

Early-life cockroach allergen and polycyclic aromatic hydrocarbon exposures predict cockroach sensitization among inner-city children

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Background: Sensitization to cockroach is one of the strongest identified risk factors for greater asthma morbidity in low-income urban communities; however, the timing of exposures relevant to the development of sensitization has not been elucidated fully. Furthermore, exposure to combustion byproducts, including polycyclic aromatic hydrocarbons (PAHs), can augment the development of allergic sensitization. **Objective:** We sought to test the hypotheses that domestic cockroach allergen measured prenatally would predict cockroach sensitization in early childhood and that this association would be greater for children exposed to higher PAH concentrations. **Methods:** Dominican and African American pregnant women living in New York City were enrolled. In the third trimester expectant mothers wore personal air samplers for measurement of 8 nonvolatile PAHs and the semivolatile PAH pyrene, and dust was collected from homes for allergen measurement. **Glutathione-S-transferase μ 1 (GSTM1) gene polymorphisms**

were measured in children. Allergen-specific IgE levels were measured from the children at ages 2, 3, 5, and 7 years. **Results:** Bla g 2 in prenatal kitchen dust predicted cockroach sensitization at the ages of 5 to 7 years (adjusted relative risk [RR], 1.15; $P = .001$; $n = 349$). The association was observed only among children with greater than (RR, 1.22; $P = .001$) but not less than (RR, 1.07; $P = .24$) the median sum of 8 nonvolatile PAH levels. The association was most pronounced among children with higher PAH levels and null for the *GSTM1* gene (RR, 1.54; $P = .001$).

Conclusions: Prenatal exposure to cockroach allergen was associated with a greater risk of allergic sensitization. This risk was increased by exposure to nonvolatile PAHs, with children null for the *GSTM1* mutation particularly vulnerable. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: Bla g 2, cockroach, polycyclic aromatic hydrocarbon, IgE, allergy, inner-city, GSTM, GSTP

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Sensitization to cockroach allergens is one of the strongest identified risks for greater asthma morbidity in low-income urban populations.¹ Although several studies among preschool- and school-age children have demonstrated associations between cockroach allergen measured in the home and sensitization,^{2,3} studies have not yet demonstrated prospectively whether cockroach allergen in a child's house dust predicts the development of sensitization. Understanding whether exposure to cockroach allergen in the prenatal and early postnatal time period leads to sensitization could inform primary prevention interventions.

Emerging evidence suggests that environmental coexposures in addition to allergens, including microbial products and diesel exhaust particles (DEPs), could modify the risk of allergic sensitization.^{4,5} For example, Diaz-Sanchez et al^{6,7} demonstrated in human *in vivo* experiments that DEPs can act as adjuvants to promote sensitization to novel allergens and enhance the T_H2 response to established sensitization. Like cockroach allergen, DEPs and other combustion products are ubiquitous exposures in urban communities, beginning prenatally.⁸⁻¹⁰ One class of combustion byproducts found in DEPs, the polycyclic aromatic hydrocarbon (PAH), has been investigated extensively for its contribution to the development of cancer.^{11,12} We and others also demonstrated associations between PAHs and respiratory outcomes, and these associations appeared to differ with exposure to a composite variable of 8 highly correlated nonvolatile PAHs ($\sum_8 \text{PAH}_{\text{nonvolatile}}$) compared with exposure to the less well-correlated and semivolatile pyrene.¹³⁻¹⁵

Common polymorphisms in glutathione-S-transferase μ (GSTM) and glutathione-S-transferase π (GSTP) have been shown

Abbreviations used

DEP:	Diesel exhaust particle
<i>GSTM</i> :	Glutathione-S-transferase μ gene
<i>GSTP</i> :	Glutathione-S-transferase π gene
KLH:	Keyhole limpet hemocyanin
PAH:	Polycyclic aromatic hydrocarbon
$\sum_8\text{PAH}_{\text{nonvolatile}}$:	Sum of 8 nonvolatile polycyclic aromatic hydrocarbons
RR:	Relative risk

to alter the conjugation kinetics of PAHs.^{16–18} These same polymorphisms appear to modify the adjuvant effect of DEPs on allergic sensitization¹⁹ and have been associated with other allergic disease–related health outcomes (eg, lung function and asthma).^{20–23} However, whether these polymorphisms modify the effect of PAHs on allergic sensitization still needs to be elucidated.

We hypothesized that domestic cockroach allergen measured prenatally would predict cockroach sensitization in early childhood and that the magnitude of this association would be greater for children also exposed prenatally to higher PAH levels. We tested this hypothesis in a well-characterized birth cohort study of children of women of African American and Dominican ethnicity living in low-income neighborhoods in New York City. We also tested whether the magnitude of the association between Bla g 2, PAHs, and sensitization would be greater among children with polymorphisms in *GSTM* and *GSTP*.

METHODS

As part of the Columbia Center for Children's Environmental Health, 727 nonsmoking, pregnant African American or Dominican women between the ages of 18 and 35 years who were living in Northern Manhattan and the South Bronx were enrolled.^{8,10,24} Women with a history of asthma or allergies were not recruited preferentially. Detailed questionnaires were administered to the participants before the child was born. Environmental tobacco smoke exposure during pregnancy was assessed by means of questionnaire. The children were followed prospectively (Fig 1). Columbia University's Institutional Review Board approved this study.

Allergen exposures

Bed and kitchen dust samples were collected from the participants' homes during the third trimester and again when the child was 1, 3, and 5 years old.²⁴ Dust samples were extracted without prior sieving, but large debris was removed. Kitchen and bed samples were assayed for Bla g 2 (Indoor Biotechnologies, Charlottesville, Va) and mouse urinary protein, and bed samples were assayed also for Der f 1 by using an ELISA, as previously described.²⁴ Estimations of Bla g 2 and Der f 1 concentrations were based on the universal allergen standard curve, and thus comparisons with our results published before 2011 and those of other studies not using the universal allergen standard will require conversions, as previously described.^{3,25} For results of less than the limit of detection, values of half of the limit of detection were used in analyses.

