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Relationships among Prenatal Aeroallergen Exposure, Maternal and Cord Blood Immunoglobulin E: Project ACCESS

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Abstract

Background—While some evidence suggests that antigen sensitization may begin prenatally, the influence of maternal allergen exposure during pregnancy has not been fully elucidated.

Objectives—We examined the relationship between prenatal maternal aeroallergen exposure and cord blood total immunoglobulin E (IgE) and the potential mediating/indirect effect of maternal immune response.

Methods—This study was performed in 301 mother-infant pairs enrolled in the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) project, a study examining the effects of prenatal and early life social and physical environmental exposures on urban asthma risk. Dust samples collected prenatally from mothers' bedrooms were analyzed for cockroach and dust mite allergens. Cord blood was analyzed for total IgE and maternal serum collected during pregnancy for total and specific IgE. We assessed the relationship between prenatal exposure and cord blood total IgE and the potential mediation effect adjusting for maternal age, race, education, smoking status and dust collection season; and child's gender and season of birth.

Results—In multivariate models, elevated prenatal dust mite levels ($> 0.2 \mu\text{g/g}$) increased cord blood IgE concentrations by 29% ($p=0.08$) and continuous dust mite concentration was associated with a significant non-linear increase in cord blood IgE ($p=0.02$). Elevated prenatal exposure to cockroach allergen ($> 2 \text{ U/g}$) was not associated with cord blood IgE, but showed a significant indirect relationship through maternal total IgE ($\beta=0.23$; 95% CI: 0.08, 0.41).

Conclusions—These results demonstrate that maternal prenatal exposure to household allergens may impact cord blood IgE albeit the underlying mechanism may be allergen-specific.

Clinical Implications—Maternal prenatal inhalant allergen exposure may precipitate infant immune response although the pathway of the effect may differ by allergen.

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Capsule Summary—Prenatal exposure to dust mite was associated with increased cord blood total IgE whereas the relationship between prenatal cockroach exposure and total cord blood IgE was only observed through the indirect effect of maternal allergic response.

Keywords

Allergen; Dust Mite; Cockroach; Maternal; Prenatal; Cord Blood; Immunoglobulin E; IgE; Urban

INTRODUCTION

Atopy is a major risk factor for asthma development and has as its key feature the production of immunoglobulin E (IgE) antibodies against specific antigens.¹ It has been proposed that individuals with altered immune response at birth have an increased risk of developing allergic diseases.² In particular, elevated cord blood IgE has been associated with aeroallergen sensitization and the development of allergic diseases in children, particularly in those with a family history of atopy.^{3–5} In addition, indoor allergen exposure is considered an important risk factor for both developing and exacerbating asthma in susceptible populations.⁶ Therefore, a logical place to examine the effect of the environment on asthma development would be to investigate the effect of prenatal allergen exposure on *in utero* IgE response.¹

Recent papers by Rowe et al⁷ and Bønnelykke et al⁸ have fueled the debate on the relative importance of prenatal versus postnatal exposure on allergen sensitization. One of the criticisms of attributing effect to prenatal exposure is the lack of evidence showing a quantitative relationship between maternal allergen exposure and offspring immunological response.⁷ Studies assessing the possible role of prenatal maternal antigen exposure on the neonatal immune response have primarily been experimental studies,^{9–11} or human studies using surrogates of allergen exposure such as building conditions and pet ownership^{12–14} or investigating cord blood cytokine or T cell proliferation in response to antigen stimulation.^{15–18} Proliferation in response to allergens does not correlate with IgE levels and the relevance of cord blood antigen-induced proliferation as a marker of *in utero* priming and as a predictor of subsequent allergic immune response is still in question.^{15, 18–20}

In this study, we investigate the relation of allergen exposure during pregnancy to cord blood IgE, adjusting for important risk factors, and whether prenatal maternal total or specific IgE mediates this relationship. We hypothesize that maternal exposure to household inhalant allergens of dust mite and cockroach measured during pregnancy would be associated with elevated cord blood IgE. We further hypothesize that the influence of aeroallergen exposure on cord blood IgE may be mediated through its effect on prenatal maternal allergic responses.

