



Cockroach allergen exposure and plasma cytokines among children in a tropical environment



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ABSTRACT

Background: Little is known about the effects of socioeconomic status or cockroach allergen on immune responses in school-age children, particularly in tropical environments.

Objective: To examine whether cockroach allergen and/or socioeconomic status is associated with plasma cytokine levels in Puerto Rican children.

Methods: This was a cross-sectional study of 532 children (6–14 years old) with ($n = 272$) and without ($n = 260$) asthma in San Juan (Puerto Rico). House dust allergens (cockroach [Bla g 2], dust mite [Der p 1], cat dander [Fel d 1], dog dander [Can f 1], and mouse urinary protein [Mus m 1]) were quantified using monoclonal antibody arrays. A panel of 14 cytokines (interleukin [IL]-1 β , IL-4, IL-6, IL-10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, interferon- γ , and tumor necrosis factor- α) was measured in plasma samples. Low household income was defined as less than \$15,000 per year (below the median income for Puerto Rico in 2008–2009). Linear regression was used for the analysis of cockroach allergen and plasma cytokines.

Results: In a multivariable analysis adjusting for low income and other allergen levels, cockroach allergen was significantly associated with decreased IL-17A and with increased levels of 8 cytokines (IL-4, IL-10, IL-17F, IL-21, IL-25, IL-31, interferon- γ , and tumor necrosis factor- α). After stratifying this analysis by cockroach allergy (ie, having a cockroach positive immunoglobulin E reaction), our findings remained largely unchanged for children sensitized to cockroach but became weaker and statistically nonsignificant for non-sensitized children.

Conclusion: Cockroach allergen has broad effects on adaptive immune responses in school-age children in a tropical environment, particularly in those sensitized to cockroach.

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Introduction

Asthma is a major public health problem and the most common chronic non-communicable disease in children in the United States.¹ In this country, the burden of asthma is unequally shared among racial or ethnic groups, with Puerto Ricans having a higher prevalence of childhood asthma (20.7%) than non-Hispanic blacks (13.4%) or non-Hispanic whites (7.5%).^{2,3}

Racial or ethnic disparities in asthma are mediated in part by low socioeconomic status (SES).^{3–6} Among US residents in 2010,

the estimated prevalence of asthma was higher (11.2%) in individuals living below the federal poverty level (FPL) than in those living at 100% to 200% of the FPL (8.7%) or in those living 200% above the FPL (7.3%).⁵ Similar results were reported in 2013, when asthma prevalence was 10.9% among individuals living below the FPL vs 6% to 7% among those living above the FPL.³ This link between low SES and asthma or asthma morbidity is likely explained by environmental and behavioral risk factors correlated with poverty.

Low SES is associated with poor housing conditions⁷ leading to exposure to cockroach allergen, particularly at high levels.^{8,9} In 1 study, residential areas where poverty was common (>20% of homes below the FPL) had 33 times higher odds of cockroach allergen exposure than other residential areas.¹⁰ Not surprisingly, sensitization to cockroach allergen is common in inner-city children (36.8%)¹¹ and Puerto Rican children (41.5%), who are disproportionately represented among the poor.¹²

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Cockroach allergen exposure can lead to alterations in adaptive and innate immunity, including allergic sensitization and atopic asthma.¹³ Cockroach sensitization, a strong risk factor for asthma, occurs more frequently in residents of neighborhoods with high asthma prevalence than in those living in neighborhoods with low asthma prevalence.¹⁴ Moreover, cockroach allergen exposure is a causative factor for severe asthma exacerbations, particularly in sensitized individuals.¹⁵ For example, children who are exposed and sensitized to cockroach allergen are 3.4 times more likely to be hospitalized for asthma than unexposed children.¹¹ In 1 neighborhood-based study, housing code violations (which are correlated with cockroach allergen exposure) accounted for 22% of the variability in asthma-related emergency department visits, even after accounting for income.¹⁶

Poverty has been linked to increased circulating interleukin (IL)-6 in children and adults, with limited evidence suggesting a similar link with circulating T-helper cell type (T_H) T_H1 or T_H2 cytokines in adolescents. In studies of school-age children and middle-age adults, low SES during childhood has been associated with increased serum IL-6 measured after stimulation of peripheral blood mononuclear cells with mitogen or endotoxin.^{17,18} In a study of 30 adolescents with persistent asthma in Saint Louis, Missouri, subjects living in low-SES neighborhoods had higher levels of IL-5 and interferon- γ (IFN- γ), measured after mitogen stimulation of peripheral blood mononuclear cells, than those living in high-SES neighborhoods.¹⁹

Given that cockroach allergen leads to cockroach allergy in humans, surprisingly few studies have examined cockroach allergen exposure and immune responses or circulating cytokines in children. In a study of 560 children with parental history of asthma or allergies, levels of *Blattella germanica* (Bla g 1) in bed dust were not associated with any mononuclear cell cytokine response to adaptive stimuli at birth.²⁰ In another study of 114 children with parental history of asthma or allergies, indoor cockroach allergen level at 3 months of age was associated with increased cockroach-specific lymphoproliferative responses at 2 years.²¹

To date, little is known about the relation between poverty or cockroach allergen and adaptive immune responses in school-age children. We hypothesized that low SES would lead to broadly abnormal adaptive immune responses in school-age children, and that this would be mainly explained by cockroach allergen exposure. To test this hypothesis, we conducted a cross-sectional study of low household income, cockroach allergen exposure, and plasma cytokine levels (encompassing T_H1 , T_H2 , regulatory T cell, and T_H17 -related cytokines) of 532 Puerto Rican children living in San Juan (Puerto Rico).

