Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy

ORIGINAL ARTICLE EPIDEMIOLOGY AND GENETICS

Prenatal negative life events increases cord blood IgE: interactions with dust mite allergen and maternal atopy

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To cite this article: Peters JL, Cohen S, Staudenmayer J, Hosen J, Platts-Mills TAE, Wright RJ. Prenatal negative life events increases cord blood IgE: interactions with dust mite allergen and maternal atopy. *Allergy* 2012; **67**: 545–551.

Keywords
allergens; cord blood IgE; dust mite; prenatal stress; urban.

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Accepted for publication 29 December 2011

DOI:10.1111/j.1398-9995.2012.02791.x

Edited by: Bodo Niggemann

Abstract

Background: Prenatal exposure to both stress and aeroallergens (dust mite) may modulate the fetal immune system. These exposures may interact to affect the newborn immune response. We examined associations between prenatal maternal stress and cord blood total IgE in 403 predominately low-income minority infants enrolled in the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) project. We also examined potential modifying effects of maternal atopy and maternal dust mite exposure.

Methods: The Crisis in Family Systems survey was administered to mothers prenatally, and a negative life event domain score was derived to characterize stress. Dust mite allergen was quantified in dust from pregnant mothers' bedrooms. Cord blood was analyzed for total IgE. Using linear regression, we modeled the relationship of stress with cord blood IgE and interactions of stress with dust mite and/or maternal atopy, adjusting for potential confounders.

Results: Higher prenatal maternal stress ($\beta = 0.09$; $P = 0.01$) was associated with increased cord blood IgE. The interactive effects between stress and dust mite groups (high *vs* low) were significantly different for children of atopic *vs* nonatopic mothers (P for three-way interaction = 0.005). Among children of atopic mothers, the positive association between stress and IgE was stronger in the high dust mite group. In children of mothers without a history of atopy, the positive association between stress and IgE was most evident in the low allergen group.

Conclusions: Prenatal stress was independently associated with elevated cord blood IgE. Mechanisms underlying stress effects on fetal immunomodulation may differ based on maternal atopic status.

Prenatal maternal stress may influence the programming of autonomic nervous system and neuroendocrine responses, which may then modulate fetal immune development (1, 2). This neuroimmune cross-talk may result in functional changes in immune reactivity and potentiate the propensity for type 2 T-helper (Th2) allergic response and enhanced IgE production (1).

In animal studies, gestational exposure to maternal stress has been associated with altered development of humoral immunocompetence and response to antigens in offspring. Nogueira and colleagues (3) demonstrated that prenatal stress increased allergen-induced airway inflammation in adult mice offspring. Others report a dysregulated immune response upon antigen challenge in prenatally stressed adult mice, reflected by a predominantly Th2 adaptive response and increased IgE expression(4). Evidence in primates suggests that prenatal stress impacts the infant's response to

Abbreviations
ACCESS, Asthma Coalition on Community, Environment, and Social Stress; CI, confidence interval; CRISYS-R, Crisis in Family Systems—Revised; ELISA, enzyme-linked immunosorbent assay; IgE, immunoglobulin E; Th2, type 2 T helper.

antigens even at birth (5). While these data are suggestive, human studies examining the effects of prenatal stress on the infant atopic response are sparse. Lin and colleagues (6) reported an association between maternal self-reported nervousness during pregnancy and elevated cord blood total IgE, and the Avon Longitudinal Study of Parents and Children (ALSPAC) showed associations between maternal anxiety during pregnancy and asthma development in preadolescent children (7).

While still debated (8, 9), evidence suggests that prenatal maternal exposure to some aeroallergens, specifically dust mite, which has been shown to reach the fetal circulation (10), may also influence the neonatal immune response. Our laboratory (11) and others (12, 13) have previously demonstrated a direct relationship between prenatal maternal dust mite exposure and increased cord blood IgE.

Taken together, evidence that both maternal prenatal stress and mite exposure may polarize the fetal immune system toward increased IgE production suggests the potential for dual exposure *in utero* to have a synergistic effect, although this interaction has not been previously examined.