METHODS

Study participants

Cross-sectional analyses were conducted in the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) project, an ongoing prospective cohort of mother-child pairs originally funded to recruit N=500 pregnant women and their children to study the main effects of prenatal maternal and early life stress and other environmental risk factors on urban childhood asthma risk [described in detail elsewhere²¹]. Briefly, English or Spanish-speaking pregnant women who were at least 18 years of age receiving prenatal care at Brigham & Women's Hospital, Boston Medical Center, three urban community health centers and their associated Women, Infants and Children (WIC) programs in metropolitan Boston and surrounding suburbs were recruited in their 2nd or 3rd trimester between August 2002 and January 2005. Those enrolled in this phase constituted 78.1% of the women who were approached. Those women who did not want to participate in the prospective study answered

a brief screener questionnaire including information on race/ethnicity and annual household income; we observed no significant differences in these covariates between those who agreed to participate and those who declined. Written informed consent was obtained and the study was approved by the Brigham & Women's Hospital and Boston Medical Center human studies committees.

Serum IgE assays

At the time of these analyses, 301 of the 500 children (60%) had information on cord blood IgE, allergen exposure and all potential confounders. Of these, 198 (66%) also had matching prenatal maternal total and allergen-specific IgE. Serum from mothers collected in their 2nd or 3rd trimester and venous placental cord blood collected at birth were analyzed using CAP fluorescent enzyme immunoassay (Pharmacia [now Phadia], Uppsala, Sweden). Total and allergen-specific IgE levels were determined for mothers. Specific IgE was assessed for dust mite (*Dermatophagoides pteronyssinus* and *D. farinae*) and cockroach (*Blattella germanica*). Cord blood total IgE and allergen-specific IgE levels were determined with the same system using a modified protocol reducing the lower limit of detection (LLOD) from 2.0 IU/mL to 0.2 IU/mL.²² We compared the 198 mother-infant pairs with matching maternal IgE versus the 103 who did not have this information. Among those without maternal IgE data, mothers were more likely Black, higher educated, and had higher levels of cockroach allergen.

Prenatal dust collection

Settled dust was collected during pregnancy as a combined sample from the mother's bed and bedroom floor using a standardized protocol.²³ Briefly, two square meters of the bedroom floor was first vacuumed for 5 minutes then all layers of the mother's bed were vacuumed for an additional 5 minutes. Dust mite allergens (Der f 1 and Der p 1) and cockroach allergens (Bla g 1 and Bla g 2) were measured by monoclonal antibody enzyme-linked immunosorbent assay (ELISA) (Indoor Biotechnologies, Charlottesville, VA). The LLOD for Der f 1 and Der p 1 was 0.02 µg/g and for Blag 1 was 0.40 U/g and Bla g 2 1.0 U/g.

Statistical analysis

We first investigated the association between prenatal aeroallergen levels and cord blood total IgE and then performed mediation analysis to test whether the pathway between aeroallergen exposure and cord blood IgE occurred through maternal IgE (see Figure 1).

To evaluate the effect of aeroallergen on cord blood IgE, we used Tobit regression with continuous log-transformed IgE concentrations (Tobit regression accommodates data that is truncated by detection limitation).²⁴

For pathway analysis, we performed the following previously recommended series of tests: (1) association between aeroallergen levels and cord blood total IgE (described above); (2) association between aeroallergen levels and maternal IgE (potential intermediary); and (3) association between maternal IgE and cord blood total IgE.²⁵ However, we also performed a formal test of an indirect pathway between aeroallergen exposure and cord blood IgE through maternal IgE.^{26–28} For (2), we used generalized linear models with identity link on log-transformed maternal total IgE and logistic regression with dichotomized specific IgE (> 0.35 IU/mL (CAP class 1 or greater)). For (3), we used Tobit regression and for (4), we used a bootstrap approach for significance testing of the indirect/mediation effect,^{26, 27} which is preferable here because it does not require specific assumptions, such as normality.^{26–28}

Composite concentrations of Der f 1 plus Der p 1 (hereafter referred to as dust mite allergen) and of Bla g 1 plus Bla g 2 (hereafter referred to as cockroach allergen) were used for analyses. Allergen exposures were dichotomized as elevated (003E 0.20 µg/g) vs non-elevated (≤ 0.20