Methods

Subject Recruitment

Details on subject recruitment and study design have been previously reported.^{22,23} 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 at least 1 resident was a child 6 to 14 years old who had 4 Puerto Rican grandparents and had lived in the household for at least 1 year. Of 1,111 eligible households, 438 (~39%) had at least 1 child with asthma (defined as physician-diagnosed asthma and ≥ 1 episode of wheeze in the prior year). From those 438 households, 1 child with asthma was selected (at random, if there was > 1 such child). Similarly, 1 child without asthma was randomly selected from the remaining 673 households. In an effort to reach a target sample size of approximately 700 children (which would provide $\geq 90\%$ power to detect an odds ratio ≥ 2 for exposures with a prevalence $\geq 25\%$), we attempted to enroll a random sample ($n = 783$) of these 1,111 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. Of the 678 study participants, 532 (79%) had complete data on household income, cockroach allergen levels in house dust, and plasma cytokines and thus were included in the present analysis.

Study Procedures

Participants completed a protocol including questionnaires and collection of house dust and blood samples. The questionnaire, a modified version of one used in the Collaborative Study of the Genetics of Asthma,²⁴ was completed by one of the child's parents (usually [$\geq 93\%$] the mother). This questionnaire was used to obtain information about the child's general and respiratory health and sociodemographic characteristics. Dust samples were obtained from 3 areas in the home: the one in which the child slept (usually the child's bedroom), the living room or television room, and the kitchen. The dust was sifted through a 50-mesh metal sieve, and the fine dust was reweighed, extracted, and aliquoted for analysis of allergens from *B. germanica* (Bla g 2), *Dermatophagoides pteronyssinus* (Der p 1), cat dander (Feld d 1), dog dander (Can f 1), and mouse urinary protein (Mus m 1) using monoclonal antibody multiplex array assays with the same reagents used in the established enzyme-linked immunosorbent.²⁵ Endotoxin was measured in a subset of participants ($n = 348$) using the kinetic chromogenic limulus amebocyte lysate assay, multiple dilutions, and a 12-point standard curve based on control standard endotoxin from *Escherichia coli* (range 0.0244–50.0 EU/mL).²⁶ Nondetectable levels of allergens or endotoxin were assigned a small constant, with all levels $\log_{10}$ -transformed for analysis.

A panel of 14 cytokines (enriched for T_H17 cytokines and including IL-1 β , IL-4, IL-6, IL-10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, IFN- γ , and tumor necrosis factor [TNF]- α) was measured in plasma samples using the Bio-Plex Pro Human T_H17 cytokine panel on the BioPlex HTF system (Bio-Rad Laboratories, Hercules, California) according to the manufacturer's instructions, with all samples measured in duplicate. After assigning a small constant (half the lowest detectable level; Table 1) to nondetectable levels, plasma cytokine levels were $\log_{10}$ -transformed for data analysis, which led to an approximately normal distribution for all cytokines. To account for multiple testing, we calculated a Bonferroni-corrected P value for statistical significance (.05 for 14 tests, or .00357).

For each participant, global percentage of African ancestry was estimated from genomewide genotypic data using the Local Ancestry in admixed Populations (LAMP) method and software^{27,28}

Table 1
Lowest Detectable Limit of Assays Used for Cytokine Measurements (N = 532)

Cytokine	LLD (pg/mL)	Value under LLD, n (%)
IL-1 β	0.02	19 (3.6)
IL-4	0.52	210 (39.5)
IL-6	0.67	56 (10.5)
IL-10	0.3	166 (31.2)
IL-17A	0.49	142 (26.7)
IL-17F	0.8	197 (37.0)
IL-21	2.13	330 (62.0)
IL-22	0.03	177 (33.3)
IL-23	1.55	474 (89.1)
IL-25	0.07	3 (0.56)
IL-31	0.49	97 (18.2)
IL-33	0.58	39 (7.33)
Interferon- γ	0.43	175 (32.9)
Tumor necrosis factor- α	0.07	1 (0.2)

Abbreviations: IL, interleukin; LLD, lowest limit of detection.

as previously described.²² Immunoglobulin E (IgE) reaction to cockroach allergen (Bla g 2) was measured in plasma using the UniCap 100 system (Kalamazoo, Michigan). A positive cockroach-specific IgE reaction was defined as at least 0.35 IU/mL.

Written parental consent was obtained for participating children, from whom written assent also was obtained. The study was approved by the institutional review boards of the University of Puerto Rico (San Juan, Puerto Rico), Brigham and Women's Hospital (Boston, Massachusetts), and the University of Pittsburgh (Pittsburgh, Pennsylvania).

