Prenatal and Postnatal Maternal Stress and Wheeze in Urban Children

Effect of Maternal Sensitization

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***Rationale*: Critical periods for programming early wheeze risk may include pregnancy and infancy. Effects of timing remain poorly understood.**

***Objectives*: Associations among prenatal and postnatal maternal stress and children's wheeze were prospectively examined in 653 families. Effect modification by maternal sensitization was also examined.**

***Methods*: Stress was indexed by a maternal negative life events (NLEs) score (range, 0–9) ascertained during pregnancy and between 1 and 2 years postpartum. Mothers reported child wheeze every 3 months up to age 2 years. Relationships of prenatal and postnatal maternal NLEs with repeated wheeze ($\geq$2 episodes) were examined using logistic regression adjusting for covariates. Penalized splines were implemented to explore possible nonlinear associations. We also examined the interaction between prenatal stress and maternal sensitization indexed by allergen-specific IgE from maternal prenatal serum.**

***Measurements and Main Results*: Adjusted models considering prenatal or postnatal NLEs alone both showed an exposure-response relationship between higher stress and child wheeze. When considering prenatal and postnatal stress concurrently, only children of mothers with high stress in both periods were significantly more likely to wheeze (adjusted odds ratio, 3.04; 95% confidence interval, 1.67–5.53) than children of mothers reporting low stress in both periods. Associations between high prenatal stress and wheeze were significant in children born to nonsensitized mothers (any IgE $<$0.35 kU/L) but not in the sensitized group (*P* for interaction = 0.03).**

***Conclusions*: Although children have heightened sensitivity to maternal stress *in utero* and in early childhood, those with higher stress in both periods were particularly at risk for wheeze. The prenatal maternal immune milieu modified effects.**

Keywords: negative life events; stress; pregnancy; maternal sensitization; childhood wheeze

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The influence of stress on respiratory health likely starts in early development. Although critical periods for stress-related programming of early childhood wheeze might include pregnancy and infancy, the effect of timing of exposure remains poorly understood.

What This Study Adds to the Field

These findings suggest that although prenatal and postnatal maternal stress are independently associated with increased repeated wheeze in urban children, children born to mothers experiencing higher stress in both developmental periods were particularly at risk for wheeze. The maternal immune milieu assessed in pregnancy modified the association between prenatal maternal stress and childhood repeated wheeze.

Childhood wheezing illnesses account for significant morbidity and health care use (1). Recurrent wheeze may be a precedent of asthma and reduced lung function (2). An important step in identifying children at risk for costly respiratory disorders is characterizing risk factors and mechanisms that lead to and maintain early predisposition.

Although the spectrum of wheeze phenotypes is complex and mechanisms of early environmental influences are incompletely understood (3, 4), aberrant proinflammatory states are central determinants (5, 6). Glucocorticoid action and sympathovagal balance are important in regulating immune function and airway response in early development (7, 8). Thus, environmental factors, such as psychosocial stressors, that influence the programming of regulatory systems involved in these processes (i.e., hypothalamic-pituitary-adrenal [HPA] axis, autonomic nervous system, immune function) may be particularly relevant.

Evidence links psychosocial stress to wheeze, asthma, and airway hyperresponsiveness (9). Animal studies suggest effects begin prenatally. Prenatal stress increases allergen-induced airway inflammation (10, 11) and airway hyperresponsiveness (12) in mice offspring and impacts the newborn's antigen response in primates (13). Although no prospective human study has measured prenatal maternal stress directly in association with wheeze or other early asthma phenotypes in children, three have considered maternal psychologic functioning as a correlate of stress exposure. A study in China (n = 334) found that

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increased prenatal maternal nervousness predicted elevated cord blood IgE adjusting for family history, maternal age, education, and prenatal smoking (14). An Australian study (n = 5,810) linked higher prenatal anxiety to increased asthma with airway hyperesponsiveness in school-aged children adjusting for sex, prematurity, maternal age, education, atopy, prenatal smoking, and postnatal maternal anxiety (15). Reyes and colleagues (16) reported an association between a composite measure of prenatal psychologic functioning (maternal demoralization) and increased risk of wheeze in an urban New York sample adjusting for maternal (age, ethnicity, education, asthma, IgE) and child (sex, tobacco smoke exposure) factors. Postnatal stress may also play a role. For example, greater caregiver-perceived stress in infancy has been prospectively associated with repeated wheeze in children (17). Although critical periods for stress-related programming of wheeze may include pregnancy and early childhood, the influence of timing of exposure is not well understood.

