



Prenatal and postnatal stress and wheeze in Mexican children Sex-specific differences

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ABSTRACT

Background: Increasing evidence links early-life exposure to psychosocial stress with adverse childhood respiratory outcomes. The influence of exposure timing has not been completely elucidated.

Objective: To examine the association between prenatal and postnatal maternal stress and wheeze in 417 children enrolled in a prospective birth cohort in Mexico City.

Methods: Maternal negative life event (NLE) scores were ascertained in the second or third trimester of pregnancy and at the 48-month postnatal visit. Children's respiratory outcomes, caregiver report of ever wheeze, and wheeze in the past 12 months were obtained from the International Study of Asthma and Allergies in Childhood survey administered at 48 months. Associations between prenatal and postnatal NLE scores and wheeze were analyzed using a modified Poisson regression approach adjusting for covariates.

Results: In separate models, higher maternal psychosocial stress during pregnancy (relative risk [RR], 1.12; 95% CI, 1.00–1.26) and postnatally (RR, 1.21; 95% CI, 1.08–1.35) were associated with increased risk of wheeze in the past 12 months with an evident exposure-response relationship. There was a significant interaction between postnatal stress and sex in relation to current wheeze. In a sex-stratified model, the association between postnatal stress and risk of wheeze in the past 12 months was stronger in girls (RR, 1.35; 95% CI, 1.13–1.61) than in boys (RR, 1.11; 95% CI, 0.97–1.27) (P for interaction = .04).

Conclusion: Prenatal and postnatal stress in mothers was associated with wheeze in preschool-aged children, and the effect of postnatal stress was stronger in girls. Understanding the temporal- and sex-specific effects of stress may better inform prevention strategies.

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Introduction

Childhood wheezing is an important contributor to morbidity and health care use in Latin America.^{1,2} The study of environmental risk factors for the development of childhood wheezing and asthma

in Latin America is an increasing area of interest.^{3,4} Identifying critical exposure windows for prevalent risk factors can provide insight into the mechanisms through which these exposures lead to respiratory disease in childhood and ultimately inform the timing of public health interventions.

Although asthma and childhood wheeze are heterogeneous conditions, inflammation is a central pathologic feature.⁵ Psychosocial stress leads to the activation of systems involved in the regulation of inflammatory processes (ie, hypothalamic-pituitary-adrenocortical [HPA] axis, autonomic nervous system) and alterations in innate and adaptive immune responses.⁶ Hormones and neuropeptides released after the activation of stress response systems are involved in inflammatory⁷ and airway responses,⁸ so the study of psychosocial stressors as environmental risk factors for respiratory disease might be particularly relevant.

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An increasing number of prospective epidemiologic studies have found associations between increased prenatal maternal stress or stress correlates (eg, maternal anxiety) and early asthma phenotypes.^{9–13} In Boston, Massachusetts, children whose mothers reported higher numbers of negative life events (NLEs) during both the prenatal and early postnatal periods were 3 times more likely to have recurrent wheeze by 2 years of age when compared with mothers with low stress during both periods.⁹ An inner-city cohort study in New York City reported associations between prenatal maternal demoralization, a broad measure of maternal psychological functioning, and increased risk of transient and persistent wheeze in children.¹² Another multisite US inner-city cohort study reported associations between prenatal perceived stress and wheeze in 1-year-old infants.¹⁴ Maternal pregnancy-specific hassles were associated with a composite measure of respiratory illnesses during infancy.¹⁵ In a study in the Netherlands, maternal distress assessed using the Brief Symptom Inventory during pregnancy was associated with increased odds of wheezing in children followed up to 6 years of age; maternal distress examined postnatally was not associated with child wheeze.¹³ A recent study linked higher intrafamilial adverse childhood experiences with increased odds of asthma diagnosis in children in the National Survey of Children's Health.¹⁶ Overlapping evidence suggests that exposure to stress may be an important contributing factor to respiratory morbidity in Latin America because of the high prevalence of intimate partner violence,¹⁷ local violence,¹⁸ perinatal depression,¹⁹ and lack of data on stress-reduction strategies.⁴ Despite increasing evidence in this area, similar studies in Latin American countries are lacking.