Furthermore, elevated cord blood IgE has been associated with subsequent aeroallergen sensitization and later development of allergic diseases, particularly in children with a family history of atopy, with strongest effects with maternal history (14). This may reflect how environmental factors (e.g., stress, allergens) may differentially influence the immune response depending on which direction the mother's immune system (i.e., the production of biological mediators including cytokines and chemokines known to cross the placenta (15)) is already biased (i.e., atopic *vs* nonatopic).

We add to this collective literature by examining both the independent effect of maternal prenatal stress on cord blood IgE and whether there was an interaction between prenatal maternal stress and dust mite allergen exposure in association with cord blood in an inner-city, low-income, largely minority population. We hypothesized that higher stress levels would be associated with increased cord blood IgE adjusting for relevant confounders and that children of mothers exposed to both higher levels of stress and dust mite allergens during pregnancy would have greatest risk of elevated cord blood IgE. We further hypothesized that the effects would be greatest in those with a maternal history of atopy.

Method

Participants

Analyses were conducted in the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) project, an ongoing prospective cohort of mother–child pairs, which recruited $N = 500$ pregnant women and their children, as previously described (11, 16). In brief, English- or Spanish-speaking pregnant women ($\geq$18 years old) receiving care at Brigham & Women's Hospital (BWH), Boston Medical Center (BMC), and affiliated clinics were enrolled mid- to late pregnancy between August 2002 and June 2007. Among eligible women approached during mid- to late pregnancy (mean gestation ± SD of 28.4 ± 7.9 weeks), 500 (78.1%) agreed to enroll. Of these, 488 gave birth to a live-born infant and continued follow-up. Women who chose not to participate in the prospective study answered a brief screener questionnaire including information on race/ethnicity, household income, and perceived stress; there were 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 BWH and BMC human studies committees.

Psychological stress

The 63-item Crisis in Family Systems—Revised (CRISYS-R) questionnaire, validated in English and Spanish (17, 18), was administered in pregnancy (29 ± 5.0 weeks). The CRISYS-R assesses life events over the previous 6 months, encompassing 11 domains (i.e., financial, legal, career, relationships, medical pertaining to respondent and to others, safety in the community and at home, other home issues, difficulty with authority, and discrimination) with multiple items within each domain. Sample questions include "Did your income decrease by a lot?; Did someone treat you unfairly because of your race?; and "Did something happen in your neighborhood that made you feel unsafe?". Participants endorsed which events they had experienced and rated each as positive, negative, or neutral. As stress research suggests increased vulnerability when adverse events are experienced across multiple domains (19), the number of domains with one or more reported negative event was summarized to create a negative life event domain score, which ranged from 0 to 9, with higher scores indicating greater stress.

Cord IgE

Cord blood total and allergen-specific IgE was assayed using CAP fluorescent enzyme immunoassay (Phadia, Uppsala, Sweden) utilizing a modified protocol reducing the lower limit of detection from 2.0 to 0.2 IU/ml (11). Cord blood IgE was available for $N = 403$ subjects. Analyses focus on total IgE only for the following reasons. Prior studies (8, 20), including other Boston cohorts (21), have reported the low prevalence of newborns with measureable allergen-specific IgE in cord serum, particularly related to dust mite (~2.5%) (20). In this sample, we conducted a sensitivity analysis testing for allergen-specific IgE on 43 newborn serum samples with total IgE >3 IU/ml. Only one had detectable dust mite–specific IgE at $\geq$0.35 IU/ml.

Prenatal dust

Settled dust was collected during pregnancy using a standard protocol by vacuuming all layers of the mothers' bedding for 5 min and then 2 m^2 of adjacent floor for an additional 5 min. Dust mite allergen was measured by enzyme-linked immunosorbent assay (ELISA) (Indoor Biotechnologies, Charlottesville, VA, USA). Composite concentrations of

*Dermatophagoides pteronyssinus and D. Farinae (*Der f 1 plus Der p 1) were dichotomized as 'low' (≤0.20 μg/g) and 'high' (>0.20 μg/g) exposure as previously described (11). Dust was available for $N = 380$ participants, who did not differ from the larger sample relative to other covariates considered in the analyses.