Prenatal stress may influence infant respiratory disease through transplacental passage of maternal hormones and other metabolic cues and by impacting maternal–fetal immune interactions (18). Children born to allergic mothers are exposed to a unique prenatal biologic environment compared with those of nonallergic mothers (19). Thus, it is possible that prenatal stress effects may differ based on maternal sensitization.

We examined whether higher maternal stress, assessed in pregnancy and postnatally, was associated with increased repeated childhood wheeze taking into account timing of exposure. Specifically, we examined whether higher stress in early developmental periods was significantly associated with children's repeated wheeze, considering prenatal or postnatal stress alone and stress persisting over both sensitive periods. We also examined whether prenatal stress effects differed relative to maternal sensitization indexed by specific IgE to common aeroallergens assessed in pregnancy. Some of the results of these analyses were presented at the 2012 American Thoracic Society International Conference (20).

METHODS

Study Participants

Between August 2002 and September 2009, English- or Spanish-speaking women receiving prenatal care at two Boston hospitals and affiliated community health centers were recruited into the Asthma Coalition on Community, Environment, and Social Stress project, a pregnancy cohort examining the effects of perinatal stress and other environmental factors on urban childhood asthma risk (21). Among women approached in mid-to-late pregnancy (28.4 ± 7.9 wk gestation) who were eligible, 989 (78.1%) agreed to enroll. Based on screening data, there were no significant differences for race and ethnicity, education, and income between participants who enrolled and those who declined. Of those enrolled, 955 gave birth to a live-born infant and continued follow-up. This study included a subset of 653 mother–child pairs with two or more postnatal interviews followed-up to age 2 years and data on prenatal and postnatal stress. Procedures were approved by human studies committees at the Brigham and Women's Hospital and Boston Medical Center and written consent was obtained.

Negative Life Events

Prenatal and postnatal maternal stress were respectively measured within 2 weeks of enrollment and between 12 and 18 months postnatally using the Crisis in Family Systems-Revised survey, validated in English and Spanish (22, 23). The survey assesses life events experienced across 11 domains (e.g., financial, relationships, violence, other housing issues, and discrimination and prejudice). Mothers endorsed events experienced in the past 6 months and rated each as positive, negative, or neutral. Because research suggests increased vulnerability when experiencing events across multiple domains (24), the number of domains with one or more negative event was summed to create a negative life events (NLEs) domain score, with higher scores indicating greater stress. Although the survey inquires about events across 11 domains, participants in this study reported experiencing events in none to a maximum of nine domains.

Repeated Wheeze

Maternal-reported child wheeze was ascertained from birth to age 2 years through telephone and face-to-face interviews at approximately 3-month intervals. Mothers were asked, "Since we last spoke with you on (date), has your infant/child had wheezing or whistling in the chest?" Repeated wheeze was defined as greater than or equal to two episodes (3). Of the 653 children, 414 (63.4%) never wheezed; 159 (24.4%) wheezed once; and 45 (6.9%), 24 (3.7%), 9 (1.4%), and 2 (0.3%) had two, three, four, and five wheeze episodes, respectively.

Covariates

Potential confounders, pathway variables, and modifying variables were considered. Maternal age, race and ethnicity, education, atopic history (ever having clinician-diagnosed asthma, eczema, or hay fever), and prepregnancy height and weight and child's sex, season of birth, and birthweight were ascertained by questionnaire. Maternal body mass index (BMI) was calculated as weight divided by height squared (kilogram per square meter). Mothers reported smoking at baseline and in the third trimester; women were classified as prenatal smokers if smoking at either visit. Postnatal smoking was reported at each 3-month postpartum interview.

Prenatal exposure to traffic-related air pollution, specifically black carbon (BC), was estimated based on resident address (updated if participants moved) over the entire pregnancy using a previously described validated spatiotemporal land use regression model (25). Childrens' postnatal exposure from birth to 2 years was similarly estimated.

Settled dust collected within 2 weeks of enrollment from the mother's bedroom using a standardized protocol (26) was assayed for cockroach allergen (*Blatella germanica*, [*Bla g 1* and *2*]) using a monoclonal antibody-based ELISA (Indoor Biotechnologies, Charlottesville, VA). High exposure was defined as *Bla g 1* or *2* greater than 2 U/g.