PAH measures

Personal air sampling was conducted for the mothers during the third trimester of pregnancy, as previously described.^{10,13} Briefly, women wore a small backpack during the waking hours and placed the sampler near the bed at night. Air was sampled for 48 hours at 4 L/min. Particulate matter of 2.5 μm in diameter or less was collected on a quartz microfiber filter, and semivolatile components were collected on polyurethane foam plug backups. Filters and polyurethane foams were extracted together and analyzed by using

gas chromatography/mass spectrometry at the Southwest Research Institute for benz(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(ghi)perylene, benzo(a)pyrene, chrysene/isochrysene, dibenz(a,h)anthracene, indeno(1,2,3-cd)pyrene, and pyrene.²⁶

IgE

IgE antibodies to cockroach, mouse, *Dermatophagoides farinae*, and cat were measured in sera collected from children at ages 2, 3, 5, and 7 years. As described previously, 40 of the initial samples collected at ages 2 and 3 years were assayed by using the Fluorescence Allergosorbent Test (Bio-Whittaker, Walkersville, Md), and all of the subsequent samples were assayed by using ImmunoCAP (ThermoFisher, Uppsala, Sweden).^{27,28} A subset of samples was analyzed by using both methods to confirm concordance (data not shown). Specific IgE levels of greater than 0.35 IU/mL were considered positive. Children with at least 1 positive specific IgE level at ages 5 or 7 years were considered positive at ages 5 to 7 years, and a similar variable was created for ages 2 to 3 years.

***GSTM* and *GSTP* genotyping**

DNA was isolated from the child's cord blood cells or at a later age (between the ages of 2 and 5 years) from PBMCs. The deletion of *GSTM1* was assessed by using the Multiplex PCR system.²⁹ Children who were homozygous (+/+) or heterozygous (–/+) for *GSTM1* were classified as *GSTM1* positive, and those who were homozygous deleted (–/–) were classified as *GSTM1* null. Polymorphisms in *GSTP1* (Ile105Val, rs1695) were assessed with the use of the ABI 7500 System in the TaqMan genotyping assay with primers and probes obtained from Applied Biosystems (Foster City, Calif). *GST-P1* primers were *GST-P1-F* CCTGGTGGACATGGTGAATGAC and *GST-P1-R* CAGATGCTCACATAGTTGGTGTAGA.

Data analyses and statistics

Analyses were restricted to children who had complete data on PAH and Bla g 2 levels measured prenatally and IgE levels measured at age 5 years, 7 years, or both. The greatest Bla g 2 concentration measured in kitchen dust at age 1, 3, or 5 years was assigned as the postnatal Bla g 2 level. Allergen and PAH levels were approximately natural log-normally distributed; natural log-transformed variables were used in analyses. For visualization of the associations between allergen exposure and allergic sensitization, logistic regression curves were plotted. For multivariable analyses of these associations, relative risks (RRs) with 95% CIs were calculated by using binomial regressions in generalized estimating equations. The potential cofounders and covariates of sex, race/ethnicity, maternal asthma, material hardship, prenatal environmental tobacco smoke exposure, birth order, and age of the child at IgE measurement were included in all multivariable models. Multiplicative interaction terms were included in the multivariable models to test for effect modification. As we have reported previously, the 8 nonvolatile PAHs showed a high degree of correlation with each other, but the semivolatile pyrene did not correlate well with these other PAHs.¹³ Therefore in keeping with the previous analytic strategy, PAH levels were analyzed as the sum of 8 individual nonvolatile PAHs ($\sum_8\text{PAH}_{\text{nonvolatile}}$) and, separately, pyrene. A previously defined home heating season variable was included in all models that included PAHs or pyrene.²⁶ Data were analyzed in SPSS software (version 17; SPSS, Chicago, Ill) and visualized in R version 2.14.0 software.

RESULTS

There were 349 children with prenatal Bla g 2, prenatal PAH, and IgE levels measured at least once between the ages of 5 and 7 years (see Fig E1 in this article's Online Repository at www.jacionline.org). Of these, 317 children also had a Bla g 2 level measured at least once in kitchen dust between the ages of 1 and 5 years. The demographics of the mothers are reported in Table I.³⁰ When comparing children who were included in the analyses with those who were enrolled but excluded from the

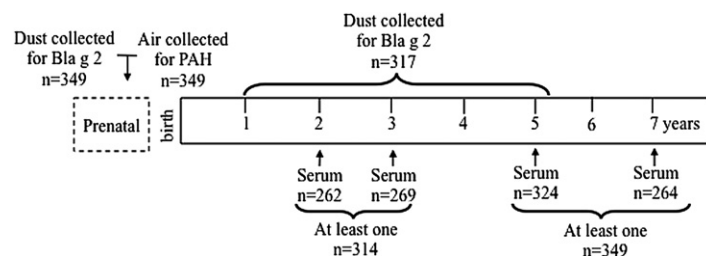


FIG 1. Overview of study and children included in analyses. Of the 727 children enrolled prenatally, analyses for the current study were restricted to the 349 who had valid measurements of prenatal Bla g 2 and PAH and allergen-specific IgE at age 5 years, age 7 years, or both.