µg/g) based on sensitivity analyses, which revealed that at cut-points between 0.02 µg/g (LLOD) and 0.20 µg/g, categories of dust mite allergen showed distinguishable, significant differences in cord blood IgE. These results agree with prior research suggesting dust mite effects *in utero* and in the first three years of life above 0.2 µg/g.^{29, 30} For cockroach, no clear cut point was found when sensitivity analyses were conducted; so we used the postnatal sensitivity cut point of 2 U/g.³¹ For the purposes of comparison with some existing literature on postnatal exposure, we also divided allergen exposures into 4 categories: dust mite was categorized in µg/g <0.02 (LLOD), 0.02–0.20, 0.21–2.0, and >2.0 and cockroach was categorized in U/g <0.40 (LLOD), 0.40–2.0, 2.1–8.0, and >8. We additionally ran generalized additive (nonparametric smoothing) models, which relax the assumption of linearity, using continuous log-transformed allergen levels.³² To minimize bias in the latter analyses, measures < LLOD were assigned a random number <LLOD.²⁴

Spearman correlation was used to determine correlation and the rank-sum test to assess group differences (e.g. those with and without maternal IgE measures). Multivariate analyses adjusted for maternal age, race, smoking status, education and season of dust collection (spring, summer, fall, or winter) and children's gender and season of birth. Maternal allergic disease with symptoms was defined as self-report of ever having been diagnosed with asthma, eczema or hay fever. We used graphical plotting of Cook's D and studentized residuals to identify influential points and outliers, respectively, which resulted in the removal of two that were both extreme influential points and outliers. Analyses were conducted using SAS software 8.2 (SAS Institute, Cary, NC). P value <0.05 was considered significant.

RESULTS

Sample characteristics

Characteristics of the study participants are shown in Table I. The mean maternal age was 26.6 years. The population was predominately Hispanic (61.8%) and 36% of the mothers had a history of allergic disease with symptoms.

The percent of homes with dust mite allergen concentrations > 0.20 µg/g was 67.6% and > 2 µg/g was 38.1%. The percent of homes with cockroach allergen concentrations > 2 U/g was 18.5% and > 8 U/g was 8.33%.

Cord blood IgE was detected in 82.4% of the samples and maternal IgE in 98.0%; maternal total IgE was moderately correlated with cord blood total IgE ($r=0.39$; $P<0.01$). Dust mite- and cockroach-specific IgE was detected in 25.3% and 19.2% of the maternal prenatal samples, respectively. We also analyzed 43 cord blood sera with total IgE levels >3 IU/mL for allergen-specific IgE²² and only one was detectable for dust mite at ≥ 0.35 IU/mL.³⁰

Direct relationship between aeroallergen concentrations and cord blood IgE

In multivariate Tobit regression models, elevated residential dust mite concentrations (>0.2 µg/g) were associated with a 29% ($p=0.08$) increase in cord blood IgE. No relationship was seen with cockroach allergen ($P=0.86$). Table II provides the result divided by the allergen exposure categories. Of note, there were significant increases in cord blood IgE at dust mite concentrations 0.02–0.20 µg/g and >2.0 µg/g compared with those with < 0.02 µg/g, but no significant increase at concentrations between 0.21–2.0 µg/g. The continuous (dose-dependent) relationship between dust mite levels and cord blood total IgE was not significant ($p=0.09$). However, notably, the spline model revealed a significant inverse quadratic relationship ($p=0.02$) (Figure 2) similar to the pattern seen with the four dust mite exposure categories in Table II. No association was observed between continuous cockroach allergen and cord blood IgE in these models (Figure 3).

Relationship between aeroallergen concentrations and maternal total and specific IgE

We assessed the relations between elevated dust allergen levels and maternal total and specific IgE in multivariate analyses. Elevated cockroach allergen (> 2 U/g) was significantly associated with maternal total IgE ($p<0.01$); but dust mite allergen was not associated (Table II shows relationship across the 4 allergen exposure categories). None of the allergens were significantly associated with the corresponding allergen-specific IgE levels in mothers (see Table II).

Relationship between maternal total and specific IgE and cord blood IgE

In multivariate analysis, maternal total IgE was significantly associated with cord blood total IgE ($p<0.01$). Maternal specific cockroach IgE was significantly associated with cord blood IgE ($p=0.01$), while specific dust mite IgE was marginally associated ($p=0.05$).