Statistical Analysis

The outcome of interest was log₁₀-transformed plasma cytokine levels. Exposures of interest were low household income (defined as <\$15,000/year, the median household income for Puerto Rico in 2008–2009)²⁹ and log-transformed cockroach allergen level in house dust. Low household income was selected as the primary indicator of SES based on our prior work in Puerto Rico. Linear regression was used for bivariate and multivariable analyses of plasma cytokines. All multivariable models of low income or cockroach allergen (first analyzed separately and then within the same model) and plasma cytokines were adjusted for age, sex, and case and control status. Because of their potential correlation with household income and/or cockroach allergen, the following covariates were examined in bivariate analyses and considered for inclusion in the multivariable models: low parental education (neither parent completed high school vs ≥1 parent completed high school), percentage of African ancestry,²² current exposure to secondhand smoke (SHS),³⁰ early life (in utero or before 2 years of age) exposure to SHS, log-transformed levels of other allergens (dust mite, dog dander, cat dander, and mouse urinary protein) and endotoxin,^{31,32} and residential distance to a major roadway (meters).³³ In secondary analyses, we stratified children by case and control status or by having a positive cockroach-specific IgE reaction; these secondary analyses were not adjusted for endotoxin levels because of the small sample.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

Compared with subjects excluded from this analysis (n = 146), those included (n = 532) were significantly more likely to have low income and low parental education. However, there were no significant differences in indoor level of any allergen (including cockroach) or endotoxin, age, sex, early or current exposure to SHS, residential distance to a major road, or percentage of African ancestry between those who were and were not included in the analysis (data not shown).

Table 2 presents the main characteristics of the 532 study participants. Compared with control subjects, children with asthma (cases) were significantly younger, more likely to be male, and more likely to have been exposed to a lower cat allergen level. There were no significant differences in household income, parental education, exposure to SHS (currently or in early life), residential distance to a major road, percentage of African ancestry, or house dust levels of other allergens (Bla g 2, Der p 1, Can f 1, or Mus m 1) or endotoxin between cases and controls.

In bivariate analyses, cockroach allergen was most significantly and consistently associated with plasma cytokines (Table 3). Cockroach allergen was significantly associated with decreased IL-17A and increased IL-4, IL-6, IL-10, IL-17F, IL-21, IL-22, IL-25, IL-31, IL-33, IFN-γ, and TNF-α. Cat and dog allergen levels were each significantly associated with increased IL-10 and IL-22. Age, sex, low household income, low parental education, and residential distance to a road were each significantly associated with 1 to 2

Table 2
Main Characteristics of Study Participants^a

	Controls (n = 260)	Cases (n = 272)
Age (y)	11.1 (2.7)	10.6 (2.6) ^b
Boys	125 (48.1%)	156 (57.4%) ^b
Annual household income <\$15,000	171 (65.8%)	188 (69.1%)
Neither parent completed high school	57 (21.9%)	51 (18.8%)
Bla g 2 in house dust (U/g) ^c	0.272 (0.667)	0.311 (0.721)
Der p 1 in house dust (μg/g) ^c	0.648 (0.504)	0.663 (0.513)
Mus m 1 in house dust (ng/g) ^c	0.957 (0.930)	1.040 (1.018)
Fel d 1 in house dust (μg/g) ^c	−1.344 (1.100)	−1.558 (0.913) ^b
Can f 1 in house dust (μg/g) ^c	−0.713 (0.885)	−0.708 (0.981)
Endotoxin (EU/mL) ^{c,d}	3.20 (0.38)	3.28 (0.41)
Secondhand smoke in early life (in utero or <2 y old)	109 (42.1%)	135 (49.6%)
Current secondhand smoke	97 (37.3%)	118 (43.4%)
Residential distance to a major road (m)	376 (301)	338 (270)
African ancestry (%)	25.2 (12.9)	25.4 (11.9)

^aData are presented as mean (SD) for continuous variables and number (percentage) for binary variables.

^bP < .05 for comparison between groups.

^cLevels were log₁₀-transformed for data analysis.

^dBased on data for 348 children (174 cases and 174 controls).

cytokines. None of the other variables (dust mite allergen, mouse allergen, endotoxin, early SHS, current SHS, and African ancestry) was significantly associated with any cytokine.

Figure 1 and eTable 1 present the multivariable analysis of low income and/or cockroach allergen and plasma cytokines. After adjustment for age, sex, and case and control status, low income was not significantly associated with any cytokine (model A in eTable 1). In an analysis adjusting for the same covariates as in model A (minus income), cockroach allergen was significantly associated with 12 of the 14 cytokines tested (model B in eTable 1). Then, we conducted a multivariable analysis including low household income, cockroach allergen, and levels of cat, dog, and mouse allergens (Fig 1 and model C in eTable 1). In this analysis, cockroach allergen was significantly associated with decreased IL-17A and with increased IL-4, IL-10, IL-17F, IL-21, IL-25, IL-31, IFN-γ, and TNF-α. As an example, each log₁₀-unit increment in cockroach allergen level was significantly associated with an increment of 1.71 pg/mL in IL-4 level (95% confidence interval 1.28–2.29). We repeated the analysis after additional adjustment for house dust endotoxin (model D in eTable 1) and obtained similar results despite the smaller sample.

eTables 2 and 3 list the results of the multivariable analysis after stratification by case and control status. Among cases, this analysis yielded similar results to those of the analysis in all children. Although most associations observed in all 532 children (except for IL-10) became statistically nonsignificant in the 272 cases, there was little or no change in the magnitude and direction of the estimated effect of low income or cockroach allergen on plasma cytokines (eTable 2). Similar results were obtained in the multivariable analysis for the 260 controls, in whom the associations observed in all 532 children were minimally changed in direction or magnitude (eTable 3). In controls, cockroach allergen remained significantly associated with decreased IL-17A and with increased IL-4, IL-17F, IL-21, IL-25, and IFN-γ.