TABLE I. Demographics of mothers

Age, mean (SD)*	25.2 (5.0)
Race/ethnicity	
African American, no. (%)*	135/349 (38.7)
Dominican, no. (%)	214/349 (61.3)
Self-reported health	
Asthma, no. (%)†	79/349 (22.6)
Allergy, no. (%)‡	149/346 (42.7)
Sociodemographics	
No high school degree, no. (%)*	132/344 (38.1)
Receiving Medicaid, no. (%)*	325/349 (93.1)
Material hardship in last 6 mo, no. (%)§	164/349 (47.0)
Domestic environment	
Smoker in home, no. (%)*	119/349 (34.1)
Cockroach sightings common, no. (%)	153/319 (48.0)
Mouse sightings common, no. (%)	67/319 (21.0)
Cat in home, no. (%)*	36/348 (10.3)
Dog in home, no. (%)*	15/348 (4.3)

*Reported on the prenatal questionnaire.

†Mother reported either during pregnancy or on a questionnaire 3 months after the child was born that she had asthma.

‡Mother replied yes to a question about having allergies asked during the first year after the child was born.

§Mother reported on the prenatal questionnaire that in the past 6 months she and her family could not afford needed food, rent, clothing, or medical care or that gas/electricity was suspended because of bill nonpayment.³⁰

||Cockroaches or mice seen at least weekly.

analyses, there were no statistically significant differences, except a slightly higher frequency of African American subjects and women receiving Medicaid (see Table E1 in this article's Online Repository at www.jacionline.org).

Prenatal indoor allergen measures and development of sensitization

There was no correlation between Bla g 2 levels in kitchen dust and nonvolatile $\sum_8$ PAH_{nonvolatile} values ($r = 0.003$, $P = .95$; see Fig E2 in this article's Online Repository at www.jacionline.org) or pyrene levels ($r = 0.060$, $P = .20$) measured in the air prenatally. Bla g 2 levels measured in kitchen dust prenatally and the highest postnatal measure available between the ages of 1 and 5 years correlated minimally ($r = 0.15$, $P = .007$, see Fig E2). Bla g 2 levels measured in the kitchen and bed dust prenatally correlated ($r = 0.49$, $P < .001$), as described previously.²⁴

The prevalence of IgE to cockroach increased as the children aged from 2 (13/262 [5.0%]) to 3 (24/269 [8.9%]) to 5 (66/324 [20.4%]) to 7 (82/264 [31.1%]) years. In univariate analyses (Fig 2) and after controlling for potential confounders, prenatal

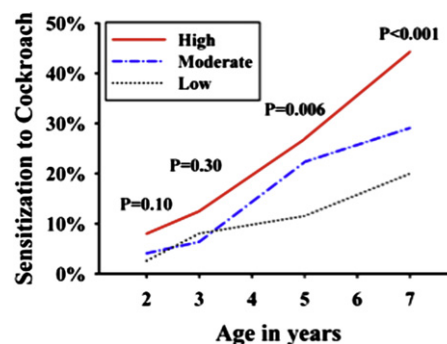


FIG 2. Prevalence of sensitization to cockroach with tertiles of prenatal Bla g 2 levels in kitchen dust. Tertiles of Bla g 2 levels were defined as follows: Low, less than 0.73 ng/g; Moderate, 0.73 to 772 ng/g; and High, greater than 772 ng/g. Sensitization was defined as greater than 0.35 IU/mL IgE to cockroach.

cockroach allergen was associated with cockroach sensitization at the ages of 5 to 7 years (RR, 1.15; 95% CI, 1.06-1.24; $P = .001$). A similar, although statistically nonsignificant, trend was observed for sensitization at age 2 to 3 years (RR, 1.09; 95% CI, 0.93-1.28; $P = .28$). Among the 317 children with postnatal allergen exposure, in multivariable analyses both prenatal (RR, 1.11; 95% CI, 1.03-1.19; $P = .009$) and postnatal (RR, 1.12; 95% CI, 1.10-1.31; $P < .001$) kitchen Bla g 2 levels independently predicted age 5- to 7-year cockroach sensitization (same model). Prenatal Bla g 2 levels in bed dust were not associated with sensitization at age 5 to 7 years (RR, 1.06; 95% CI, 0.95-1.17; $P = .32$). Although there appeared to be modest effect modification of the association between Bla g 2 exposure and sensitization by race/ethnicity, sex, and maternal asthma (Table II),³⁰ none of these interaction terms approached statistical significance (all $P_{\text{interaction}} > .20$). Among the subset of children for whom we had measured maternal total IgE levels ($n = 229$), there was no effect modification by high (>100 IU/mL) maternal total IgE levels (data not shown). Inclusion of the number of persons living in the home (to assess crowding) in these models did not alter the main effect estimates.

Mouse sensitization also increased between the ages of 2 and 3 years (7.8%) and 5 and 7 years (14.3%) but was not associated with mouse (mouse urinary protein) allergen exposure measured in prenatal kitchen or bed dust (all multivariable $P \geq .38$). Sensitization to *D. farinae* increased between the ages of 2 and 3 years (4.1%) and 5 and 7 years (16.0%). Geometric mean Der f 1 allergen levels in prenatal bed dust were significantly higher among children sensitized to dust mite at age 2 to 3 years compared with those who were not ($P = .001$); however, the multivariable

TABLE II. Adjusted RRs[‡] for sensitization to cockroach at age 5 to 7 years with prenatal kitchen Bla g 2 concentrations stratified by potential effect-modifying variables

Potential effect modifier [§]	No.	RR (95% CI) for sensitization with Bla g 2 [‡]
Unstratified	349	1.15 (1.07-1.25) [†]
Sex of child		
Male	166	1.15 (1.02-1.29)*
Female	183	1.17 (1.05-1.31) [†]
Race/ethnicity		
African American	135	1.21 (1.07-1.37) [†]
Dominican	214	1.11 (0.99-1.23)
Maternal asthma		
No	270	1.17 (1.07-1.28) [†]
Yes	79	1.11 (0.94-1.31)
Maternal "allergy" [§]		
No	197	1.18 (1.07-1.31) [†]
Yes	149	1.12 (0.98-1.27)
High school degree		
No	132	1.12 (0.99-1.26)
Yes	212	1.16 (1.05-1.29) [†]
Material hardship		
No	185	1.13 (1.02-1.27)*
Yes	170	1.19 (1.05-1.34) [†]
Environmental tobacco smoke		
No	230	1.16 (1.04-1.29) [†]
Yes	119	1.14 (1.01-1.29)*
Birth order of child		
Firstborn	167	1.19 (1.06-1.34) [†]
Second or later	182	1.13 (1.02-1.25)*

* $P < .05$.[†] $P < .01$.