A measure of neighborhood disadvantage was derived by linking enrollment addresses with aggregated data (census tract) from the 2000 US Census indexed as an average z score for percentages of residents living below poverty, the unemployed, non-US citizens, and nonwhite in the neighborhood (27). Z scores are interpreted in a relative sense; neighborhoods with the most positive scores are most disadvantaged and those at the most negative end are least disadvantaged.

Mother's serum collected in the second or third trimester was analyzed for specific IgE using CAP fluorescent enzyme immunoassay (Pharmacia [now Phadia], Uppsala, Sweden). Sensitization was defined as having a specific IgE greater than or equal to 0.35 kU/L to one or more common aeroallergens: *Dermatophagoides pteronyssinus 1*, *Bla g 1* or *2*, *Canis familiaris 1*, *Felis domesticus 1*, ragweed, rye grass, *Aspergillus fumigatus*, or *Alternaria alternata*.

Analysis

When comparing those enrolled, those included in the analyses, and those excluded, the distributions were similar across covariates (*see* Table E1 in the online supplement). Characteristics of the 653 mother–child pairs included in analyses are summarized in Table 1. Sensitization data were available on 401 pairs and the distributions were similar across covariates between subjects included in analyses with and without IgE (Table 1). Missingness on covariates was approximately 5% or less, thus the missing indicator method was used in analyses.

Spearman correlations between maternal NLEs scores and other environmental factors were low to moderate (Table 2); thus, all were included in analyses. Prenatal and postnatal BC levels were highly correlated (Spearman $r = 0.96$; $P < 0.001$); therefore, analyses

considered only prenatal BC. Multivariate logistic regression analyses first considered associations between the NLEs score and child wheeze including prenatal and postnatal NLEs in separate models (i.e., independent effects of stress in each respective period). The NLEs score was categorized *a priori* as 0, 1–2, 3–4, or greater than or equal to 5 to assess exposure-response relationships and the possibility of nonlinearity. To examine the effects of the combination of prenatal and postnatal NLEs, we next collapsed NLEs scores into low (0–2, at or below the median) and high (≥3, above the median) groups, and categorized maternal stress into four combinations: (*1*) low prenatal–low postnatal, (*2*) high prenatal–low postnatal, (*3*) low prenatal–high postnatal, and (*4*) high prenatal–high postnatal stress. This model examined whether stress in one developmental period (prenatal or postnatal) or stress persisting over both sensitive developmental periods was most significantly associated with child repeated wheeze, compared with low stress in both periods. To ensure these results were not unduly affected by the choice of NLE cutpoints, we also explored the exposure-response relationships considering NLEs as continuous using generalized additive models (GAMs) with smooth penalized spline terms (28) for the NLEs effects. We did this by fitting separate GAM models containing a smooth term for a single NLEs score for each developmental period, and a GAM model that assessed the joint effects of prenatal and postnatal NLEs using a bivariate spline (i.e., two-dimensional smooth) term.

Infant sex and season of birth were entered as standard controls. We then considered covariates linked to stress and wheeze in previous research. Maternal age, race, educational status, and self-reported atopy were considered as confounders. To further account for neighborhood-level physical or social environmental determinants that may confound the relationship between individual-level stress and child wheeze, traffic-related air pollution, household cockroach exposures, and the neighborhood disadvantage index were also controlled. Variables that may be in the pathway between prenatal maternal stress and offspring wheeze, including prepregnancy BMI, prenatal and postnatal smoking, and child's birthweight adjusting for gestational age (29), were also considered. Effect modification by maternal sensitization was examined using stratified analysis and by fitting interaction terms among those 401 mother–child pairs with IgE measurements. Most analyses were performed using SAS (version 9.1.3, SAS Institute, Inc., Cary, NC); GAMs were implemented in the mgcv package in R (version 2.13.0, The R Foundation for Statistical Computing, Vienna, Austria).