Increasing evidence from animal models indicates that the timing of stress exposure (prenatal vs postnatal) is important and that critical windows of vulnerability may differ by sex of the offspring for a number of developmental outcomes.^{20,21} For example, one study found that male offspring of dams exposed to stress early in the prenatal period revealed maladaptive behavioral stress responsivity in a series of tests.²² In another study, females had increased anxiety-related behavior after exposure to prenatal stress, whereas males had decreased memory for novel objects and novel spatial locations.²³ Although mechanisms have not been fully elucidated, studies suggest that sex-specific effects can arise through differential placental effects and fetal sex hormones.^{24,25} For example, one recent study looking at prenatal socioeconomic adversity and epigenetic changes in placenta, found sex differences in methylation of 11 β -hydroxysteroid dehydrogenase type 2, the enzyme responsible for the conversion of cortisol into inactive cortisone, suggesting that prenatal environmental cues may affect fetal programming to respond to stress postnatally in a sex-specific manner.²⁶

Epidemiologic studies considering sex-specific effects of perinatal stress on childhood respiratory disorders are sparse and have yielded mixed results. In a large study using electronic records in Sweden, boys born to women who experienced bereavement, defined as the loss of a close family member during the second trimester, were found to have higher risk of asthma.²⁷ Another small study looking at subjective distress experienced during pregnancy due to the 1998 Quebec ice storm found that only girls had higher odds of lifetime wheezing, physician diagnosis of asthma, and asthma medication use by 12 years of age.²⁸ However, these studies were limited by their inability to examine prenatal and postnatal stress concurrently and adjust for other important confounders.

We examined whether higher maternal stress, assessed in pregnancy and postnatally, was associated with increased likelihood of wheeze in children enrolled in a Mexico City pregnancy cohort followed up to 4 years of age. Specifically, we first examined the effects of prenatal and postnatal stress in separate

models. Next, we mutually adjusted for prenatal and postnatal stress. Finally, we examined joint effects of exposure to increased stress in both pregnancy and at 4 years of age. We also examined whether temporal effects of perinatal stress differed relative to the child's sex.

Methods

Study Population

The Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) project recruited pregnant women who were receiving health insurance and prenatal care through the Mexican Social Security System (Instituto Mexicano del Seguro Social [IMSS]) between July 2007 and February 2011. The IMSS provides health care to affiliated private sector employees, most of whom are low- to middle-income workers, and their families. Women were eligible to participate in the study if they met the following criteria: less than 20 weeks gestation, greater than 18 years of age, planned to stay in Mexico City for the next 3 years, had access to a telephone, had no medical history of heart or kidney disease, did not consume alcohol daily, and did not use any steroid or antiepilepsy medications. After birth, 815 mother-child dyads had at least 1 follow-up visit, and 417 had all the necessary covariates for these analyses. There were no significant differences between participants who had all necessary covariates when compared with those who did not by mother's age at delivery, maternal asthma, child's sex, or prenatal ETS exposure (eTable 1). Procedures were approved by institutional review boards at the Harvard School of Public Health, Icahn School of Medicine at Mount Sinai, and the Mexican National Institute of Public Health. Women provided written informed consent.

Measures of Psychosocial Stress

The Crisis in Family Systems—Revised (CRISYS) survey, which has been validated in Spanish,²⁹ was administered by a trained psychologist during the second or third trimester of pregnancy and during the 48-month visit. The CRISYS questionnaire assesses life events across 11 domains: financial, legal, career, relationship, home safety, neighborhood safety, medical issues (self and others), home, prejudice, and authority. Participants rated life events occurring in the past 6 months as positive, negative, or neutral. Previous research has found increased vulnerability across multiple domains; therefore, domains with 1 or more NLE were summed into an NLE domain score, with higher scores indicating greater stress.^{9,30}

Outcome Measures

The validated Spanish version of the International Study of Asthma and Allergies in Childhood questionnaire was administered starting at the 48-month visit. Ever wheeze was determined based on caregiver response to the question, "Has your child ever had wheezing or whistling in the chest at any time in the past?" and current wheeze was defined based on response to the question, "Has your child had wheezing or whistling of the chest in the past 12 months?"