[‡]RRs were adjusted for sex, race/ethnicity, age of child when sensitization was measured, maternal asthma, material hardship, prenatal environmental tobacco smoke, and older siblings. Variables tested in stratification were removed from the models for which they were stratified. Effect modification was tested with a multiplicative interaction term ("variable" by Bla g 2) in the fully adjusted model. All interaction terms for the variables in the table had a P value of greater than 0.20.

[§]Mother replied yes to a question about having allergies asked during the first year after the child was born.

^{||}Mother reported during pregnancy that in the past 6 months she and her family could not afford needed food, rent, clothing, or medical care or that gas/electricity was suspended because of bill nonpayment.³⁰

model did not reach convergence. There was no association between prenatal Der f 1 exposure and sensitization at age 5 to 7 years (RR, 0.98; 95% CI, 0.83-1.15; $P = .78$).

Effect modification by PAHs

There were no associations between $\sum_8\text{PAH}_{\text{nonvolatile}}$ values and sensitization to cockroach at age 2 to 3 years ($P = .13$) or 5 to 7 years ($P = .33$) or mouse or dust mite at these ages, nor were there any associations between pyrene levels and sensitization. In bivariate analyses Bla g 2 levels in prenatal kitchen dust were associated with sensitization to cockroach at age 2 to 3 and 5 to 7 years (Fig 3) among the children with higher (greater than the median) prenatal measures of $\sum_8\text{PAH}_{\text{nonvolatile}}$ but not those with lower $\sum_8\text{PAH}_{\text{nonvolatile}}$ exposure. Similarly, in multivariable models prenatal kitchen Bla g 2 levels were associated with sensitization to cockroach at age 2 to 3 years among children with higher (RR, 1.42; 95% CI, 1.14-1.77; $P = .002$) but not lower (RR, 0.93; 95% CI, 0.75-1.15; $P = .49$) $\sum_8\text{PAH}_{\text{nonvolatile}}$ exposure ($P_{\text{interaction}} = .009$). In similar models sensitization to cockroach

at age 5 to 7 years was associated with Bla g 2 levels among children with higher (RR, 1.22; 95% CI, 1.0801-1.36; $P = .001$) but not lower (RR, 1.07; 95% CI, 0.96-1.20; $P = .24$) prenatal $\sum_8\text{PAH}_{\text{nonvolatile}}$ exposure ($P_{\text{interaction}} = .088$). Among the children with higher prenatal $\sum_8\text{PAH}_{\text{nonvolatile}}$ exposure, the association between prenatal Bla g 2 exposure and sensitization at age 5 to 7 years held after adjustment for postnatal Bla g 2 exposure (RR, 1.17; 95% CI, 1.02-1.35; $P = .023$). In sensitivity analyses similar associations were observed when $\sum_8\text{PAH}_{\text{nonvolatile}}$ exposure dichotomization considered whether measurement was conducted in the heating or nonheating season (data not shown).

There was no effect modification of the association between prenatal Bla g 2 levels and sensitization by prenatal pyrene exposure in univariate or multivariable analyses (see Fig E3 in this article's Online Repository at www.jacionline.org).

Effect modification by polymorphisms in *GSTM* and *GSTP*

There were no differences in sex, maternal asthma, sensitization to cockroach, or Bla g 2 or PAH concentrations between children with and without the *GSTM* and *GSTP* genes studied (see Table E2 in this article's Online Repository at www.jacionline.org).¹⁹ There was a modest difference in the frequency of the *GSTP* polymorphism but not the *GSTM* deletion by race/ethnicity.

The association between Bla g 2 levels and sensitization among children with higher $\sum_8\text{PAH}_{\text{nonvolatile}}$ exposure appeared to be of greater magnitude among those children null for *GSTM1* compared with those with the gene in univariate analyses (Fig 4). In multivariable analyses, among children with higher prenatal $\sum_8\text{PAH}_{\text{nonvolatile}}$ exposure, Bla g 2 levels were associated (borderline) with cockroach sensitization at age 5 to 7 years among the children with *GSTM* ($n = 114$; RR, 1.15; 95% CI, 1.00-1.33; $P = .046$). The RR was greater among the children without the *GSTM* ($n = 38$; RR, 1.54; 95% CI, 1.18-2.01; $P = .001$) and the interaction term (Bla g 2 $\times$ *GSTM*) was a P value of .12. We did not observe effect modification by polymorphisms in *GSTP* (see Fig E4 in this article's Online Repository at www.jacionline.org).¹⁹

DISCUSSION

In this inner-city birth cohort cockroach allergen measured in kitchen dust during pregnancy predicted cockroach sensitization by age 5 to 7 years, even after controlling for cockroach allergen measured at age 1 to 5 years. The association was modified by airborne prenatal nonvolatile PAH concentrations. Children lacking the common *GSTM1* gene polymorphism appeared to be more susceptible to sensitization with the combined cockroach allergen and PAH exposure.