Formal test of indirect effect (pathway analysis)

We used the bootstrap approach to test the indirect relationship between elevated residential aeroallergen concentrations and cord blood IgE operating through maternal IgE (elevated allergen→maternal IgE→cord blood total IgE) in multivariate analyses. An indirect relationship was seen between elevated cockroach allergen and cord blood total IgE through maternal total IgE ($\beta=0.23$; $p<0.05$) (see Figure 1). There was no indirect relationship of maternal total IgE between dust mite allergen and cord blood total IgE.

DISCUSSION

In this study, we examined the impact of prenatal maternal exposure to dust mite and cockroach allergens on cord blood IgE and the relationships among allergen exposure, maternal immune response and cord blood IgE. We found that elevated dust mite in household dust measured during pregnancy significantly affected cord blood IgE levels. Conversely, we observed no association of cockroach allergen with cord blood IgE concentrations, but instead found a significant indirect relationship operating through maternal total IgE. These data suggest that effects of prenatal maternal allergen exposure on infants' immune response may differ depending upon the specific allergen.

These findings should be interpreted in the context of the extant literature on the relationship of prenatal allergen exposure and infant immune response^{15, 18, 33–35} Reports include those showing mixed results by allergen and study site between early life exposure (i.e., within 3 months of birth) and sensitization at age 4³⁶ and modification of effect by prenatal exposure to a farm environment.³⁷ Our results corroborate those of Miller et al¹⁵ and Hagendrons et al,¹⁸ as we found no relationship between dust mite and cockroach allergen and maternal antigen-specific IgE. We did not find a linear dose-response relationship between elevated IgE and dust mite allergen concentrations as was reported by Schönberger et al³⁴ However, our results showed the same inverse quadratic relationship between cord blood IgE and dust mite concentrations using nonparametric smoothing (generalized additive models) as reported by Heinrich and colleagues.³⁵ The absence of a linear dose-dependence between maternal exposure and cord blood reactivity and allergen-specificity may reflect the accumulation of most of the allergen in placental tissue and the energy-dependence of transplacental transfer as previously discussed.³⁸

As far as we know, there is no previous study formally investigating the intermediate effect of maternal prenatal IgE in the relationship between measured allergen exposure and cord blood IgE. Ege et al³⁷ reported a relationship of farm-related exposures and cord blood IgE even after adjusting for maternal IgE, concluding that maternal IgE is not the source of cord blood IgE. Alternatively, Bønnelykke et al⁸ found a complete match of specific IgE in cord blood and

maternal blood and concluded from these results and IgA measurements, that there was maternal-fetal transfer of IgE. However, another study found specific cord blood IgE to dust mite allergen in the absence of maternal specific IgE to dust mite.^{8, 39} This is consistent with our findings that prenatal maternal IgE did not appear to be an intermediary between the effect of maternal dust mite exposure and cord blood IgE, but was between maternal cockroach exposure and cord blood IgE. We found a significant mediation effect of maternal IgE operating between maternal prenatal cockroach exposure and cord blood IgE even without a significant direct relationship between cockroach exposure and IgE production in cord blood. This may point to multiple mediators or unmeasured confounding which induce inconsistent effects.²⁶ One indication of this might be the negative relationship we observed between detected cockroach allergen and cord blood IgE when maternal IgE was included in the model as a control variable (data not shown).

As suggested above, there is evidence that the immune effect of allergen exposure *in utero* can occur through more than one pathway²² – 1) direct exposure to allergens *in utero* and 2) effect of maternal allergic response. Supportive evidence for the first pathway comes from studies which show the effectiveness of the placental barrier to IgE.^{40, 41} These studies propose that positive correlation between maternal and fetal immunoglobulin levels is related to the quantity and nature of allergens present in the family environment. Indeed, it is believed that several allergens may be transferred through the placenta or in amniotic fluid, thus gaining access to gut-associated lymphoid tissue.^{10, 42, 43} This hypothesis is supported by the detection of antigen presenting cells in the placenta during pregnancy and the detection of Der p 1 in amniotic fluid and cord blood.¹⁰