Covariates

Child's sex, mother's age at delivery, and mother's report of ever having asthma were collected through questionnaires. Exposure to environmental tobacco smoke was ascertained during pregnancy (during the second or third trimester) and during the 48-month visit through report of any smoker in the home during these periods. Exposure to particulate matter 2.5 μ m and less in diameter (PM_{2.5}) was estimated for each woman during pregnancy and

during the first postnatal year using a novel spatiotemporal model incorporating Moderate Resolution Imaging Spectroradiometer satellite-derived aerosol optical depth measurements at a 1×1 -km spatial resolution.³¹ These remote sensing data are calibrated with municipal ground-level monitors of PM_{2.5}, land use, and meteorologic data to yield estimates of daily residential PM_{2.5} levels for each study participant. Daily PM_{2.5} exposure was averaged for the entire gestational period (estimated date of conception to delivery date) and during the first postpartum year.

Statistical Analysis

Prenatal and postnatal NLE scores were analyzed in separate models. Associations were explored by modeling NLE scores as continuous measures using generalized additive models. To obtain risk ratios for our prospectively measured dichotomous outcomes, data were analyzed using a modified Poisson regression approach.³² Models were adjusted for child's sex, report of any smoker in the home during pregnancy, report of any smoker in the home at 48 months, mother's age at delivery, maternal ever asthma, and mean PM_{2.5} exposure during pregnancy and at 1 year postnatally. Socio-economic status was also examined as a potential confounder but was not independently associated with the outcome, did not significantly affect the estimate, and was therefore excluded from final analyses. Potential sex differences were examined by including an interaction term for sex by NLE score in each model and by stratifying by sex. Interactions between prenatal and postnatal stress were also explored in the entire cohort and in models stratified by sex.

Results

Table 1 gives the distribution of covariates for the entire sample and stratified by child sex. The range of prenatal and postnatal NLE domain scores was 0 to 11 and 0 to 9, respectively; 25% of children had ever wheeze, and 12% had current wheeze. Sample characteristics did not significantly differ by sex with the exception of wheeze outcomes, which were both more frequent among boys ($P < .05$; Table 1). As seen in Table 2, prenatal and postnatal NLE scores (Spearman $\rho = 0.45$, $P < .001$) and mean PM_{2.5} concentrations during pregnancy and 1 year postnatally (Spearman $\rho = 0.31$, $P < .001$) were moderately correlated. The NLE domain scores and PM_{2.5} concentrations were not significantly correlated.

In fully adjusted models, there was a significant association between each unit increase in prenatal stress and risk of ever wheeze (relative risk [RR], 1.08; 95% CI, 1.00–1.16) and wheeze in the past 12 months (RR, 1.12; 95% CI, 1.00–1.26). Increasing postnatal stress was also significantly associated with an increase in risk of ever wheeze (RR, 1.12; 95% CI, 1.04–1.21) and wheeze in the past

Table 2

Spearman correlations between prenatal and postnatal stress and ambient air pollution concentrations

Variable	Prenatal NLE score		Postnatal NLE score		Prenatal PM _{2.5} concentration	
	ρ	P value	ρ	P value	ρ	P value
Postnatal NLE score	0.45	<.001				
Prenatal PM _{2.5} concentration	–0.01	.77	–0.01	.77		
Postnatal year 1 PM _{2.5} concentration	0.02	.64	0.06	0.18	0.31	<.001

Abbreviations: NLE, negative life event; PM_{2.5}, particulate matter 2.5 μ m and less in diameter.