We repeated the multivariable analysis in all participants after stratification by cockroach allergy (ie, a positive IgE reaction to cockroach). In children with cockroach allergy, this analysis yielded similar results to those of the analysis in all children (Table 4). In particular, cockroach allergen remained significantly associated with decreased IL-17A and with increased IL-4, IL-10, IL-17F, IL-21, IL-25, and IFN-γ. In children without cockroach allergy, the associations observed among all 532 children remained in the same direction but were weaker. In these children, cockroach allergen was not significantly associated with any cytokine level (data not shown).

Table 3
Bivariate Linear Regression Analyses of Plasma Cytokines^a in 532 Participating Children

	IL-1	IL-4	IL-6	IL-10	IL-17A	IL-17F	IL-21	IL-22	IL-23	IL-25	IL-31	IL-33	IFN- γ	TNF- α
Age (y)	–0.006	–0.014	–0.027 ^e	–0.017	–0.019	–0.037	0.006	–0.020	–0.013	–0.014	–0.028	–0.005	–0.046	–0.013 ^e
Male sex	0.019	–0.018	0.100	0.150	–0.007	0.018	0.069	0.157	0.033	0.101	0.186	0.062	0.154	0.064 ^e
Low household income ^b	0.005	0.217	0.101	0.322 ^e	–0.204	0.263	0.070	0.077	–0.038	0.085	0.240	0.005	0.148	0.056
Low parental education ^b	0.081	0.106	0.155	0.312	–0.216	0.152	0.122	0.232	–0.068	0.109	0.205	0.162	0.288	0.075 ^e
Bla g 2 (U/g)	0.057	0.289 ^e	0.106 ^e	0.341 ^e	–0.231 ^e	0.290 ^e	0.181 ^e	0.180 ^e	–0.054	0.103 ^e	0.256 ^e	0.154 ^e	0.291 ^e	0.055 ^e
Der p 1 (μ g/g)	0.055	–0.016	0.053	0.124	–0.099	0.059	0.051	0.046	0.018	0.043	0.130	0.052	0.055	0.012
Mus m 1 (mg/g)	–0.013	–0.138	–0.022	–0.104	0.030	–0.103	0.066	–0.076	0.012	–0.022	–0.058	–0.008	–0.086	–0.013
Fel d 1 (μ g/g)	0.024	0.088	0.010	0.153 ^e	–0.101	0.013	0.073	0.145 ^e	0.011	0.038	0.084	0.065	0.015	0.015
Can f 1 (μ g/g)	0.015	0.112	0.046	0.144 ^e	0.011	0.028	0.049	0.131 ^e	0.032	0.031	0.089	0.063	0.025	0.014
Endotoxin (EU/mL) ^c	0.024	0.058	0.019	0.128	–0.140	0.165	0.079	0.055	0.058	0.052	–0.007	–0.012	0.069	0.051
Early-life SHS	0.056	–0.005	0.042	0.138	0.013	0.110	0.102	0.100	–0.020	0.005	0.072	0.049	0.061	0.052
Current SHS	–0.012	–0.038	0.011	–0.007	–0.052	0.113	–0.003	–0.093	–0.115	0.013	0.044	–0.043	0.035	0.003
Residential distance to a major road ^d	–0.010	–0.030	–0.02	–0.03	0.003	–0.04	–0.02	–0.002	0.01	–0.01	–0.05 ^e	–0.01	–0.04	–0.005
African ancestry	–0.0007	0.002	0.0003	0.004	–0.0009	0.0006	–0.0012	0.0039	0.0026	0.0009	0.010	0.0024	0.0043	–0.0009

Abbreviations: early-life SHS, secondhand smoke in utero or before 2 years of age; IFN, interferon; IL, interleukin; SHS, secondhand smoke; TNF, tumor necrosis factor.

^aPlasma cytokine levels and allergen levels were log10-transformed for data analysis.

^bLow household income is defined as less than \$15,000 per year; low parental education is defined as neither parent completed high school.

^cEndotoxin levels available in 348 of 532 study participants.

^dPer 100 m.

^e $p < .00357$ (.05 for 14 tests).