In support of the second pathway, studies have demonstrated fetal exposure to intact IgE occurring via the gastrointestinal tract.^{44,45} First, amniotic fluid has been found to contain intact IgE that might bind to IgE receptors in the fetal gastrointestinal tract and the level of IgE found was not explained by fetal circulating IgE levels.⁴⁴ Second, a significant correlation has been found between maternal circulating IgE and amniotic fluid IgE at mid and late pregnancy⁴⁵ and between maternal- and cord blood-specific IgE at all levels of IgA.⁸ The hypothesis is then that specific IgE-mediated allergen focusing or non-specific priming in an environment that favors elevated IgE production ‘educates’ the fetal immune system about the maternal environment.^{44, 46} Alternatively, elevated maternal IgE is associated with an increased production of cytokines and chemokines, which are known to cross the placental barrier^{47, 48} that can, in turn, influence the fetal immune system. It is to be noted however, that *in utero* exposure to elevated IgE may not translate into offspring sensitization.⁸

House dust mite and cockroach allergens are both believed to play a significant role in the development of allergic diseases. These data suggest that their mechanisms of action may be different. For example, it has been suggested that one of the mechanisms by which dust mite produces IgE is through enzymatic activity. Der p 1, the most studied of the dust mite allergens, has been shown to directly promote IgE synthesis;^{49, 50} disrupt bronchial epithelium and cause the release of proinflammatory cytokines;^{51, 52} as well as disrupt tight junctions and facilitate transepithelial allergen delivery and processing.^{53, 54} On the other hand, cockroach allergens do not, to our knowledge, demonstrate functional enzyme activity. Bla g 2 shows homology to the aspartic proteinase family of enzymes, but is an inactive proteinase.⁵³

One concern with our findings may be that because we did not measure IgA, our results may reflect maternal contamination of cord blood IgE at birth. However, as noted above, our dust mite results were similar to those of a study by Heinrich et al.³⁵ where IgA was measured for detecting contamination. Of note, in that study, of the 1,322 cord blood measurements, no single IgA exceeded 32 µg/L. Bønnelykke et al.⁸ also found no IgA in cord samples even at the lowest proposed cutoff level of 10 mg/L.⁵⁵ Another limitation is that we did not measure

IgG and the IgE/IgG ratio may be a key factor modifying prenatal allergen-specific immune response⁵⁶ and should be considered in future studies. In addition, we did not investigate the role of shared genetic factors between mother and infant that could influence the response to allergen exposure leading to greater immune response.

The combined strength of this study includes the reasonably large sample size together with measured residential allergen concentrations as well as assays of cord blood and maternal total IgE. With the inclusion of prenatal allergen exposure levels, we were able to explain more of the variability in cord blood IgE. In addition, the percent of detected cord blood IgE (82.3%) (most other reported studies have much lower detection levels of cord blood) allowed us to investigate the relationships in multivariate models both by dichotomized cord blood concentrations (data not shown) and by continuous concentrations with similar findings. Our ability to detect cord blood IgE was increased by using a modified protocol, which lowered the limit of detection by an order of magnitude. Another Massachusetts study had comparable levels at 59%, but other studies reported levels such as 17 to 33 percent.^{35, 57}

It is also worthwhile to compare allergen detection patterns in the current study and others performed in urban settings. Our dust mite percent detect was typical of the Northeast region,^{23, 58} but our cockroach levels were less typical of low-income populations,^{15, 59, 60} probably owing to differing recruitment criteria. In addition, our prenatal dust samples were bedroom samples which may not have allowed us to adequately assess cockroach allergen exposure, as this would be more typically found in the kitchen. However, cockroach allergen levels in bedroom and kitchen are significantly correlated, with bedroom samples actually being a better indicator of prolonged exposure and more predictive of sensitization.^{61, 62}

And finally, it is worth pointing out that even though we adjusted for maternal age, race, smoking, education, season of dust collection, and offspring gender and season of birth (unlike other U.S. studies that only perform univariate analyses^{15, 18, 33}), there is the potential for unmeasured or inadequately-measured confounders. Thus, this study uniquely combines information about prenatal maternal exposure to allergen, prenatal maternal total and specific IgE and cord blood total IgE, as well as adjusts for several important risk factors and potential confounders.