12 months (RR, 1.21; 95% CI, 1.08–1.35). Figures 1 and 2 depict the association between NLE domain scores for each period and wheeze outcomes for the overall sample and stratified by child sex. In the overall sample, the most parsimonious fit from the smooth generalized additive model function was a linear association of increasing risk with number of reported NLE domains for both ever and current wheeze outcomes. In sex-stratified models, boys seemed more affected by increasing prenatal stress, whereas girls seemed more affected by higher postnatal stress in relation to ever wheeze (Fig 1). In Figure 2, associations seemed more similar in boys and girls, although the associations between increasing postnatal stress and current wheeze was steeper among girls compared with boys. Table 3 gives the results for interaction models between sex and prenatal and postnatal stress. The interaction term was only significant for sex $\times$ postnatal stress in relation to current wheeze. Furthermore, after stratifying by sex, postnatal stress was associated with increased risk of current wheeze only in girls ($P = .04$). We also explored a potential interaction between higher stress in both the prenatal and postnatal periods in relation to wheeze outcomes. In adjusted models, interaction terms were not significant in our overall sample or in the sex-stratified models ($P > .20$ for all).

Discussion

This is the first study, to our knowledge, to prospectively examine associations between prenatal and postnatal stress and wheeze outcomes in an urban pediatric population in Mexico. In general, we saw an exposure-response relationship between stress in these early-life periods and wheeze outcomes in these Mexican children. Our findings of an exposure-response relationship between maternal NLEs in the perinatal period and early childhood asthma phenotypes are consistent with another US study.⁹ In addition, there was a suggestion that prenatal stress was more strongly associated with wheeze outcomes in boys compared with

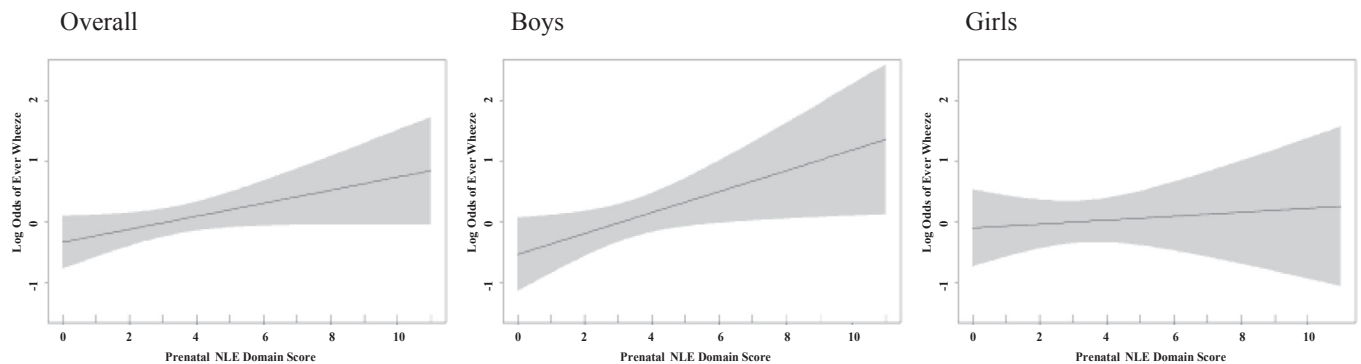
Table 1
Sample characteristics

Characteristic	Overall (N = 417)	Boys (n = 211)	Girls (n = 206)	P value ^a
Maternal asthma, No. (%)	7 (1.7)	6 (2.8)	1 (0.5)	.12
Prenatal ETS exposure, No. (%)	160 (38.4)	78 (37)	82 (39.8)	.55
Postnatal ETS exposure, No. (%)	53 (13)	24 (11.4)	29 (14.1)	.41
Mother's age at delivery, median (IQR)	28 (24–32)	28 (24–32)	27 (23–31)	.30
Prenatal PM _{2.5} , μ g/m ³ , median (IQR)	23 (21–24)	23 (21–24)	23 (20–24)	.23
PM _{2.5} at postnatal year 1, median (IQR)	23 (20–24)	23 (20–24)	23 (20–24)	.53
Prenatal NLE domain score, median (range)	3 (0–11)	3 (0–11)	3 (0–10)	.93
Postnatal NLE domain score, median (range)	3 (0–9)	3 (0–8)	3 (0–9)	.51
Ever wheeze, No. (%)	107 (26)	63 (29.9)	44 (21.4)	.05
Current wheeze, No. (%)	55 (13)	36 (17.1)	19 (9.2)	.02