TABLE 1. ASTHMA COALITION ON COMMUNITY, ENVIRONMENT, AND SOCIAL STRESS PARTICIPANT CHARACTERISTICS

	All Participants ($n = 653$)		With IgE Data ($n = 401$)	
	n	%	n	%
Categorical variables				
Repeated wheeze until age 2 yr*				
No	573	87.8	354	88.3
Yes	80	12.3	47	11.7
Child's sex				
Female	318	48.7	207	51.6
Male	335	51.3	194	48.4
Race				
Hispanic	356	54.5	248	61.9
Black	189	28.9	100	24.9
White/other	97	14.9	53	13.2
Missing	11	1.7	0	0
Season of birth				
Winter	172	26.3	112	27.9
Spring	148	22.7	89	22.2
Summer	141	21.6	82	20.5
Fall	192	29.4	118	29.4
Maternal education				
>12 yr	214	32.8	118	29.4
≤12 yr	404	61.9	270	67.3
Missing	35	5.4	13	3.2
Maternal atopy†				
No	391	59.9	245	61.1
Yes	228	34.9	148	36.9
Missing	34	5.2	8	2
Maternal smoking				
Never smoked	522	79.9	333	83
Smoked prenatally, but not postnatally	32	4.9	21	5.2
Did not smoke prenatally, but smoked postnatally	36	5.5	14	3.5
Smoked both prenatally and postnatally	63	9.7	33	8.2
Continuous variables				
Prenatal negative life events (range 0–9; median, IQR)‡	2	1 to 4	2	1 to 4
Postnatal negative life events (range 0–9; median, IQR)‡	2	1 to 3	2	1 to 3
Maternal age at enrollment, yr (mean, SD)	27	5.9	27.4	6.10
Maternal prepregnancy body mass index, kg/m^2 (mean, SD)	28.8	6.3	28.2	5.89
Gestational age at birth, wk (mean, SD)	39.1	3	39.1	1.84
Birthweight percentile adjusting for gestational age (mean, SD)	43.8	31.2	41.1	29.6
Neighborhood disadvantage, *z* score (median, IQR)	0.25	−0.50 to 0.54	0.25	−0.43 to 0.54
Prenatal black carbon level, μg/m^3 (median, IQR)	0.38	0.30 to 0.51	0.39	0.31 to 0.50
Bla g 1, U/g (median, IQR)	0.20	0.20 to 0.40	0.20	0.2 to 0.4
Bla g 2, U/g (median, IQR)	0.50	0.50 to 0.85	0.50	0.5 to 0.7

Definition of abbreviations: *Bla g* = *Blatella germanica*; IQR = interquartile range.

* Maternal reported wheeze (≥2 episodes).

† Ever self-reported doctor-diagnosed asthma, eczema, or hay fever.

‡ Assessed using Crisis in Family Systems-Revised survey; multiitem survey summarized into a continuous score.

TABLE 2. SPEARMAN CORRELATIONS BETWEEN PRENATAL AND POSTNATAL STRESS AND PHYSICAL ENVIRONMENTAL EXPOSURES

	Prenatal NLEs		Postnatal NLEs		Prenatal BC Level		Prenatal Household *Bla g 1*		Prenatal Household *Bla g 2*	
	r	*P*	*R*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Postnatal NLEs	0.59	<0.001	—	—	—	—	—	—	—	—
Prenatal BC level	0.20	<0.001	0.21	<0.001	—	—	—	—	—	—
Prenatal household *Bla g 1*	0.08	0.10	0.06	0.21	0.18	<0.001	—	—	—	—
Prenatal household *Bla g 2*	0.03	0.46	0.05	0.26	0.15	<0.001	0.80	<0.001	—	—
Neighborhood disadvantage, *z* score	0.13	<0.001	0.18	<0.001	0.57	<0.001	0.20	<0.001	0.17	<0.001

Definition of abbreviations: BC = black carbon; *Bla g* = *Blatella germanica*; NLE = negative life events.

RESULTS

Mothers were primarily ethnic minority (55% Hispanic, 29% African American), low socioeconomic status (62% having ⩽12 yr of education), and nonsmokers during pregnancy (80%); 80 (12%) children had repeated wheeze. The prevalence of stress experienced across the stress domains based on wheeze status is shown in Table E2.

Independent Relationships of Prenatal and Postnatal Maternal NLEs with Repeated Wheeze

Table 3 presents the exposure-response relationship across NLEs categories in relation to wheeze, considering prenatal and postnatal NLEs in separate models. In models adjusted for child sex and season of birth (Model 1), children born to mothers in the highest-exposure group compared with those born to women with lowest stress had approximately threefold to fourfold increased odds of repeated wheeze, with similar effects for prenatal and postnatal stress. Effects remained significant in fully adjusted models (Model 3). Further inclusion of maternal BMI, smoking, and birthweight did not substantively alter these findings (data not shown). Penalized spline regressions confirmed a linear exposure-response relationship (Figure 1).