Analyses

Cord blood IgE was log-transformed to mitigate the effects of data skewness. Using linear regression, we first determined the association between global stress and cord blood IgE for all participants and then stratified by maternal atopic status defined as self-report of ever having physician-diagnosed asthma, eczema, or hay fever. We next assessed the stress–allergen interaction by modeling the main effects of stress and dust mite plus an interaction term of stress times dust mite to predict cord blood IgE. We tested for a three-way interaction between stress, allergen exposure, and maternal atopic status to determine whether the allergen effect on the stress–IgE relationship differed significantly based on maternal atopy. All analyses were adjusted for maternal age, race/ethnicity, smoking status and education, and child's gender, birth weight for gestational age (22), and season of birth. Generalized linear models (identity link) were implemented using SAS 8.2 (SAS Institute, Cary, NC, USA), and results are reported as parameter estimates (β) corresponding to the change in cord blood IgE concentration per unit change in the negative domains stress score.

Results

Table 1 summarizes the descriptive statistics across the total sample and stratified by maternal atopic status. Overall, mean maternal age was 26.6 years, mothers were primarily Hispanic (62%), and the majority had less than a high school education (69%). Approximately one-third of the mothers had a history of atopy.

In multivariable analysis, the negative domains score was positively associated with increased cord blood IgE (Table 2). Cord blood IgE levels increased 0.10 IU/ml for each unit increase in the number of negative domains reported by the mother (95% CI: 0.03–0.16). In stratified analysis, the association between an increasing negative domains score and cord blood IgE was significant only among children of atopic mothers (Table 2). However, the difference in the association between atopic and nonatopic strata was not significant (*P*-value for interaction = 0.27).

For the sample as a whole for whom dust mite allergen was available ($n = 380$), there was no evidence for an interaction between stress and dust mite exposure level (Table 3). When we performed multivariable-adjusted three-way interactions looking at the differences in the stress–allergen relationship by atopic status, the interactive effects between stress and the dust mite allergen groups were significantly different for children of atopic mothers compared to those with nonatopic mothers (*P*-value for three-way interaction = 0.005). We further explored interactions within strata of maternal atopic status. For children of atopic mothers in the high dust mite allergen group, there was an increase of 0.21 IU/ml cord blood IgE for each unit increase in the negative domains stress score, while there was no association between IgE and stress in the low dust mite allergen group (Table 3 and Fig. 1). For children of nonatopic mothers, cord blood IgE showed no association with stress in the high dust mite group, while in the low dust mite group, cord blood IgE increased 0.17 IU/ml for each unit increase in stress (Table 3 and Fig. 2).

Discussion

This study makes two unique contributions to the literature. First, to our knowledge, these are among the first prospective data demonstrating a linear relationship between prenatal maternal stress and cord blood IgE. Second, this is the first human study that examines the combined effect of prenatal stress and prenatal allergen exposure on cord blood IgE, demonstrating differing effects among those with and without a maternal history of atopy.

The association between increased prenatal maternal stress and cord blood IgE remained when adjusted for a number of important confounders. In the United States, low socioeconomic status and minority-group status have been related to elevated IgE (23) as well as differential exposure to stress (19). Prenatal stress influences fetal growth and maturation characteristics (24), which have also been related to cord blood IgE (25). Additionally, individuals experiencing greater stress may be more likely to adopt unhealthy coping behaviors such as smoking (26), which may, in turn, influence IgE expression (27). Notably however, even when adjusting for maternal race/ethnicity, education, and smoking status as well as birth weight for gestational age, stress effects remained significant.