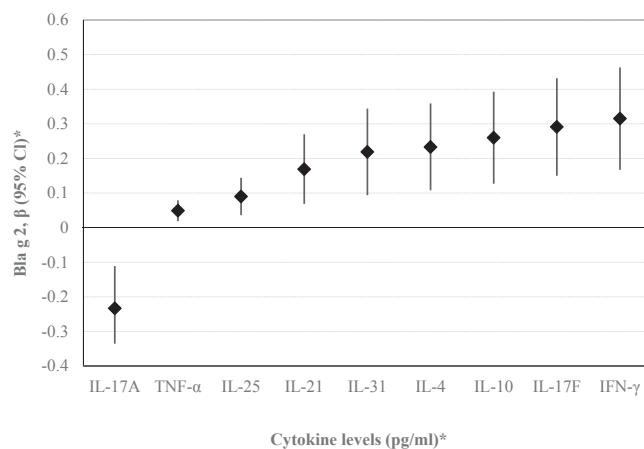


Figure 1. Multivariable analysis of cockroach allergen exposure and plasma cytokines in study participants. *Bla g 2 level in house dust (units per gram) and plasma cytokine levels (picograms per milliliter) were logarithmically transformed for data analysis. For each cytokine, models were adjusted for age, sex, low household income, case and control status, and house dust levels of Mus m 1, Fel d 1, and Can f 1. All reported associations were significant at $P < .00357$ (.05 for 14 tests). CI, confidence interval; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

Discussion

In this study, low household income was not significantly associated with any plasma cytokine. Conversely, cockroach allergen was significantly associated with decreased IL-17A and increased levels of 8 cytokines (IL-4, IL-10, IL-17F, IL-21, IL-25, IL-31, IFN- γ , and TNF- α), independently of household income and other allergens. Most associations observed in all children remained similar for magnitude, direction, and statistical significance in children with cockroach allergy but became weaker and statistically nonsignificant in children without cockroach allergy. These results suggest that cockroach allergen has broad effects on T_H1 , T_H2 , T_H17 , and regulatory T cell immune responses in school-age children living in a tropical environment (Puerto Rico), particularly in children sensitized to cockroach allergen.

Previous studies in children or adolescents have shown an association between low SES and serum IL-5, IL-6, and IFN- γ ,^{17,34} but we did not replicate those findings for IL-6 or IFN- γ .

Our findings are partly consistent with those of an experimental model in which exposure to German cockroach feces was associated with increased production of IL-6, IL-23, and IL-12p70 from bone marrow-derived myeloid dendritic cells.¹³ In that mouse model, levels of IL-5, IL-17A, and IL-6 in whole lung cultures were increased 18 hours after exposure to cockroach allergen feces, suggesting a mixed T_H2 and T_H17 response.¹³ Our results are further supported by other experiments showing that cockroach allergen can act through protease activated receptor-2 (PAR-2) pathways to induce innate cellular immunity¹⁵ and by known effects of cockroach allergen on T_H2 (allergic) immune responses.

Our study has several strengths, including a well-characterized cohort of high-risk minority children and the ability to adjust for confounding factors. We also recognize several study limitations. First, we cannot assess temporal relations between low SES or cockroach allergen and plasma cytokines in a cross-sectional study. For example, the observed association between cockroach allergen and IL-10 could represent an attempt to downregulate T_H2 immune responses in exposed children. However, cockroach allergen has been proved as a causal factor for asthma morbidity in longitudinal studies and clinical trials.¹⁵ Second, selection bias is possible in any observational study. Nonetheless, cockroach allergen level was similar and not significantly different between children who were and were not included in this analysis, making selection bias

Table 4Multivariable Analysis of Cockroach Allergen Exposure and Plasma Cytokines^a in Children With a Positive Immunoglobulin E Reaction to Cockroach

Cytokine	Covariate	β coefficient (95% CI) ^b		
		Model A (n = 244)	Model B (n = 244)	Model C (n = 244)
IL-1	low income ^c	−0.287 (−0.188 to 0.131)	—	−0.057 (−0.218 to 0.105)
	Bla g 2	—	0.104 (0.001–0.208)	0.090 (−0.022 to 0.201)
IL-4	low income	0.089 (−0.194 to 0.373)	—	0.032 (−0.244 to 0.309)
	Bla g 2	—	0.372 ^d (0.193–0.551)	0.311 ^d (0.120–0.502)
IL-6	low income	0.092 (−0.062 to 0.245)	—	0.063 (−0.090 to 0.215)
	Bla g 2	—	0.183 ^d (0.086–0.281)	0.164 (0.059–0.269)
IL-10	low income	0.358 (0.045–0.668)	—	0.295 (−0.005 to 0.596)
	Bla g 2	—	0.481 ^d (0.286–0.676)	0.398 ^d (0.190–0.605)
IL-17A	low income	−0.372 (−0.617 to −0.128)	—	−0.321 (−0.565 to −0.077)
	Bla g 2	—	−0.218 (−0.378 to −0.058)	−0.235 ^d (−0.403 to −0.066)
IL-17F	low income	0.258 (−0.046 to 0.562)	—	0.199 (−0.103 to 0.501)
	Bla g 2	—	0.382 ^d (0.188–0.576)	0.364 ^d (0.155–0.573)
IL-21	low income	0.015 (−0.210 to 0.239)	—	−0.055 (−0.276 to 0.165)
	Bla g 2	—	0.322 ^d (0.182–0.463)	0.316 ^d (0.164–0.468)
IL-22	low income	0.056 (−0.220 to 0.332)	—	0.009 (−0.262 to 0.280)
	Bla g 2	—	0.273 ^d (0.097–0.450)	0.178 (−0.009 to 0.365)
IL-23	low income	−0.082 (−0.220 to 0.055)	—	−0.078 (−0.217 to 0.063)
	Bla g 2	—	−0.052 (−0.142 to 0.037)	−0.063 (−0.159 to 0.034)
IL-25	low income	0.119 (−0.003 to 0.241)	—	0.090 (−0.030 to 0.210)
	Bla g 2	—	0.169 ^d (0.092–0.246)	0.148 ^d (0.065–0.231)
IL-31	low income	0.276 (0.008–0.544)	—	0.219 (−0.043 to 0.480)
	Bla g 2	—	0.378 ^d (0.208–0.548)	0.292 ^d (0.111–0.473)
IL-33	low income	0.006 (−0.200 to 0.212)	—	−0.056 (−0.260 to 0.148)
	Bla g 2	—	0.246 ^d (0.115–0.377)	0.221 ^d (0.080–0.361)
IFN- γ	low income	0.164 (−0.157 to 0.485)	—	0.099 (−0.219 to 0.418)
	Bla g 2	—	0.408 ^d (0.204–0.612)	0.374 ^d (0.154–0.593)
TNF- α	low income	0.052 (−0.026 to 0.130)	—	0.036 (−0.042 to 0.114)
	Bla g 2	—	0.090 ^d (0.041–0.140)	0.078 (0.024–0.131)