Combined Prenatal and Postnatal Maternal Stress and Repeated Wheeze

Figure 2 presents the results from fully adjusted models comparing those reporting high–high, low–high, and high–low prenatal–postnatal stress combinations with those reporting low stress in both periods. Children born to mothers with high stress in both pregnancy and the postpartum period were significantly more likely to have repeated wheeze (adjusted odds ratio [OR], 3.04; 95% confidence interval [CI], 1.67–5.53) compared with children of mothers reporting low stress in both periods. This finding was further confirmed by fitting bivariate penalized splines showing the joint effects of prenatal and postnatal NLEs as continuous indicators (*see* Figure E1).

The multivariable logistic regression models also showed that boys were more likely to have repeated wheeze compared with girls (adjusted OR, 2.28; 95% CI, 1.34–3.88) and maternal atopy was associated with increased repeated wheeze (adjusted OR, 1.58; 95% CI, 0.95–2.64), although the latter was borderline insignificant.

Interaction between Maternal Sensitization and Prenatal Stress

Figure 3 shows the relationship between prenatal NLEs and repeated wheeze stratified by maternal sensitization indexed by any specific IgE level greater than or equal to 0.35 kU/L measured during pregnancy. We observed a significant positive association between the higher NLEs score (⩾3) relative to lower stress (NLEs 0–2) and repeated wheeze in children born to mothers without a positive specific IgE level (adjusted OR, 2.35; 95% CI, 1.04–5.29) but not in the sensitized group (adjusted OR, 0.27; 95% CI, 0.07–1.08) (*P* for interaction = 0.03).

TABLE 3. MULTIVARIABLE LOGISTIC REGRESSION MODELS EXAMINING MATERNAL NLES IN RELATION TO REPEATED WHEEZE IN URBAN CHILDREN AT AGE 2 YEARS

						Multivariable-adjusted Models*								
			Univariate Model			Model 1			Model 2			Model 3		
NLEs Domain Score (*range 0–9*)	n	No. with Repeated Wheeze (%)	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
						Prenatal NLEs Model								
0	117	6 (5.1%)	Ref	—	—	Ref	—	—	Ref	—	—	Ref	—	—
1–2	261	25 (9.5%)	1.96	0.78	4.91	2.04	0.81	5.14	1.95	0.77	4.97	1.95	0.76	5.00
3–4	171	30 (17.5%)	3.93	1.58	9.78	4.06	1.62	10.2	3.77	1.48	9.63	3.55	1.38	9.15
⩾5	104	19 (18.3%)	4.13	1.58	10.8	4.34	1.64	11.4	4.03	1.50	10.8	3.79	1.39	10.3
						Postnatal NLEs Model								
0	127	10 (7.9%)	Ref	—	—	Ref	—	—	Ref	—	—	Ref	—	—
1–2	274	23 (8.4%)	1.07	0.49	2.33	1.07	0.49	2.34	1.00	0.45	2.19	0.96	0.43	2.15
3–4	159	24 (15.1%)	2.08	0.96	4.53	2.18	0.97	4.63	1.99	0.90	4.41	1.88	0.83	4.26
⩾5	93	23 (28.8%)	3.85	1.73	8.55	3.93	1.75	8.82	3.66	1.60	8.35	3.35	1.42	7.86

Definition of abbreviations: CI = confidence interval; NLE = negative life events; OR = odds ratio.

Model 1 included standard control variables (child's sex, season of birth).

Model 2 additionally included demographic variables (race/ethnicity, education, and self-reported maternal history of atopy).

Model 3 additionally included other physical and social environmental exposures (prenatal traffic-related air pollution [black carbon], household cockroach allergen, neighborhood disadvantage index).

*Multivariable-adjusted logistic regressions (Models 1–3) predicting repeated wheeze (dependent variable).