Our observations suggest that there may be a more direct influence of maternal stress on the developing fetal immune response. Maternal stress may influence fetal programming of key physiological systems beginning *in utero* that lead to immunomodulation. For example, prenatal maternal stress may disrupt maternal physiology (e.g., hypothalamic–pituitary–adrenal (HPA) axis, sympathetic–adrenal–medullary (SAM) system), which, in turn, may upregulate maternal and fetoplacental Th2 cell predominance and cytokine production. An enhanced Th2 cytokine/chemokine milieu might affect fetal immune function development including IgE isotype development (1). Thus, infants exposed to increased maternal stress *in utero* may be more likely to express increased IgE at birth.

Recently, we reported a direct association between increased dust mite exposure in mothers during pregnancy and elevated cord blood levels in their infants in this cohort (11). The analyses reported here demonstrate a synergistic effect of increased prenatal maternal stress and mother's exposure to dust mite allergen in relation to cord blood IgE expression that differed based on maternal history of atopy. The enhanced response observed in those with atopic

Table 1 Characteristics and measurements of the 403 study participants

Variable	Total sample *N* (%)	Atopic mother *N* (%)	Nonatopic mother *N* (%)	*P*-value
Maternal				
Age (mean years±SD)	26.6 ± 5.78	26.3 ± 5.71	26.8 ± 5.82	0.36
Education				
≤High school education	278 (69.0)	88 (64.2)	190 (71.4)	0.14
>High school education	125 (31.0)	49 (35.8)	76 (28.6)	
Race				
White	15 (3.72)	6 (4.38)	9 (3.38)	0.26
Black	119 (29.5)	45 (32.9)	74 (27.8)	
Hispanic	248 (61.5)	76 (55.5)	172 (64.7)	
Other	21 (5.21)	10 (7.30)	11 (4.14)	
Smoking during pregnancy				
Yes	49 (12.2)	23 (16.8)	26 (9.77)	0.04
No	345 (87.8)	114 (83.2)	240 (90.2)	
Atopic status†				
Yes	137 (34.0)			
No	266 (66.0)			
Offspring				
Gender				
Female	193 (47.9)	63 (46.0)	130 (48.9)	0.58
Male	210 (52.1)	74 (54.0)	136 (51.1)	
Birth gestational age (mean weeks±SD)	39.2 ± 1.71	38.9 ± 1.86	39.4 ± 1.60	0.002
Birth weight (mean g±SD)	3320 ± 567	3180 ± 509	3391 ± 584	0.001
Season				
Spring	101 (25.1)	38 (27.7)	63 (23.7)	0.18
Summer	89 (22.1)	26 (19.0)	63 (23.7)	
Fall	106 (26.3)	30 (21.9)	76 (28.6)	
Winter	107 (26.6)	43 (31.4)	64 (24.1)	
Cord blood IgE (mean IU/ml ± SD)	1.24 ± 5.22	2.04 ± 8.69	0.87 ± 1.57	0.003
Dust mite allergen‡				
<0.20μg/g	108 (28.4)	34 (26.8)	73 (28.9)	0.67
≥0.20μg/g	272 (71.6)	93 (73.2)	180 (71.2)	
CRISYS stress measure (mean score±SD)§				
Negative domains score (NDS)	1.85 ± 1.82	2.37 ± 2.01	1.58 ± 1.66	<0.001

†Atopic status defined as the history of ever having had physician-diagnosed asthma, eczema, or hay fever.
‡Composite of Der f 1 and Der p 1; $N = 380$.
§Crisis in Family Systems—Revised (CRISYS-R) encompasses 11 domains: financial; legal; career; relationships; medical issues pertaining to the respondent; medical issues pertaining to others; safety in the community; safety at home; other home issues; difficulty with authority; and discrimination. NDS, the number of domains in which subjects endorsed one or more negative life event with higher scores indicating greater stress.

