Rico in 2008–2009) [12], parental (paternal or maternal) history of asthma, exposure to SHS in early life (*in utero* or before age 2 years) [13], allergic rhinitis (defined as physician-diagnosed allergic rhinitis and naso-ocular symptoms apart from colds in the previous year) [14], obesity (defined as a BMI z-score $\geq 95\text{th}$ percentile) [15], an unhealthy diet (a score of 1 or 2 in a diet scale, indicating higher consumption of sweets and dairy products) [16], and (in children 9 years and older only) lifetime exposure to gun violence (defined as having heard two or more gunshots) [17]. Parental asthma, early-life SHS, allergic rhinitis (at age 4 years, when this diagnosis is more common), and obesity (at age 4 years) were defined in BAMSE in the same manner as in the Puerto Rico study. Data on exposure to violence or diet were not available in BAMSE.

Bivariate analyses were conducted using Fisher's exact tests for binary variables and two-tailed t-tests for pairs of binary and continuous variables. A backward stepwise regression approach was used to build the multivariable models in the Puerto Rico study. The initial models included all variables listed above. Variables that were significantly associated with asthma at $P < 0.05$ or changed the effect estimate ([OR]) $\geq 10\%$ were included in the final models. In Puerto Rico, separate models were built for all children (ages 6 to 14 years) and for children 9 years and older. Variables from the final models were then used to create a risk score for each age group in Puerto Rico, and then in BAMSE.

For the risk score, population attributable risk (PAR) estimates proportion of the incidence of a disease in the population (exposed and unexposed) that is due to the exposure. It is the incidence of disease in the population that would be eliminated if exposure were eliminated. The PAR was calculated by subtracting the incidence in the unexposed (I_u) from the incidence in total population (exposed and unexposed) (I_p). Population attributable risk percent (PAR%) was then calculated by dividing the PAR by the incidence in the total population and then multiplying by 100: $[(I_p - I_u)/I_p] * 100$.

SAS version 9.3 (SAS Institute, Cary, NC) and STATA (release 13; Stata Corp., College Station, TX, USA) were used for data analysis.

3. Results

The main characteristics of the 609 participants in the Puerto Rico study are summarized in Table 1. Compared with control subjects, children with asthma (cases) were significantly younger and more likely to be male, to have been exposed to SHS in early life, and to have a parental history of asthma, allergic rhinitis and an unhealthy diet. Among 426 children ages 9 and older, cases were also more likely to have ever been exposed to gun violence than control subjects. There was no significant difference in household income between cases and

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