Abbreviations: CI, confidence interval; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

^aPlasma cytokine levels and allergen levels were log₁₀-transformed for data analysis.^bAll models (A–D) were adjusted for age, sex, and case and control status. Model A included low income; model B included cockroach allergen (Bla g 2) level in house dust; model C included low income, Bla g 2 house dust level, and house dust levels of Mus m 1, Fel d 1, and Can f 1; and model D included all variables in model C and endotoxin levels.^cLow income defined as an annual household income lower than \$15,000.^dP < .00357 (.05 for 14 tests).

unlikely as a major explanation for our results. Third, our findings are not generalizable to children living in temperate climates (or those living in households with no or low levels of cockroach allergen) but are relevant to children living in inner-city areas in the United States. Fourth, we had limited statistical power to examine the modification of the effect of cockroach allergen by case and control status or cockroach allergy. However, we found similar results in cases and controls and could demonstrate differences for the strength and significance of the associations between children with and without cockroach allergy. Fifth, as in prior work, we used 1 measurement (low household income) as the primary indicator of SES, but we obtained the same results for cockroach allergen in multivariable analyses including an alternative measurement of SES (low parental education). Sixth, we did not examine exposure to violence or other indicators of psychosocial stress (which are correlated with low SES and can affect immune responses),³⁵ because we had such data in only a subset of participants.

In summary, our findings suggest that indoor exposure to cockroach allergen leads to strong stimulation of adaptive immune responses (including T_H1, T_H2, regulatory T cell, and T_H17 responses) in Puerto Rican children, particularly in those sensitized to cockroach. Thus, cockroach abatement (through extermination or improved housing conditions)³⁶ could decrease the burden of allergic diseases and asthma in these children.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jana.2017.05.008>.

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eTable 1Multivariable Analysis of Cockroach Allergen Exposure and Plasma Cytokines^a

Cytokine	Covariate	β Coefficient (95% CI) ^b			
		Model A (n = 532)	Model B (n = 532)	Model C (n = 532)	Model D (n = 348)
IL-1	low income ^c	0.002 (−0.099 to 0.103)	—	−0.012 (−0.114 to 0.090)	−0.095 (−0.235 to 0.045)
	Bla g 2	—	0.060 (−0.007 to 0.127)	0.058 (−0.016 to 0.133)	0.145 (0.046–0.244)
IL-4	low income	0.213 (0.039–0.386)	—	0.158 (−0.014 to 0.330)	0.125 (−0.092 to 0.342)
	Bla g 2	—	0.287 ^d (0.173–0.401)	0.233 ^d (0.108–0.359)	0.377 ^d (0.223–0.530)
IL-6	low income	0.078 (−0.022 to 0.178)	—	0.061 (−0.040 to 0.161)	−0.002 (−0.141 to 0.138)
	Bla g 2	—	0.107 ^d (0.041–0.173)	0.094 (0.021–0.167)	0.186 ^d (0.084–0.284)
IL-10	low income	0.311 ^d (0.125–0.496)	—	0.243 (0.060–0.426)	0.240 (0.001–0.479)
	Bla g 2	—	0.347 ^d (0.226–0.469)	0.260 ^d (0.127–0.393)	0.409 ^d (0.240–0.578)
IL-17A	low income	−0.218 (−0.373 to −0.063)	—	−0.157 (−0.311 to −0.002)	−0.259 (−0.462 to −0.056)
	Bla g 2	—	−0.231 ^d (−0.334 to −0.129)	−0.223 ^d (−0.335 to −0.111)	−0.217 ^d (−0.361 to −0.073)
IL-17F	low income	0.236 (0.043–0.429)	—	0.176 (−0.017 to 0.370)	0.170 (−0.081 to 0.421)
	Bla g 2	—	0.283 ^d (0.155–0.410)	0.291 ^d (0.150–0.432)	0.407 ^d (0.229–0.584)
IL-21	low income	0.073 (−0.065 to 0.211)	—	0.030 (−0.107 to 0.169)	−0.015 (−0.201 to 0.172)
	Bla g 2	—	0.186 ^d (0.095–0.278)	0.169 ^d (0.069–0.270)	0.249 ^d (0.117–0.381)
IL-22	low income	0.060 (−0.111 to 0.231)	—	0.023 (−0.147 to 0.194)	0.019 (−0.201 to 0.239)
	Bla g 2	—	0.188 ^d (0.075–0.301)	0.105 (−0.019 to 0.229)	0.244 ^d (0.089–0.400)
IL-23	low income	−0.051 (−0.153 to 0.051)	—	−0.035 (−0.138 to 0.068)	0.026 (−0.094 to 0.145)
	Bla g 2	—	−0.055 (−0.123 to 0.013)	−0.084 (−0.159 to −0.009)	−0.047 (−0.131 to 0.038)
IL-25	low income	0.071 (−0.004 to 0.145)	—	0.048 (−0.026 to 0.123)	0.023 (−0.086 to 0.132)
	Bla g 2	—	0.105 ^d (0.056–0.154)	0.090 ^d (0.036–0.144)	0.145 ^d (0.068–0.222)
IL-31	low income	0.215 (0.043–0.387)	—	0.164 (−0.008 to 0.335)	0.145 (−0.078 to 0.368)
	Bla g 2	—	0.261 ^d (0.148–0.375)	0.219 ^d (0.094–0.344)	0.417 ^d (0.260–0.575)
IL-33	low income	0.0004 (−0.129 to 0.130)	—	−0.034 (−0.124 to 0.096)	−0.056 (−0.233 to 0.260)
	Bla g 2	—	0.159 ^d (0.073–0.245)	0.140 (0.045–0.234)	0.260 ^d (0.135–0.345)
IFN- γ	low income	0.106 (−0.097 to 0.308)	—	0.040 (−0.163 to 0.243)	0.058 (−0.206 to 0.326)
	Bla g 2	—	0.287 ^d (0.154–0.421)	0.315 ^d (0.167–0.463)	0.440 ^d (0.251–0.629)
TNF- α	low income	0.044 (0.003–0.086)	—	0.033 (−0.009 to 0.074)	0.032 (−0.027 to 0.092)
	Bla g 2	—	0.055 ^d (0.028–0.083)	0.049 ^d (0.019–0.079)	0.083 ^d (0.041–0.125)