In summary, we have demonstrated that maternal prenatal exposure to dust mite allergen was directly associated with cord blood IgE, whereas maternal prenatal exposure to cockroach was associated with cord blood IgE indirectly through its association with maternal IgE. Our study supports the hypothesis that the maternal environment significantly affects the developing immune system, and that the mechanism of effect may differ by allergen. Improving understanding of the association of maternal residential exposure during pregnancy in relationship to maternal and cord blood IgE may expand our understanding of effectors of early immune development and may be helpful in directing future intervention strategies aimed at reducing the development of childhood allergy and asthma.

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Abbreviations

ACCESS, Asthma Coalition on Community, Environment, and Social Stress; ELISA, Enzyme-linked immunosorbent assay; IgE, Immunoglobulin E; LLOD, Lower limit of detections.

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Figure 1.

Summary diagram of the modeled relationships between residential allergen concentrations, maternal total IgE, and cord blood total IgE including the indirect effects from mediation analysis using the bootstrap approach.

^aAll models adjust for maternal age, race, education, smoking status and season of dust collection, and child's gender and season of birth.

*significant relationship ($p < 0.05$)

Figure 2.

Adjusted smoothed associations between dust mite allergen and cord blood IgE. The lower limit of detection is $-3.9 \mu\text{g/g}$ for dust mite on the log scale.

Figure 3.

Adjusted smoothed associations between cockroach allergen and cord blood IgE. The lower limit of detection is -0.92 U/g for cockroach on the log scale.

Table I

Characteristics of study participants (N=301).

Variable	N (%)	Mean $\pm$ SD
Maternal		
Age (years)		26.6 $\pm$ 5.80
Education (%)		
<=High school education	206 (68.4)	
> High school education	95 (31.6)	
Race (%)		
White	7 (2.33)	
Black	90 (29.9)	
Hispanic	186 (61.8)	
Other	18 (5.98)	
Smoking during pregnancy(%)		
Yes	42 (14.0)	
No	259 (86.0)	
Allergic disease with symptoms ^a (%)		
Yes	107 (35.6)	
No	194 (64.4)	
Offspring		
Gender (%)		
Female	146 (48.5)	
Male	155 (51.5)	
Season (%)		
Spring	71 (24.6)	
Summer	77 (25.6)	
Fall	80 (26.6)	
Winter	71 (23.6)	

^a Allergic disease with symptoms is defined as history of asthma, eczema or hay fever.

Table II

Parameter estimates of the effect of prenatal allergen exposure on cord total blood IgE, maternal total IgE and maternal specific IgE in multivariate regression^a.

Variable	Allergens and cord blood IgE ^b β (p-value) N=299 ^c	Allergens and Maternal total IgE ^d β (p-value) N=196	Allergens and Maternal specific IgE ^e β (p-value) N=196
Dust mite (composite) ^f			
> 2.0 µg/g	0.73 (0.02)	0.46 (0.09)	0.34 (0.64)
0.21 - 2.0 µg/g	0.37 (0.24)	0.46 (0.11)	0.10 (0.89)
0.02 - 0.20 µg/g	0.60 (0.03)	0.28 (0.44)	0.37 (0.56)
< 0.02 µg/g	0.00 (Referent)	0.00 (Referent)	0.00 (Referent)
Cockroach (composite) ^g			
> 8.0 U/g	0.07 (0.83)	0.91 (0.01)	0.88 (0.22)
2.0 to 8.0 U/g	-0.07 (0.82)	0.81 (0.02)	-0.36 (0.68)
0.40 to 2.0 U/g	0.10 (0.57)	0.81 (0.37)	0.27 (0.56)
< 0.40 U/g	0.00 (Referent)	0.00 (Referent)	0.00 (Referent)

^a All models adjust for maternal age, race, education, smoking status and season of dust collection, and child's gender and season of birth.

^b Evaluates the relationship between aeroallergen exposure and log-transformed cord blood total IgE.

^c Two influential data points were removed bringing the N to 299 for those with cord blood IgE and all other covariates and to 196 for those also with matching maternal total and specific IgE,

^d Evaluates the relationship between aeroallergen exposure and log-transformed maternal total IgE.

^e Evaluates the relationship between aeroallergen exposure and the presence of specific IgE (> 0.35 IU/mL) to the corresponding allergen.

^f Composite of Der f 1 + Der p 1.

^g Composite of Bla g 1 + Bla g 2.