These findings build on associations between domestic cockroach allergen concentrations and sensitization observed in cross-sectional studies among 4- to 7-year-old children in New York City.^{2,3} However, these findings are novel because they demonstrate that cockroach allergen exposure at earlier ages, prenatally or early postnatally, is contributing to sensitization development at later ages. Given that both prenatal and age 1- to 5-year cockroach allergen exposures were associated independently with sensitization, it seems that exposure throughout early childhood can contribute to sensitization. The modest correlation we observed between prenatal and postnatal cockroach

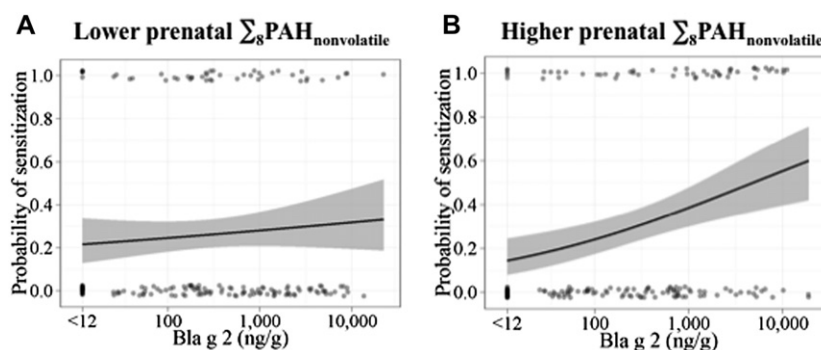


FIG 3. Probability of sensitization to cockroach at age 5 to 7 years with prenatal Bla g 2 exposure among children with lower (**A**) and higher (**B**) prenatal airborne $\Sigma_8\text{PAH}_{\text{nonvolatile}}$ exposure. $\Sigma_8\text{PAH}_{\text{nonvolatile}}$ concentrations were dichotomized at the median (2.25 ng/m^3). Unadjusted logistic regression lines are depicted with 95% CIs in the gray shaded area. **A**, $P = .34$; **B**, $P < .001$.

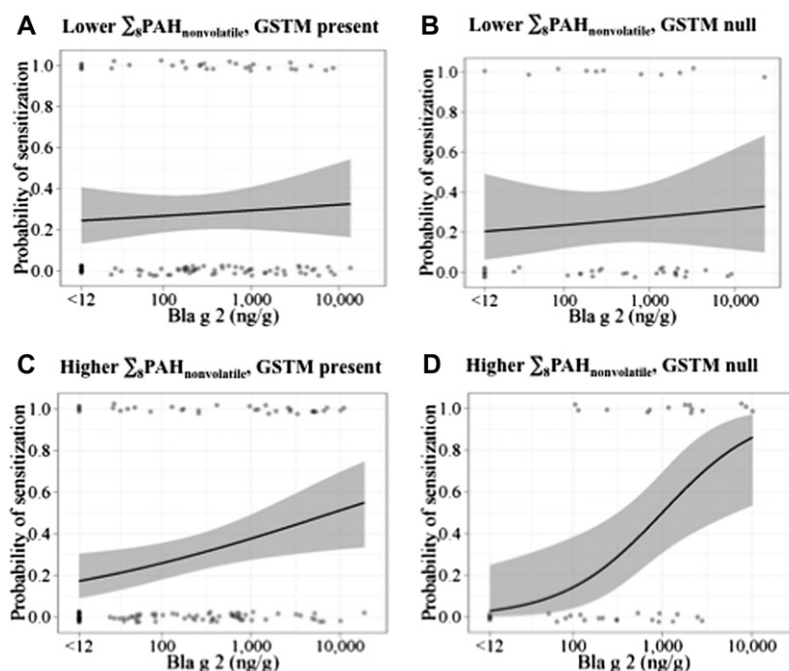


FIG 4. Probability of sensitization to cockroach at age 5 to 7 years with prenatal Bla g 2 exposure stratified by prenatal $\Sigma_8\text{PAH}_{\text{nonvolatile}}$ exposure and *GSTM* polymorphisms. $\Sigma_8\text{PAH}_{\text{nonvolatile}}$ concentrations were dichotomized at the median (2.25 ng/m^3). Unadjusted logistic regression lines are depicted with 95% CIs in the gray shaded area. **A**, $P = .43$; **B**, $P = .60$; **C**, $P = .017$; **D**, $P = .005$.

allergen exposure was not as strong as has been observed for dust mite and cat over similar time periods,³¹ which might reflect changes in infestation. This study design did not allow for the resolution of whether the relevant exposures were *in utero* or early postnatal (eg, the first year) because we did not measure allergen or PAH levels immediately after the child was born. Still, it is unlikely that such measures would have been sufficiently variable to evaluate these exposure times independently (ie, not many mothers changed residence). Previously, we published findings from this cohort showing antigen-specific cord blood mononuclear cell responses, including those to cockroach allergens, that offer evidence of immune priming *in utero*⁸; however, the cord blood proliferative responses did not predict specific IgE development to cockroach at age 5 years.²⁸ Collectively, our findings with cockroach and those from

prospective studies of dust mite exposure³²⁻³⁴ demonstrated that the path to allergen-specific sensitization can begin early in life.

Exposure to nonvolatile PAHs modified the risk for sensitization with cockroach allergen exposure. Evidence for associations between combustion byproducts and allergic sensitization to inhalant allergens initially came from studies observing a higher prevalence of aeroallergen sensitization in cities with higher air pollution (ie, in East Germany).³⁵ More direct evidence came from human *in vivo* studies in which DEPs acted as adjuvants to IgE production to keyhole limpet hemocyanin (KLH) measured in subjects' noses after nasal co-exposure to DEPs and KLH.⁷ Studies in mice further advanced these findings, demonstrating that exposure to DEPs during sensitization to *Aspergillus fumigatus* was associated with a

greater IgE response than that seen without DEPs and corresponding altered DNA methylation of IFN- γ and IL-4.³⁶ Together, these studies indicate that the higher combustion byproduct and cockroach allergen exposures seen in lower-income urban communities^{3,37} are acting synergistically, leading to greater risk of sensitization. However, based on previous studies, it seems that this effect of increased sensitization in response to combustion byproducts is due to a nonspecific effect of increasing sensitization to any allergen and not specifically cockroach.

