ONLINE REPOSITORY

Supplemental Methods

Detailed descriptions of the School Inner-city Asthma Study (SICAS) study has previously been published [1, 2], but will be briefly summarized here.

Study design

The School Inner-city Asthma Study (SICAS) is a single-center prospective cohort study of children with persistent asthma attending inner-city elementary schools in a northeastern United States city from 2008-2013. Children with persistent asthma attending these schools were recruited based on established inclusion criterion [3]; 1) history of physician diagnosed asthma and either current symptoms defined as cough, wheezing, shortness of breath, or whistling in the chest in the past 12 months, daily controller medication use, or unscheduled medical visits for asthma in the past year 2) attendance in grades kindergarten through 6th grade at a school where permission for environmental sampling had been obtained. Exclusion criteria included any significant pulmonary disease other than asthma. Written informed consent was obtained from each participant's parent or legal guardian, and assent was obtained from each participant. The protocol was approved by the Institutional Review Board (protocol number 07-11-0465) and the participating school system.

Study procedures

Screening questionnaires were collected each spring in participating schools to identify eligible asthmatics. Eligible subjects were invited to participate in a baseline comprehensive clinical phenotyping evaluation during the summer, which included a detailed questionnaire and allergy skin testing (MultiTest device, Lincoln Diagnostics, Decatur, IL) or specific IgE (ImmunoCAP, Phadia AB, Uppsala, Sweden) if skin testing was contraindicated. Self-reported race was obtained during this baseline clinic visit by asking the child's parent or taker a multiple-choice question as follows: "How would you describe [CHILD]'s race, nationality, or ethnic background?" .

Home and classroom air and dust samples were subsequently collected twice during the academic school year and linked to enrolled students and the temporally closest longitudinally collected health outcomes. Follow-up phone surveys were administered by study staff approximately 3, 6, 9, and 12 months after the initial visit.

School exposure assessment was performed in the fall and spring of the school year. One week classroom airborne dust samples were collected using charged particle samplers (Quadra, Sharper Image, California) based on a validated protocol [4, 5]. Collected dust was extracted in buffered saline and the endotoxin content was measured using the Limulus amoebocyte lysate assay (BioWhittaker Inc., Walkersville, MD).

The outcome of asthma symptom days is defined as follows, and is the same as that used in prior urban pediatric asthma studies [6-8]. It is defined as the largest of the following variables in the 2 weeks prior to each follow-up survey; 1) daytime wheezing, chest tightness, or cough OR 2)

days on which child had to slow down or discontinue play activities due to wheezing, chest tightness, or cough OR 3) nights with wheezing, chest tightness, or cough leading to disturbed sleep.

The IL4Rα-Q576R polymorphism is also referred to as the IL4Rα-Q551R polymorphism depending on the amino acid numbering approach used. Genotyping was performed on blood or saliva samples collected during the baseline evaluation during the summer. Genotyping of the *IL4R*^{Q576} and *IL4R*^{R576} alleles was carried out using the amplification resistance mutation screen PCR method [9] on DNA was extracted from either whole blood (Gentra Puregene Blood Kit; Qiagen) or saliva (prepIT L2P; DNA Genotek).

Statistical Analysis

The IL4Rα-Q576R genotypes were modeled as a three-group categorical variable (*Q/Q*, *Q/R*, or *R/R* genotypes, with the *Q/Q* genotype as the reference group). We chose this approach because we did not want to assume a linear dose-response effect of the genotypes in our modeling approach. School endotoxin exposure was modelled as a log-transformed continuous variable given the skewed distribution. To test the hypothesis that the genotypes differed by self-reported race, Fisher's exact tests were performed. To test the hypothesis that a gene-environment interaction was present, a multiplicative term between classroom endotoxin levels (continuous) and genotype (3-level categorical variable) was included in binomial family generalized estimating equations with a logit link and an overdispersion parameter. These models included only observations during the school year, and adjusted for age, gender, self-reported race, allergic sensitization, baseline asthma severity, use of asthma controller medications, annual income, and season (using linear and quadratic terms for days since school start). All statistical analyses were performed in Stata version 13.1 (StataCorp). Two-sided p-values of <0.05 were considered statistically significant for main effects; p-values of <0.10 were considered statistically significant for interactions.

Supplemental Results

In univariate analyses adjusting for repeated measures of asthma symptom days in the same participant, the average number of asthma symptom days in a 14-day period for these children differed based on their IL4Rα-Q576R polymorphism status, with average symptom days being 2.9 ± 4.0, 3.0 ± 4.1, and 3.6 ± 4.4 in children with the wild type, heterozygote, and homozygote mutant alleles, respectively, though these results did not reach statistical significance ($p = 0.33$). Similarly, in univariate analyses, the association between classroom endotoxin exposure and asthma symptom days did not reach statistical significance (OR= 1.11 [0.90,1.37], p=0.31).

Supplementary Table 1. Allele frequency by self-reported race for IL4Rα-Q576R polymorphism.

Self-reported race	*Q* allele frequency	*R* allele frequency
White	0.875	0.125
Black	0.327	0.673
Hispanic	0.585	0.415
Other	0.488	0.512
Mixed	0.312	0.688

Supplementary Table 2. Predicted asthma symptom days per two-week period stratified by IL4Rα-Q576R genotype and classroom endotoxin levels. There is a gene by environment (G×E) interaction. The overall interaction p-value = 0.09; pairwise interaction p-values for *Q/R* vs. *Q/Q* = 0.115, *R/R* vs. *Q/Q* = 0.049.

	Q/Q genotype	*Q/R* genotype	*R/R* genotype
10^{th} percentile endotoxin (3.06 EU/m^3)	3.6 [2.6 – 4.6] days	2.8 [1.9 – 3.6] days	3.1 [1.9 – 4.4] days
90th percentile endotoxin (153.11 EU/m^3)	2.6 [1.7 – 3.4] days	3.1 [2.3 – 4.0] days	4.4 [3.1 – 5.7] days

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