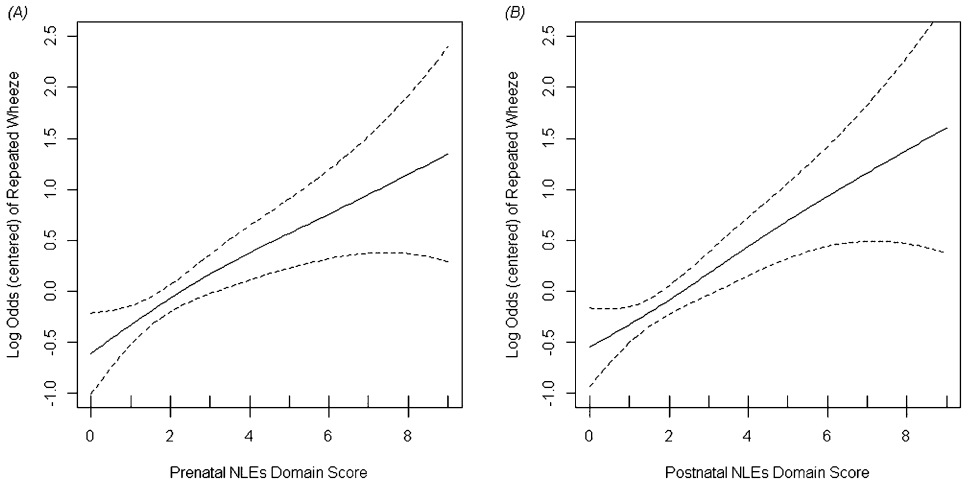

Figure 1. Exposure-response relationships between maternal negative life events (NLEs) and children's repeated wheeze. Penalized spline curves demonstrating the relationship of (*A*) prenatal maternal NLEs and (*B*) postnatal maternal NLEs in separate models with children's repeated wheeze by age 2 years are shown. *Solid line* depicts the penalized spline curve; *dotted lines* indicate the 95% confidence bounds. Models were adjusted for child's sex; season of birth; maternal race; maternal education; maternal atopy; prenatal traffic-related air pollution (black carbon); household cockroach allergen; and the neighborhood disadvantage index.

DISCUSSION

This study adds to the literature in three important ways. To our knowledge, these are the first prospective human data to show an exposure-response relationship between greater prenatal and postnatal maternal stress, when considered independently, and increased odds of early childhood repeated wheeze. Moreover, although children had heightened sensitivity to maternal stress *in utero* and in early childhood, those with higher maternal stress in both developmental periods were most likely to have recurrent wheeze. Also, effects of prenatal stress were modified based on whether mothers were sensitized to aeroallergens. Notably, observed effects remained significant when adjusting for a number of important confounders and pathway variables.

Our data indicate that cumulative exposure to greater maternal stress in the prenatal and early postnatal period was more significantly associated with repeated wheeze rather than suggesting the import of one developmental period over the other. This is consistent with other evidence suggesting that prenatal stress and psychologic correlates in mothers act in concert with postnatal stress-related factors (e.g., disrupted caregiver–child interactions) to further shape or program offspring regulatory systems that may contribute to wheeze expression (9, 30). Prenatal stress may disrupt maternal physiology (e.g., HPA axis, sympathetic-adrenal-medullary system, immunomodulation), which then may potentiate the developing fetal immune system (e.g., up-regulating maternal and fetoplacental Th2 cytokine or IgE production) (9). We have previously demonstrated that prenatal stress was associated with disrupted maternal–fetal HPA axis functioning (31, 32) and elevated cord blood IgE (33). Stress in pregnancy may also influence fetal programming of brain neurotransmitter systems, autonomic nervous system functioning, and the HPA axis, which alters the child's neural regulation of immune function. Moreover, the infant HPA system and autonomic response continue to show developmental changes postnatally (plasticity) (34, 35). Maternal functioning and caregiving during early development influences the emergence of self-regulation abilities, with sensitive caregiving associated with more optimal functioning of the child's stress response (36). Postnatally, increased maternal stress has been associated with impaired parenting behaviors and poor child stress regulation (35, 37). Perinatal maternal–child interactions may disrupt infant emotion regulation and neuroimmune development, setting the stage for altered immune and airway reactivity. That is, offspring of mothers who have stress-related biobehavioral sequelae may inherit biologic vulnerability to disrupted stress regulatory systems altering their reactivity to postnatal challenges that then further contributes to wheeze risk. This may explain the more significant effect among children born to mothers experiencing higher stress across both developmental periods.