Abbreviations: ETS, environmental tobacco smoke; IQR, interquartile range; NLE, negative life event; PM_{2.5}, particulate matter 2.5 μ m and less in diameter.

^aDifferences in categorical variables tested using Fisher's Exact test and Pearson Chi-Square test. Differences in continuous variables tested using Mann Whitney U test.

Prenatal Stress and Ever Wheeze



Postnatal Stress and Ever Wheeze

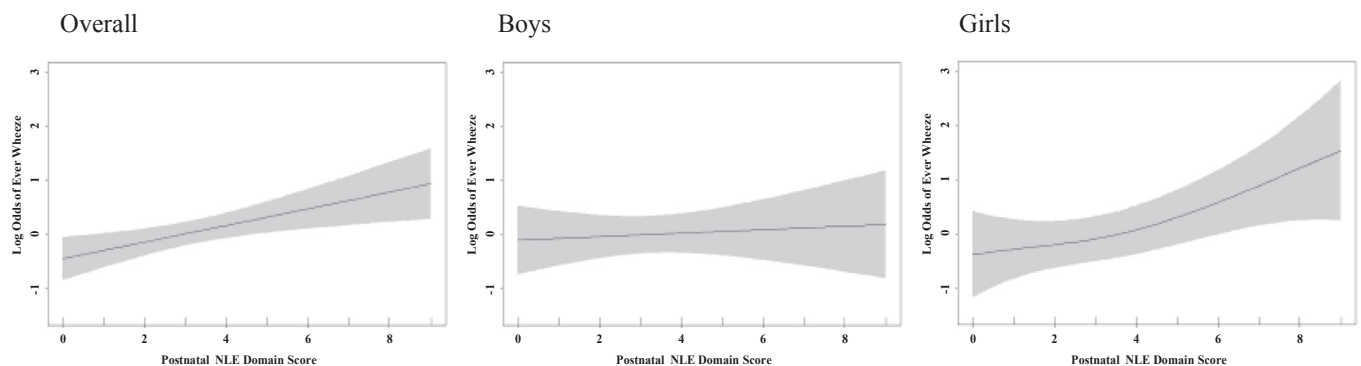


Figure 1. Exposure-response relationship between prenatal and postnatal negative life event (NLE) domain scores and ever wheeze overall, in boys, and in girls. For overall results, generalized additive models were adjusted for child's sex, maternal asthma, maternal age at delivery, mean particulate matter 2.5 μm and less in diameter ($\text{PM}_{2.5}$) during pregnancy, mean $\text{PM}_{2.5}$ at postnatal year 1, and report of a smoker in the home prenatally and at 48 months. Stratified models adjusted for maternal age at delivery, mean $\text{PM}_{2.5}$ during pregnancy, mean $\text{PM}_{2.5}$ at postnatal year 1, and report of a smoker in the home prenatally and at 48 months.

girls, whereas higher postnatal stress had a stronger association among girls. Indeed, we found a significant interaction between increased postnatal stress and child sex in relation to current wheeze with the association of stress being greater in girls. The observed associations remained significant after adjustment for a number of important confounders.