Abbreviations: CI, confidence interval; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

^aBla g 2 level in house dust (units per gram) and plasma cytokine levels were log-transformed for data analysis.^bAll models (A–C) were adjusted for age, sex, and case and control status. Model A included low income; model B included cockroach allergen (Bla g 2) level in house dust; model C included low income, Bla g 2 house dust level, and house dust levels of *Mus m* 1, *Fel d* 1, and *Can f* 1; and model D included all variables in model C and endotoxin levels.^cLow income defined as an annual household income lower than \$15,000.^d $P < .00357$ (.05 for 14 tests).

eTable 2Multivariable Analysis of Low Income and/or Cockroach Allergen, and Plasma Cytokines^a in 272 Children With Asthma (Cases)

Cytokine	Covariate	β coefficient (95% CI) ^b		
		Model A	Model B	Model C
IL-1	low income ^c	−0.017 (−0.169 to 0.134)	—	−0.034 (−0.190 to 0.122)
	Bla g 2	—	0.06 (−0.035 to 0.158)	0.049 (−0.062 to 0.160)
IL-4	low income	0.259 (0.013–0.505)	—	0.244 (−0.004 to 0.492)
	Bla g 2	—	0.240 ^e (0.083–0.397)	0.132 (−0.045 to 0.309)
IL-6	low income	0.058 (−0.092 to 0.208)	—	0.043 (−0.111 to 0.196)
	Bla g 2	—	0.097 (0.002–0.193)	0.071 (−0.038 to 0.181)
IL-10	low income	0.166 (−0.106 to 0.439)	—	0.104 (−0.166 to 0.376)
	Bla g 2	—	0.349 ^e (0.178–0.519)	0.273 ^d (0.079–0.467)
IL-17A	low income	−0.437 ^e (−0.648 to −0.225)	—	−0.370 ^e (−0.585 to −0.155)
	Bla g 2	—	−0.174 (−0.312 to −0.035)	−0.163 (−0.317 to −0.010)
IL-17F	low income	0.307 (0.036–0.578)	—	0.292 (−0.054 to 0.340)
	Bla g 2	—	0.198 (0.027–0.372)	0.143 (−0.008 to 0.344)
IL-21	low income	0.064 (−0.127 to 0.254)	—	0.044 (−0.151 to 0.238)
	Bla g 2	—	0.148 (0.027–0.269)	0.102 (−0.037 to 0.240)
IL-22	low income	0.028 (−0.282 to 0.226)	—	−0.068 (−0.326 to 0.190)
	Bla g 2	—	0.196 (0.035–0.358)	0.120 (−0.064 to 0.304)
IL-23	low income	−0.087 (−0.240 to 0.066)	—	−0.045 (−0.201 to 0.111)
	Bla g 2	—	−0.089 (−0.187 to 0.009)	−0.133 (−0.244 to −0.022)
IL-25	low income	0.069 (−0.035 to 0.173)	—	0.058 (−0.048 to 0.164)
	Bla g 2	—	0.074 (0.007–0.140)	0.053 (−0.022 to 0.129)
IL-31	low income	0.290 (0.033–0.546)	—	0.243 (−0.016 to 0.503)
	Bla g 2	—	0.292 ^e (0.129–0.455)	0.217 (0.032–0.402)
IL-33	low income	−0.097 (−0.307 to 0.113)	—	−0.156 (−0.370 to 0.058)
	Bla g 2	—	0.170 (0.037–0.304)	0.191 (0.038–0.343)
IFN- γ	low income	0.182 (−0.116 to 0.479)	—	0.144 (−0.161 to 0.449)
	Bla g 2	—	0.198 (0.008–0.388)	0.201 (−0.010 to 0.376)
TNF- α	low income	0.041 (−0.011 to 0.093)	—	0.029 (−0.017 to 0.418)
	Bla g 2	—	0.049 ^d (0.015–0.082)	0.038 (0.001–0.076)