mothers may reflect a genetic predisposition in the offspring toward heightened IgE response with antigen presentation. It may also be a consequence of the predisposition of an atopic mother toward an enhanced allergen-induced immune response (28). The consequent elevated maternal IgE expression may be accompanied by increased production of cytokines and chemokines known to cross the placental barrier (15) that may, in turn, influence the child's developing immune response. As noted earlier, maternal stress may act on the child's immune system through its effect on maternal–fetal neuroendocrine disruption, and thus, when combined with this maternal allergen-induced response, the child's developing immune system may be impacted in a synergistic manner. Alternately or in addition, stress may disrupt gut mucosal function, increase intestinal permeability, and heighten intestinal sensitization to luminal antigens (29). Notably, the gut is involved in immune maturation (2), and fetal exposure to antigens occurs, at least in part, through access to gut-associated lymphoid tissue (10, 30). Stress-elicited processes *in utero* may enhance these effects in the fetus.

We also observed an increase in cord blood IgE in relation to increasing stress in the group exposed to low dust mite among children born to nonatopic mothers. It may be that both high dust mite and higher levels of stress similarly increase IgE production in those without a maternal atopy background, and we are unable to see effects on IgE due to stress in addition to that due to the allergen (thus, the influence of stress is more apparent at low allergen levels).

Table 2 Multivariable models examining the negative life events domain score predicting log cord blood IgE concentrations for total sample and by maternal atopic status†

	N	Log cord blood IgE β Estimate for log cord IgE (95% CI)
All mothers	403	0.10 (0.03, 0.16)*
Atopic§ mothers	137	0.13 (0.02, 0.24)*
Nonatopic mothers	266	0.05 (−0.03, 0.14)

CI, confidence interval.
†All models are adjusted for maternal age, race, smoking status and education, and child's gender, birth weight for gestational age, and season of birth.
§Maternal report of doctor-diagnosed asthma, eczema, or hay fever.
**P*-value <0.05.

Table 3 Association between the negative domains score and log cord blood IgE stratified by low (<0.20 μg/g) *vs* (≥0.20 μg/g) high prenatal dust mite allergen exposure and maternal atopic status*

	N	High dust mite β estimate for log cord IgE (*P*-value)	Low dust mite β estimate for log cord IgE (*P*-value)	Interaction β estimate (*P*-value)
All mothers	380	0.10 (0.01)	0.12 (0.07)	−0.01 (0.85)
Atopic† mothers	127	0.21 (0.002)	−0.04 (0.73)	0.25 (0.06)
Nonatopic mothers	253	−0.01 (0.87)	0.17 (0.03)	−0.17 (0.05)

*All models are adjusted for maternal age, race, smoking status and education, and child's gender, birth weight for gestational age, and season of birth.
†Maternal report of doctor-diagnosed asthma, eczema, or hay fever.

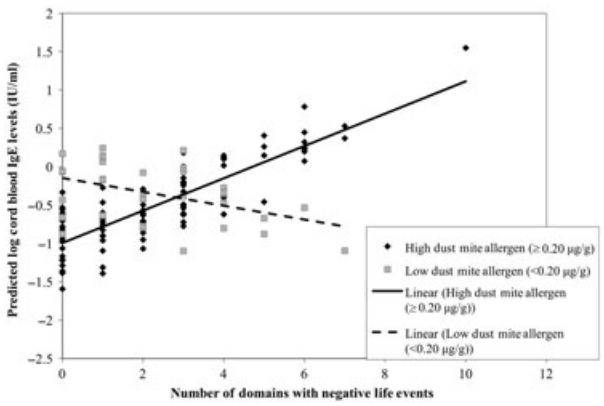

Figure 1 The multivariable predicted relationship for *atopic* mothers between log cord blood IgE and number of domains with negative life events by high *vs* low dust mite allergen.

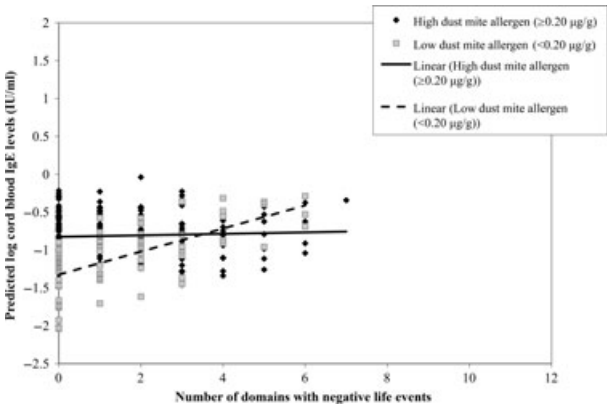

Figure 2 The multivariable predicted relationship for *nonatopic* mothers between log cord blood IgE and number of domains with negative life events by high *vs* low dust mite allergen.