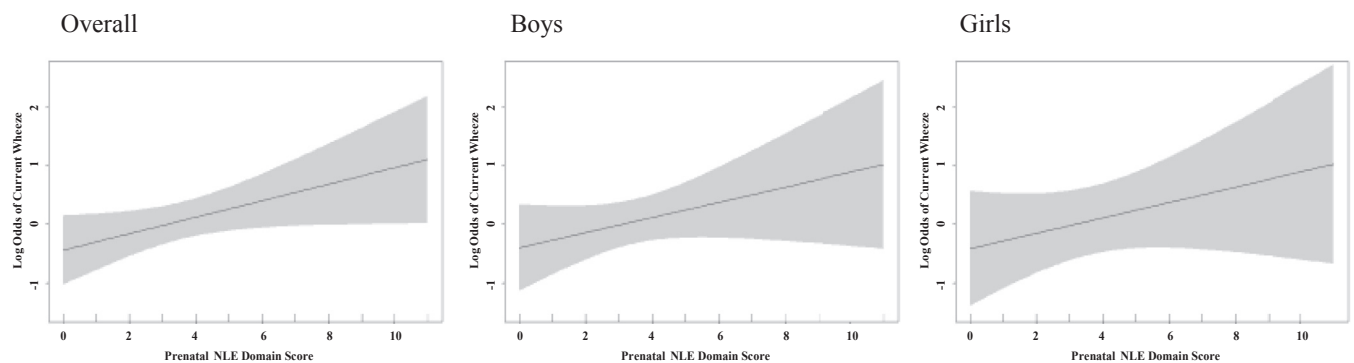
Stress during pregnancy may disrupt maternal systems, such as the HPA axis, the sympathetic-adrenal-medullary system, and immunomodulation. This disruption may lead to a potentiation of the fetal immune system through the up-regulation of maternal and fetoplacental cytokine or IgE production.^{33,34} We have previously found that prenatal stress is associated with disruption in maternal-fetal HPA-axis functioning indexed by altered cortisol production³⁵ and subsequently linked stress-related alterations in cortisol production during pregnancy with higher odds of repeated wheeze during infancy.³⁶ Prenatal stress may also influence autonomic nervous system functioning, fetal programming of brain neurotransmitter systems, and the HPA axis, which alters the child's neural regulation of immune function.^{37,38}

Children remain vulnerable to stress postnatally because the stress response systems remain highly reactive and labile in response to environmental stressors.^{39,40} For example, exposure to maternal stress during infancy and childhood has been associated with altered HPA axis functioning in children.⁴¹ There is evidence from animal models that impaired glucocorticoid function resulting from stress is associated with corticosteroid insensitivity.⁴² In a murine model, mice exposed to repeat social stress postnatally had prolonged airway inflammation after allergen challenge, activation

of both innate and adaptive immune systems, and diminished endogenous corticosteroid response.⁴³ In addition, psychosocial stress might alter mothers' health behaviors perinatally and may contribute to other factors linked to childhood wheeze, such as maternal smoking.⁴⁴ Notably, adjustment for any smoking in the home, prenatally or postnatally, did not change our findings.

In our study, the association between postnatal maternal stress and current wheeze was higher in girls than in boys, whereas there was a suggestion that boys were more vulnerable prenatally in association with ever wheeze. These findings are consistent with research indicating that the vulnerable window in which stress has the greatest influence may differ based on offspring sex and the outcome being considered. Even though these mechanisms have not been fully elucidated, differential effects of prenatal stress on developmental outcomes may be due to sex-specific placental responsiveness to prenatal maternal stress and fetal sex hormones.^{22,45} Male fetuses may be more sensitive to stress in utero because of reduced activity and/or sensitivity of placental 11 β -hydroxysteroid dehydrogenase type 2, leading to increased fetal glucocorticoid exposure, differential DNA methylation in the placenta,²⁶ or enhanced vulnerability to stress-induced oxidation in utero.⁴⁶ The interactions between sex hormones and immune-inflammatory pathways may cause females to be more vulnerable to the effects of prenatal stress on certain inflammatory disorders.²⁵ Conversely, females may also be relatively protected from the effects of prenatal stress due to sex-specific differences in the association between fetal and placental glucocorticoid response.²⁶ Exposure to prenatal stress may lead to altered programming of