The finding of associations with $\sum_8\text{PAH}_{\text{nonvolatile}}$ exposure but not pyrene exposure suggest that a nonvolatile PAH might be the compound in DEPs that acts as an adjuvant; however, we cannot exclude the possibility that $\sum_8\text{PAH}_{\text{nonvolatile}}$ concentrations correlate with other unmeasured compounds that act as the adjuvant. DEPs can act as adjuvants by activating dendritic cells, increasing their maturation and expression of T-cell costimulatory molecules.³⁸ In mice exposure to pollutants from DEPs elicited a greater T_H2 response, uptake of antigen by dendritic cells, and expression of the costimulatory molecules than exposure to particulates from automobile exhaust with lower DEP levels.^{39,40} Also, semivolatile PAHs, such as pyrene, have primarily indoor sources, whereas nonvolatile PAHs have primarily outdoor combustion sources.⁴¹ In experimental studies pyrene has demonstrated both proallergic and nonallergic immune responses.⁴²⁻⁴⁴ Also, nonvolatile PAHs can travel in air on particles, whereas the semivolatile pyrene could travel as a gas, possibly affecting inhalation into the distal airways. Hence the combustion source, exposure dynamics in the airways, and immunostimulatory capabilities all could contribute to differences seen with exposure to nonvolatile PAHs versus the semivolatile pyrene.

These findings support those from the human *in vivo* models of KLH sensitization, suggesting that subjects null for the *GSTM1* gene might be at increased susceptibility for the adjuvant effect of combustion byproducts on sensitization. Like other glutathione-S-transferases, *GSTM* catalyzes the binding of glutathione with reactive electrophiles, including those from PAHs.⁴⁵ In occupational studies null adults compared with those with the *GSTM1* gene had higher PAH DNA adduct concentrations (eg, benzo[a]pyrene diol epoxide) in lymphocytes, indicating that the *GSTM1* gene increases metabolism of PAHs from environmental sources.^{45,46} Therefore if nonvolatile PAHs are acting as adjuvants, subjects with the *GSTM1* gene might be better able to detoxify the relevant PAHs and decrease the effect of these exposures on the development of sensitization.

We did not observe consistent associations between mouse or dust mite allergen exposure and sensitization. The lack of an association with domestic mouse allergen is consistent with our observations in 2 cross-sectional studies of children living in New York City.^{2,3} It might be related to important exposure differences among mouse, cockroach, and dust mite allergens, including the aerodynamic properties of the particles that carry the allergens⁴⁷ and exposure in schools.⁴⁸ The lack of a consistent association between prenatal dust mite allergen and sensitization was not consistent with findings from several prospective studies³²⁻³⁴; however, only 12% and 9% of children in this study had dust mite allergen levels greater than the cut points described in studies by Lau et al³³ and Sporik et al,³² respectively. An association between dust mite exposure and

sensitization was observed in a cross-sectional study of 7- to 8-year-olds from a different population in New York City that included children living in freestanding homes where dust mite allergen concentrations were greater than in apartment buildings.^{3,49}

Interventions to reduce cockroach allergens are acknowledged to be difficult in the multifamily apartment buildings typically found in cities.⁵⁰ Some promise of successful allergen reduction with intervention was demonstrated by the Inner-City Asthma Study⁵⁰ and from a building-wide implementation of integrated pest management conducted by the New York City Department of Health and Mental Hygiene and the New York City Housing Authority (the largest public housing authority in North America).⁵¹ However, our data seem to suggest that allergen needs to be reduced throughout early childhood. Reduction in PAH exposures mostly require large-scale public health initiatives. The 2 principal sources of combustion byproducts in New York City homes, including PAHs, are diesel trucks and residential burning of residual fuel oil in boilers.^{10,26,37,52} Recently enacted regulations to eliminate residual oil burning in New York City could lead to some reduction in the sources of PAHs. Further public health interventions should include reduction of pollution from diesel combustion sources.

This study had several limitations. We only had complete data for these analyses on approximately half of those children originally enrolled. However, the children included in the analyses did not differ significantly from those not included in key variables, including PAH and Bla g 2 exposures. The decreased sample size might have limited our power to detect associations between the other allergens and sensitization or effect modification of these associations by PAH exposure. Also, it reduced the sample size for the models that included adjustment of postnatal Bla g 2 exposure and the stratification by PAH and genotype. Although estimates of statistical significance for some of these interaction terms fell into the range that included *P* values of greater than .05, multiplicative interaction terms were tested, and additive interactions could be considered biologically relevant. Still, the main association between Bla g 2 levels and sensitization remained statistically significant in the children exposed to higher PAH levels and, among those, the children null for *GSTM1*. We did not assess the association between exposure to seasonal aeroallergens and sensitization, which also might be modified by PAH exposure. We only assessed PAH exposure with a 48-hour sampling period; however, we have previously demonstrated a good correlation between this measurement and longer-term residential sampling in the subsequent months of pregnancy.⁵³

In summary, these findings offer further evidence that exposure to cockroach allergens and combustion byproducts contributes to allergic sensitization. To our knowledge, this study is the first to observe an interaction between domestic allergen exposure and PAHs on the development of allergen-specific IgE. The mechanisms can begin prenatally, signifying that the first step in the atopic march might occur early in the maturation of the immune system. Given the well-established link between cockroach sensitization and asthma morbidity,^{27,54} these findings suggest that early-life interventions on either cockroach allergen or combustion byproducts could reduce sensitization and thus asthma morbidity in urban communities.

We thank the participating mothers and children. This work would not have been possible without the hard work and dedication of the research workers and field technicians.

