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Pre- and postnatal stress and wheeze in Mexican children: Sex-specific Differences

Maria José Rosa, DrPH¹, Allan C. Just, PhD¹, Marcela Tamayo y Ortiz, ScD², Lourdes Schnaas, PhD³, Katherine Svensson, MS¹, Robert O. Wright, MD, MPH^{1,5}, Martha María Téllez Rojo, PhD², and Rosalind J. Wright, MD, MPH^{4,5}

Maria José Rosa: maria.rosa@mssm.edu; Allan C. Just: allan.just@mssm.edu; Marcela Tamayo y Ortiz: mtamayo@hsph.harvard.edu; Lourdes Schnaas: lschnaas@hotmail.com; Katherine Svensson: katherine.svensson@mssm.edu; Robert O. Wright: robert.wright@mssm.edu; Martha María Téllez Rojo: mmtellez@insp.mx; Rosalind J. Wright: rosaling.wright@mssm.edu

¹Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, New York, USA

²National Institute of Public Health, Cuernavaca, Mexico

³National Institute of Perinatology, Mexico DF, Mexico

⁴Kravis Children's Hospital, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, United States

⁵Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, United States

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Introduction

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

Corresponding Author: Rosalind J. Wright, MD, MPH, One Gustave L. Levy Place, Box 1198, New York, NY 10029, USA. Telephone: +1 (212) 241-5287; Fax: +1 (212) 289-8569; rosaling.wright@mssm.edu.

Authors' contributions: MJR generated data, performed analyses, interpreted data and drafted the manuscript. ACJ, MTO, LS and KS generated data, assisted in analysis and interpretation of data and revised the manuscript. ROW, MMTR and RJW conceived and designed original study, assisted in analysis and interpretation of the data and manuscript preparation and revisions.

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Although asthma and childhood wheeze are heterogeneous conditions, inflammation is a central pathological feature.⁵ Psychosocial stress leads to the activation of systems involved in the regulation of inflammatory processes (i.e., 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 responses⁸ so the study of psychosocial stressors as environmental risk factors for respiratory disease might be particularly relevant.

A growing number of prospective epidemiological studies demonstrate associations between increased prenatal maternal stress or stress correlates (e.g., maternal anxiety) and early asthma phenotypes.^{9–13} In Boston, children whose mothers reported higher numbers of negative life events during both the prenatal and early postnatal period were three times more likely to have recurrent wheeze by age 2 years when compared to 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 multi-site U.S. inner-city cohort study reported associations between prenatal perceived stress and wheeze in one 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 to age 6 years; maternal distress examined postnatally was not associated with child wheeze.¹³ A recent study linked higher intra-familial 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 due to high prevalence of intimate partner violence¹⁷, local violence¹⁸, perinatal depression¹⁹ and lack of data on stress-reduction strategies.⁴ Despite growing evidence in this area, similar studies in Latin American countries are lacking.

Growing evidence from animal models demonstrate 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 showed maladaptive behavioral stress responsivity in a series of tests.²² In another study, females exhibited increased anxiety-related behavior after exposure to prenatal stress while males showed 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 (11 β HSD2), 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

Epidemiological 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, doctor diagnosis of asthma and asthma medication use by age 12 years.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 to age 4 years. Specifically, we first examined effects of pre- and postnatal stress in separate models, next we mutually adjusted for pre-/postnatal stress, and finally we examined joint effects of exposure to increased stress in both pregnancy and the first two years of life. 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) recruited women 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 healthcare to affiliated private sector employees, the majority 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 anti-epilepsy medications. Following birth, 815 mother-child dyads had at least one 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 to those who did not by mother's age at delivery, maternal asthma, child's sex or prenatal ETS exposure (eTable 1, online supplement). 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 Spanish²⁹, 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 shown

increased vulnerability across multiple domains, therefore domains with one or more negative life event were summed into a negative life event (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 (ISAAC) questionnaire was administered starting at the 48-month visit. Ever wheeze was determined based on caregiver report of “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 “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 (either during the second or third trimester) and during the 48-month visit through report of any smoker in the home during these time periods. Exposure to particulate matter 2.5 microns and less in diameter (PM_{2.5}) was estimated for each women during pregnancy and over the first postnatal year using a novel spatio-temporal model incorporating Moderate Resolution Imaging Spectroradiometer (MODIS) satellite-derived Aerosol Optical Depth (AOD) 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 meteorological 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 over the first year postpartum.