Prenatal Stress and Current Wheeze



Postnatal Stress and Current Wheeze

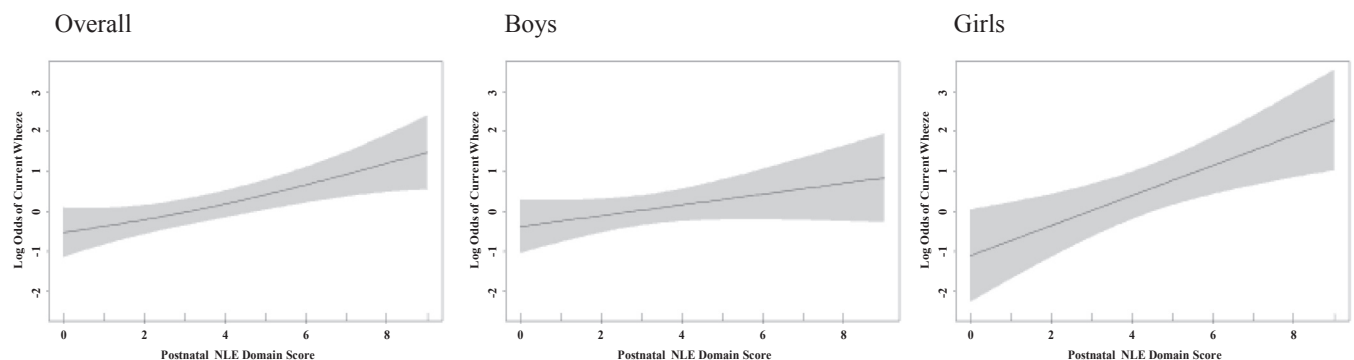


Figure 2. Exposure-response relationship between prenatal and postnatal negative life event (NLE) domain scores and current wheeze overall, in boys, and in girls. For overall results, generalized additive models were adjusted for child's sex, maternal asthma, maternal age at delivery, mean particulate matter 2.5 μm and less in diameter ($\text{PM}_{2.5}$) during pregnancy, mean $\text{PM}_{2.5}$ at postnatal year 1, report of a smoker in the home prenatally and at 48 months. Stratified models adjusted for maternal age at delivery, mean $\text{PM}_{2.5}$ during pregnancy, mean $\text{PM}_{2.5}$ at postnatal year 1, and report of a smoker in the home prenatally and at 48 months.

the stress response, and individuals exposed to stress prenatally may be more vulnerable to subsequent stressful events due to these alterations (ie, 2-hit model).⁴⁷ Moreover, studies have found that a poor postnatal environment can modulate the consequences of in utero exposure to stress in a sex-specific manner, with females

generally being more adversely affected.⁴⁸ This finding should be further explored in future research.

Strengths of our study include the prospective design, assessment of stress in pregnancy and at 48 months (ie, previously identified vulnerable developmental windows for asthma risk and stress programming) using a well-validated measure of NLEs, focus on an understudied population in Mexico City with respect to stress and children's respiratory health, and our ability to adjust for important confounders, including $\text{PM}_{2.5}$ exposure during pregnancy and the first year of life.⁴⁹ We also acknowledge some limitations. Prenatal stress was assessed based on maternal report of negative events occurring in the past 6 months, and although most women answered the CRISYS in the third trimester (92%), some variability in timing of assessment may result in measurement error. This measurement error would be expected to be similar in women regardless of whether their child develops wheeze (ie, nondifferential misclassification), resulting in an underestimation of the association between stress and asthma. Children's wheeze was reported by mothers; however, caregiver-reported wheeze is commonly used in moderate- to larger epidemiologic studies,^{50,51} and this was assessed using a standardized measure validated for Spanish-speaking populations.⁵¹ This analysis did not include a measure of the biological stress response. Even if the participants perceived an event as negative, this might not lead to a negative biological response due to that event. There is some evidence that positive life event exposure is associated with reduced cortisol levels in pregnant women⁵² and may have a protective function.^{53,54} We calculated a positive life event score (summing those