In addition, psychosocial stress might alter mothers' health behaviors perinatally, such as smoking (38), which may contribute to early wheeze. Maternal stress may contribute to mothers' obesity (39) or poor fetal growth (40) (i.e., other factors linked to child wheeze) (41, 42). However, adjusting for maternal BMI, birthweight, and maternal smoking did not affect our findings.

Because of potential covariance across exposures and evidence that social stress and other environmental toxins (e.g., pollutants, household allergens) may influence common physiologic pathways (e.g., oxidative stress, proinflammatory immune pathways,

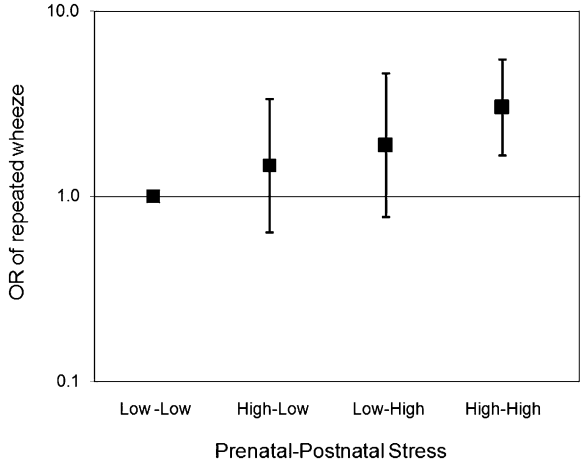

Figure 2. Relationships of combined levels of prenatal and postnatal maternal stress with children's repeated wheeze. Odds ratios (ORs) and 95% confidence intervals for repeated wheeze comparing each combination of prenatal–postnatal stress. High stress is indicated by a negative life events score greater than or equal to 3, and low stress is indicated by a negative life events score of 0–2. Logistic regression models were adjusted for child's sex; season of birth; maternal race; maternal education; maternal prenatal and postnatal smoking; maternal atopy; prenatal traffic-related air pollution (black carbon); household cockroach allergen; and the neighborhood disadvantage index.

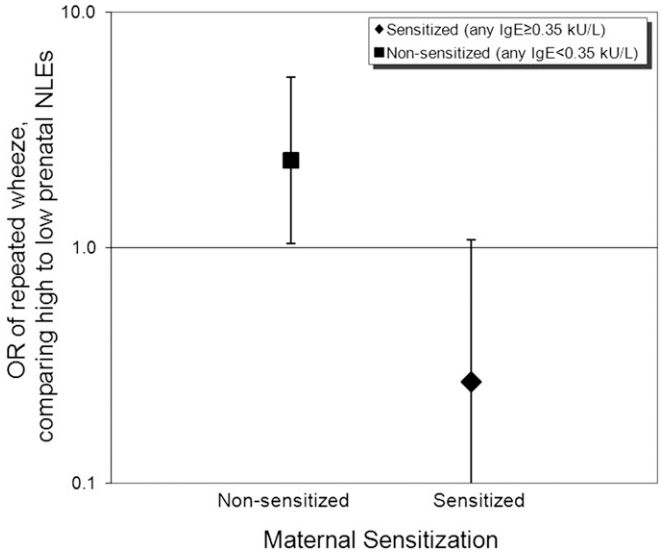

Figure 3. Associations between prenatal maternal negative life events (NLEs) and children's repeated wheeze, stratified by maternal sensitization. Odds ratios (ORs) and 95% confidence intervals for repeated wheeze comparing high prenatal NLEs (⩾3) with low prenatal NLEs (0–2) groups, stratified by maternal sensitization (defined by any IgE level ⩾0.35 kU/L). Models were adjusted for child's sex; season of birth; maternal race; maternal education; prenatal traffic-related air pollution (black carbon); household cockroach allergen; and the neighborhood disadvantage index.

autonomic disruption) contributing to wheeze, we also considered these as potential confounders. Being exposed to higher stress (more NLEs) was correlated with living in neighborhoods with greater disadvantage and higher traffic-related air pollution exposure in this urban sample, but not with cockroach exposure. Even when adjusting for these covariates, effects of stress remained.