Key messages

- Domestic exposure to cockroach allergen measured prenatally predicted sensitization to cockroach at age 5 to 7 years.
- Cockroach allergen predicted sensitization only among children also exposed to higher levels of airborne nonvolatile PAHs, indicating that these combustion byproducts can act as adjuvants in the development of cockroach sensitization in urban environments.
- These findings suggest that targeting either allergens or combustion sources with primary prevention could be successful in reducing the development of cockroach sensitization.

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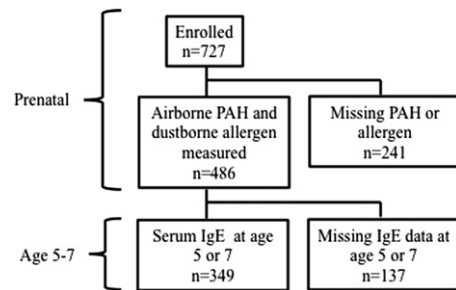


FIG E1. Schematic of participants enrolled prenatally and the subset with complete data included in the current analyses.

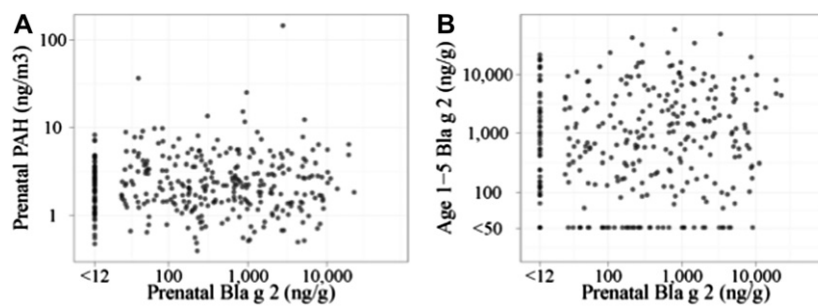


FIG E2. Correlation between Bla g 2 levels in prenatal kitchen dust and PAH levels in air measured prenatally ($r = 0.003$, $P = .96$; **A**) and Bla g 2 levels in kitchen dust at the ages of 1 to 5 years ($r = 0.15$, $P = .007$; **B**).

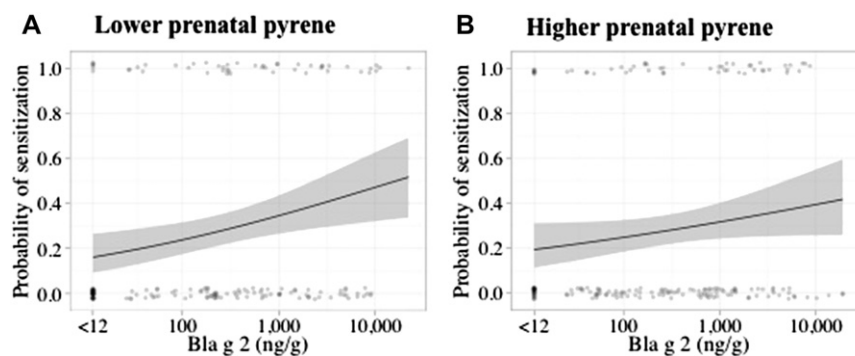


FIG E3. Probability of sensitization to cockroach at ages of 5 to 7 years with prenatal Bla g 2 exposure among children with lower (**A**) and higher (**B**) prenatal airborne pyrene concentrations. Pyrene concentrations were dichotomized at the median (2.6 ng/m³). Unadjusted logistic regression lines are depicted with 95% CIs in the gray shaded area. **A**, $P = .005$; **B**, $P = .071$. The corresponding adjusted models for Bla g 2 predicting sensitization yielded the following RRs. **Fig E1, A**: RR, 1.19; 95% CI, 1.07-1.33; $P = .001$. **Fig E1, B**: RR, 1.11; 95% CI, 0.99-1.25; $P = .085$. The Bla g 2 $\times$ pyrene interaction term resulted in a $P_{\text{interaction}}$ value of .40 in the adjusted model predicting sensitization at age 5 to 7 years.