Table 3
Sex-stratified associations between maternal stress and wheeze outcomes^a

NLE domain score	RR (95% CI)		P value for interaction
	Boys (n = 211)	Girls (n = 206)	
Ever wheeze			
Prenatal	1.12 (1.02, 1.24)	1.03 (0.92, 1.15)	.25
Postnatal	1.09 (0.99, 1.20)	1.16 (1.03, 1.30)	.48
Current wheeze			
Prenatal	1.11 (0.96, 1.28)	1.11 (0.93, 1.34)	.81
Postnatal	1.11 (0.97, 1.27)	1.35 (1.13, 1.61)	.04

Abbreviations: CI, confidence interval; NLE, negative life event; RR, relative risk.
^aOverall models were adjusted for child's sex, maternal asthma, maternal age at delivery, mean particulate matter 2.5 μm and less in diameter ($\text{PM}_{2.5}$) during pregnancy, mean $\text{PM}_{2.5}$ at postnatal year 1, and report of a smoker in the home prenatally and at 48 months. Stratified models were adjusted for maternal age at delivery, mean $\text{PM}_{2.5}$ during pregnancy, mean $\text{PM}_{2.5}$ at postnatal year 1, and report of a smoker in the home prenatally and at 48 months.

items women endorsed as positive) for both the prenatal and 48-month period, and this score was not a significant predictor of ever or current wheeze. Future studies should aim to include measures of stress response (eg, stress hormones, autonomic reactivity) and examine more definitive outcomes, including physician-diagnosed asthma or lung function, as these children continue to be followed up. It is also possible that women experiencing higher stress might underreport their child's symptoms because of being overwhelmed or not aware of the child, but this would lead to an underestimation of the true association. Conversely, women experiencing higher stress might overreport symptoms if they are more attentive to their children's health.⁵⁵ Mothers in the study were not aware of the hypothesis linking stress to wheeze in their children. In addition, it is reassuring that other variables in the model (maternal asthma, sex) were associated with wheeze in the same direction reported by previous studies.^{56,57}

Our prospective study adds to a growing literature underscoring the need to consider psychosocial stress as an important programming factor for wheezing respiratory illnesses in early life and is the first, to our knowledge, to examine these associations in a Latin American sample. Knowledge of risk factors and sex differences in early development and insight into critical windows of exposure can inform prevention and intervention strategies that may preclude persistence of symptoms or lung function deficits in later childhood. Significant sex biases in the natural history, pathophysiology, and response to treatment in respiratory disorders such as asthma are not well understood.^{58,59} Studies examining the programming of sex differences at varying developmental time points in response to maternal and early-life stress may provide unique insights into asthma cause and natural history. Future interventions should consider stress reduction modalities in pregnant women and the early postpartum period.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2015.12.025>.

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eTable 1

Sample characteristics

Characteristic	Included in analyses (n = 417)	Remainder of base cohort (n = 398)	P value ^a
Mother's age at delivery, median (IQR)	28 (24–32)	27 (24–32)	.80
Maternal asthma, %	1.7	1.8	.93
Child's sex, % male	50.6	55.3	.18
Prenatal ETS exposure, %	38.4	32.9	.10
Prenatal PM _{2.5} , median (IQR), $\mu\text{g}/\text{m}^3$	23 (21–24)	23 (21–24)	.84
PM _{2.5} at 1 postnatal year, median (IQR), $\mu\text{g}/\text{m}^3$	23 (20–24)	22 (20–24)	.11

Abbreviations: ETS, environmental tobacco smoke; IQR, interquartile range; PM_{2.5}, particulate matter 2.5 μm and less in diameter.^aDifferences in categorical variables were tested using the Pearson χ^2 test; differences in continuous variables were tested using the Mann-Whitney *U* test.