Alternatively, stress-elicited disruption of oxidant–antioxidant balance in mothers (31, 32) may induce oxidative stress in the placenta, with consequences on fetal development similar to effects of other chemical oxidants (33), which are known to enhance IgE production (34). We also note that this is not the first study to find that stress effects on allergic inflammatory markers are more evident among subjects exposed to lower levels of physical environmental exposure. Chen and colleagues (35) reported that higher chronic stress was associated with heightened atopic immune profiles in adolescent asthmatics exposed to lower air pollution levels. Further research is needed to understand the mechanisms underlying these observations.

Notably, these findings may have particular implications for furthering our understanding of observed disparities in asthma as well as other atopic disorders. We observed that the number of domains over which a pregnant mother experienced negative life events was predictive of elevated cord blood IgE in her newborn. This suggests that above experiencing discrete events, the clustering of multiple adversities may confer increased vulnerability. This may be particularly relevant in urban poor communities where exposure to multiple stressors is more prevalent (19, 36). Moreover, the same populations burdened by a greater number of stressors (e.g., socioeconomic strain, neighborhood violence) are also more likely to be exposed to adverse physical environmental conditions (e.g., indoor aeroallergens, ambient air pollution) (37). Whether this confers increased vulnerability to allergy and/or asthma in these children will be examined as we follow these children longitudinally.

While the study has a number of strengths including the relatively large, higher-risk low-income ethnically mixed sample, the concurrent assessment of maternal stress and measured dust mite exposure during prenatal development, and the ability to adjust for a number of important confounders and pathway variables, there are also limitations worth noting. The composition of this study cohort (i.e., US urban, low socioeconomic status (SES), largely African American

and Latino) may make it less generalizable, particularly to higher SES, nonminority populations. However, an inverse relation between allergy and asthma morbidity and SES is increasingly documented globally (38). Moreover, ethnic minority populations worldwide are similarly marginalized and may also bear a disproportionate burden of exposure to suboptimal living conditions – physical, social, and psychological. Thus, these findings should be replicated in other countries as well as in other racial/ethnic groups. As with all studies, we cannot rule out the possibility of residual confounding. Also, we performed subpopulation analyses (i.e., looking at the relationship by maternal atopic status), which may have lowered our power to detect some relationships.

These data suggest that prenatal maternal stress may influence fetal immune system development in children born to mothers both with and without a history of atopy. Maternal stress is amenable to intervention, and these data suggest the need to consider stress reduction interventions during critical periods of child development, including pregnancy, to reduce risk of asthma and related disorders. Moreover, the demonstration of synergistic effects of stress and aeroallergen exposure points to the need for a multi-pronged intervention approach to reducing disease risk. For example, if our efforts focus only on reducing physical environmental hazards (e.g., indoor allergens), the effects of the psychosocial environment may continue to contribute to the health burden in these high-risk populations.

Authors contributions

JLP contributed to the study hypothesis, literature search, data analysis and interpretation, and drafting the manuscript. SC contributed to data interpretation and critical revision of the manuscript. JS contributed to data analysis and interpretation, and critical revision of the manuscript. JH contributed to sample analysis. TAEPM contributed to study design and critical revision of the manuscript. RJW contributed to the study concept and design, obtaining funding, study supervision, data interpretation, and critical revision of the manuscript.

Funding

This research was supported by the U.S. National Institutes of Health (NIH) grants R01ES010932, U01HL072494, R01HL080674, R01HL080674-02S1.

Conflicts of interest

We declare that we have no conflicts of interest.

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