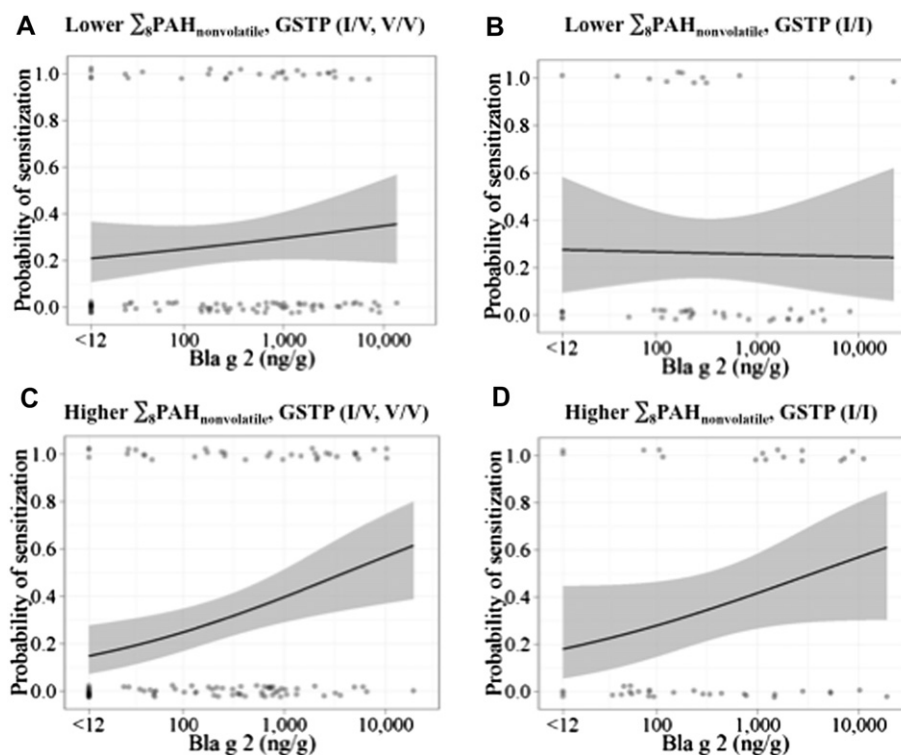


FIG E4. Probability of sensitization to cockroach at age 5 to 7 years with prenatal Blag 2 exposure stratified by prenatal $\Sigma_8\text{PAH}_{\text{nonvolatile}}$ exposure and *GSTP* polymorphisms. $\Sigma_8\text{PAH}_{\text{nonvolatile}}$ concentrations were dichotomized at the median (2.25 ng/m^3). Effect modification by the presence of the minor allele in *GSTP1* (Ile/Val or Val/Val) was evaluated based on previously reported altered susceptibility to the adjuvant effect of DEPs on sensitization.¹⁹ Unadjusted logistic regression lines are depicted with 95% CIs in the gray shaded area. **A**, $P = .26$; **B**, $P = .94$; **C**, $P = .003$; **D**, $P = .057$. The corresponding adjusted models for Blag 2 predicting sensitization yielded the following RRs. **Fig E2**, **A**: $n = 104$; RR, 1.10; 95% CI, 0.95-1.28; $P = .21$. **Fig E2**, **B**: $n = 45$; RR, 1.16; 95% CI, 0.92-1.45; $P = .21$. **Fig E2**, **C**: $n = 108$; RR, 1.22; 95% CI, 1.07-1.40; $P = .004$. **Fig E2**, **D**: $n = 42$; RR, 1.17; 95% CI, 0.91-1.50; $P = .21$.

TABLE E1. Demographics of mothers during pregnancy among those included in the analyses (n = 358) and those recruited who were excluded because of missing data

	Included (n = 349)	Enrolled but excluded (n = 378)
Age, mean (SD)	25.2 (5.0)	24.9 (4.9)
Race/ethnicity		
African American, no. (%)	135/349 (38.7)	119/378 (31.5)*
Dominican, no. (%)	214/349 (61.3)	259/378 (68.5)*
Self-reported health		
Asthma, no. (%)†	79/349 (22.6)	84/378 (22.2)
“Allergy,” no. (%)‡	149/346 (43.1)	138/340 (40.6)
Sociodemographics		
No high school degree, no. (%)	132/344 (38.1)	125/369 (33.9)
Receiving Medicaid, no. (%)	325/349 (93.1)	332/374 (88.8)*
Material hardship in last 6 mo, no. (%)§	164/349 (47.0)	157/367 (42.8)
Domestic environment		
Smoker in home, no. (%)	119/349 (34.1)	127/368 (34.5)
Cockroach sightings common, no. (%)	153/319 (48.0)	137/330 (41.5)
Mouse sightings common, no. (%)	67/319 (21.0)	82/329 (24.9)
Cat in home, no. (%)	36/348 (10.3)	41/368 (11.1)
Dog in home, no. (%)	15/348 (4.3)	20/368 (5.4)
Airborne $\sum_8$ PAH _{nonvolatile} , geometric mean (95% CI)	2.3 (2.1-2.5)	2.5 (2.3-2.7)¶
Kitchen Bla g 2 allergen (ng/g), geometric mean (95% CI)	235 (188-294)	195 (143-268)#

* $P < .05$ comparing children included with those enrolled but not included.

†Mother reported either during pregnancy or on a questionnaire 3 months after the child that she had asthma.

‡Mother replied yes to a question about having allergies that was asked during the first year after the child was born.

§Mother reported that in the past 6 months she and her family could not afford needed food, rent, clothing, or medical care or that gas/electricity was suspended because of bill nonpayment.³⁰

||Cockroaches or mice seen at least weekly.

¶Airborne $\sum_8$ PAH_{nonvolatile} exposure was available on 338 of 378 not included in analyses.

#Kitchen Bla g 2 levels were available for 174 of 378 children not included in analyses.

TABLE E2. Demographics of children and prenatal Bla g 2 and $\sum_8\text{PAH}_{\text{nonvolatile}}$ levels by *GSTM1* polymorphisms (n = 312)

	<i>GSTM</i>		<i>GSTP1</i> †	
	Present (n = 221)	Deleted (n = 81)	Ile/Ile (n = 87)	Ile/Val or Val/Val (n = 215)
Male sex, no. (%)	113/221 (48.9)	35/81 (43.2)	46/87 (52.9)	97/215 (45.1)
Mother's race/ethnicity				
African American, no. (%)	93/221 (42.1)	30/81 (37.0)	27/87 (31.0)	96/215 (44.7)*
Dominican, no. (%)	128/221 (57.9)	51/81 (63.0)	60/87 (69.0)	119/215 (55.3)*
Sensitized to cockroach				
Age 2-3 y, no. (%)	19/194 (9.8)	2/74 (6.8)	6/76 (7.9)	18/192 (9.4)
Age 5-7 y, no. (%)	64/221 (29.0)	25/81 (30.9)	27/87 (31.0)	62/215 (28.8)
Airborne $\sum_8\text{PAH}_{\text{nonvolatile}}$, geometric mean (95% CI)	2.3 (2.1-2.5)	2.3 (1.9-2.8)	2.3 (1.9-2.8)	2.3 (2.1-2.5)
Kitchen Bla g 2 allergen, geometric mean (95% CI)	214 (162-283)	328 (208-517)	314 (205-481)	221 (165-296)

* $P < .05$ comparing children with *GSTM* present or deleted (none).

†Effect modification by the presence of the minor allele in *GSTP1* (Ile/Val or Val/Val) was evaluated based on previously reported altered susceptibility to the adjuvant effect of DEPs on sensitization.¹⁹