In stratified analyses, the association between prenatal maternal stress and child's repeated wheeze was significant only among children with nonsensitized mothers. This finding may provide insight into potential underlying mechanisms. Children of sensitized mothers are already exposed to a unique biologic environment during pregnancy, which may be polarizing the child's developing immune system toward aberrant innate and acquired immune responses that may contribute to wheeze (19). Stress may also induce a greater shift toward Th2-mediated humoral immunity (43). Thus, even though the pathway through which stress is operating in children of sensitized mothers is more likely to involve an enhanced Th2 shift and increased IgE production, we may not be able to measure stress effects above what is being driven by the maternal immune milieu in sensitized women. Alternatively, finding a stronger effect among children of women who are not sensitized may indicate that stress has a greater influence on nonatopic wheeze and that pathways outside the immune framework may be operating (e.g., oxidative stress, autonomic imbalance). Future research examining the posited pathways more definitively is needed.

Strengths of this study include the prospective design; the focus on the prenatal and early postnatal exposure periods, which are critical to early childhood wheeze; the reasonably large lower socioeconomic status and ethnically mixed inner-city cohort; available data on many important confounders and potential pathway variables; and the use of biomarkers to index maternal sensitization in pregnancy. This is the first study with repeated assessments during different developmental periods using a validated standardized measure of major life events developed specifically to comprehensively measure event domains likely to be experienced by lower-income, ethnically mixed groups. Although the prenatal NLEs assessment was before postnatal wheeze, the temporal relationship between postnatal NLEs and a particular wheezing episode may not be as clear. Given that the life event questionnaire asks about events occurring in the past 6 months, it was not possible to determine when a given event occurred relative to each wheeze episode. Greater precision on this temporal relationship would be needed if the purpose of our study was to investigate whether NLEs were associated with one particular wheeze episode (i.e., more acute effects of stress on subsequent wheezing). In this study we are asking a different question, which is whether chronic or cumulative stress during a developmentally sensitive period is related to higher odds of repeated wheeze, hypothesizing that chronic stress influences underlying pathophysiology that then contributes to wheeze (e.g, greater maternal stress leading to more difficult parenting behaviors that influence emotion regulation processes in children with consequences for immunomodulation).

We also acknowledge limitations. Although maternal-reported repeated wheeze is a reasonable surrogate for those who may be more likely to develop asthma or have compromised lung function (17), it is important to examine the relationship between maternal stress and more definitive outcomes as these children grow (i.e., physician-diagnosed asthma, lung function) and see if relationships still hold. Finally, it is possible that a mother experiencing higher stress might tend to underreport her child's symptoms if overwhelmed and less aware of her child. If this were the case, observed effect estimates would underestimate the true relationship. Conversely, it is possible that a woman with higher stress and consequent psychologic dysfunction (e.g., anxiety) might overreport symptoms if she is more attentive to her child's physical states (44). It is therefore reassuring that variables related to repeated wheeze in other studies were associated in the expected direction in our data (e.g., male sex, maternal atopy) (45, 46).

Future studies should more definitively explore biologic mechanisms that may mediate effects of perinatal stress on child wheeze. For example, further research may investigate whether disruption of the maternal HPA axis, autonomic functioning or immune profiles prenatally, or stress-related alterations in immune or neuroimmune profiles in children in early life mediate associations between stress and wheeze. Studies should examine the influence of prenatal and early life stress on the expression of neuropeptides and their role in allergic sensitization or airway inflammation and response in early development. It is important to consider these systems simultaneously in research designs and explore possible interactive influences on respiratory outcomes.

In summary, early childhood wheeze is a complex problem given its heterogeneous nature with different pathogenic mechanisms that remain to be fully elucidated. A better understanding of risk factors in early development and insight into vulnerable periods of exposure will help inform prevention and intervention strategies that may preclude persistence of symptoms or lung function deficits in later childhood. Psychologic stress should be considered an important programming factor for wheezing respiratory illnesses and lung function development in early life. Our findings suggest that although children may have heightened sensitivity to maternal stress *in utero* and in early childhood, stress occurring in both developmental periods may be acting cumulatively to enhance the likelihood of repeated wheeze

in urban children. These findings may have implications for designing prenatal and postnatal psychosocial or stress-reduction interventions to reduce respiratory disease in children. For example, interventions at the individual level may be more effective if initiated during pregnancy and then extended through early child development. On a broader scale, policy-level interventions that improve socioeconomic circumstances with consequent decreased exposure to stress across a multitude of life domains in pregnant women and young families also have potential to reduce adverse respiratory outcomes in early life.

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