Abbreviations: CI, confidence interval; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

^aBla g 2 level in house dust (units per gram) and plasma cytokines were log₁₀-transformed for data analysis.^bAll models (A–C) were adjusted for age and sex. Model A included low income; model B included cockroach allergen (Bla g 2) level in house dust; and model C included low income, Bla g 2 house dust level, and house dust levels of Mus m 1, Fel d 1, and Can f 1.^cLow income defined as an annual household income lower than \$15,000.^d $P < .01$.^e $P < .00357$ (.05 for 14 tests).

eTable 3Multivariable Analysis of Low Income and/or Cockroach Allergen, and Plasma Cytokines^a in 260 Children Without Asthma (Controls)

Cytokine	Covariate	β Coefficient (95% CI) ^b		
		Model A	Model B	Model C
IL-1	low income ^c	0.023 (−0.112 to 0.157)	—	0.015 (−0.121 to 0.150)
	Bla g 2	—	0.065 (−0.030 to 0.160)	0.068 (−0.034 to 0.171)
IL-4	low income	0.157 (−0.088 to 0.401)	—	0.119 (−0.118 to 0.355)
	Bla g 2	—	0.320 ^e (0.151–0.490)	0.269 ^e (0.089–0.449)
IL-6	low income	0.098 (−0.036 to 0.232)	—	0.084 (−0.050 to 0.218)
	Bla g 2	—	0.119 (0.025–0.213)	0.116 (0.014–0.218)
IL-10	low income	0.451 ^e (0.198–0.703)	—	0.405 ^e (0.158–0.652)
	Bla g 2	—	0.338 ^e (0.159–0.517)	0.228 (0.040–0.415)
IL-17A	low income	0.010 (−0.214 to 0.234)	—	0.054 (−0.167 to 0.275)
	Bla g 2	—	−0.277 ^e (−0.433 to −0.122)	−0.257 ^e (−0.425 to −0.089)
IL-17F	low income	0.156 (−0.121 to 0.433)	—	0.107 (−0.165 to 0.379)
	Bla g 2	—	0.365 ^e (0.173–0.557)	0.398 ^e (0.191–0.604)
IL-21	low income	0.078 (−0.124 to 0.279)	—	0.046 (−0.154 to 0.245)
	Bla g 2	—	0.222 ^e (0.082–0.363)	0.210 ^d (0.058–0.361)
IL-22	low income	0.147 (−0.084 to 0.377)	—	0.123 (−0.105 to 0.351)
	Bla g 2	—	0.180 (0.017–0.343)	0.080 (−0.093 to 0.253)
IL-23	low income	−0.013 (−0.149 to 0.123)	—	−0.014 (−0.152 to 0.124)
	Bla g 2	—	−0.011 (−0.108 to 0.086)	−0.027 (−0.132 to 0.077)
IL-25	low income	0.069 (−0.038 to 0.176)	—	0.048 (−0.058 to 0.154)
	Bla g 2	—	0.136 ^e (0.062–0.211)	0.121 ^e (0.040–0.201)
IL-31	low income	0.134 (−0.094 to 0.363)	—	0.103 (−0.125 to 0.332)
	Bla g 2	—	0.212 (0.051–0.372)	0.183 (0.010–0.357)
IL-33	low income	0.099 (−0.052 to 0.251)	—	0.078 (−0.073 to 0.228)
	Bla g 2	—	0.153 ^d (0.047–0.260)	0.107 (−0.008 to 0.221)
IFN- γ	low income	0.023 (−0.254 to 0.301)	—	−0.029 (−0.302 to 0.243)
	Bla g 2	—	0.386 ^e (0.194–0.577)	0.409 ^e (0.202–0.616)
TNF- α	low income	0.046 (−0.019 to 0.110)	—	0.038 (−0.027 to 0.103)
	Bla g 2	—	0.059 (0.014–0.105)	0.055 (0.005–0.104)

Abbreviations: CI, confidence interval; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

^aBla g 2 level in house dust (units per gram) and plasma cytokines were log₁₀-transformed for data analysis.^bAll models (A–C) were adjusted for age and sex. Model A included low income; model B included cockroach allergen (Bla g 2) level in house dust; and model C included low income, Bla g 2 house dust level, and house dust levels of Mus m 1, Fel d 1, and Can f 1.^cLow household income defined as an annual income lower than \$15,000.^d $P < .01$.^e $P < .00357$ (.05 for 14 tests).