Statistical Analyses

First, prenatal and postnatal negative life domain (NLE) scores were analyzed in separate models. Associations were explored by modeling NLE scores as continuous measures using generalized additive models (GAMs). In order 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 average PM_{2.5} exposure during pregnancy and one year postnatal. Socioeconomic status (SES) was also examined as a potential confounder, but was not independently associated with the outcome nor did it significantly affect the estimate and was 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 shows the distribution of covariates over the entire sample and stratified by child sex. The range of prenatal and postnatal NLE domain scores was 0-11 and 0-9, respectively; 25% of children had ever wheeze and 12% current wheeze. Sample characteristics did not

significantly differ by sex with the exception of wheeze outcomes which were both more frequent among boys ($p < 0.05$, Table 1). As seen in table 2, pre- and postnatal NLE scores (spearman $\rho = 0.45$, $p < 0.001$) and average $PM_{2.5}$ concentrations during pregnancy and one year postnatal (spearman $\rho = 0.31$, $p < 0.001$) were moderately correlated. 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 (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 12 months (RR: 1.21, 95%CI [1.08, 1.35]). Figures 1 and 2 depict the relationship 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 GAM function was a linear association of increasing risk with number of reported negative life event domains for both ever and current wheeze outcomes. In sex-stratified models, boys seemed more impacted by increasing prenatal stress while girls seemed more impacted by higher postnatal stress in relation to ever wheeze (Figure 1). In Figure 2, associations seemed more similar in boys and girls although the relationship between increasing postnatal stress and current wheeze was steeper among girls compared to boys. Table 3 shows the results for interaction models between sex and pre- and postnatal stress. The interaction term was only significant for sex*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 ($p = 0.04$). We also explored a potential interaction between higher stress in both the pre- 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 (all p -values > 0.2).

Discussion

This is the first study to prospectively examine associations between pre- 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 negative life events in the perinatal period and early childhood asthma phenotypes are consistent with another study the U.S.⁹ In addition, there was a suggestion that prenatal stress was more strongly associated with wheeze outcomes in boys compared to girls while 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 like the HPA axis, the sympathetic-adrenal-medullary system and immunomodulation. This disruption may lead to a potentiation of the fetal immune system through the upregulation of maternal and fetoplacental cytokine or IgE production.^{33, 34} We have previously shown 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 as 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 like maternal smoking.⁴⁴ Notably adjustment for any smoking in the home, both pre- and 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 relationship to ever wheeze. These findings are consistent with research showing 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.^{45, 46} Male fetuses may be more sensitive to stress *in utero* due to reduced activity and/or sensitivity of placental 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), leading to increased fetal glucocorticoid exposure, differential DNA methylation in the placenta,²⁶ or enhanced vulnerability to stress-induced oxidation *in utero*.⁴⁷ 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 relationship between fetal and placental glucocorticoid response.²⁶ Exposure to prenatal stress may lead to altered programming of the stress response and individuals exposed to stress prenatally may be more vulnerable to subsequent stressful events due to these alterations (ie "two-hit model").⁴⁸ Moreover, studies show 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.⁴⁹ This should be further explored in future research.

Strengths of our study include the prospective design, assessment of stress in pregnancy and in the first two years of life (i.e., previously identified vulnerable developmental windows for asthma risk and stress programming) using a well-validated measure of negative life events, 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 PM_{2.5} exposure during pregnancy and the first year of life.⁵⁰ We also acknowledge some

limitations. Prenatal stress was assessed based on maternal report of negative events occurring in the past 6 months and while most women answered the CRISYS in the 3rd 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 goes on to develop wheeze (i.e., 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-sized epidemiological studies^{51, 52} and this was assessed using a standardized measure validated for Spanish-speaking populations.⁵² 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 response due to that event. There is some evidence that positive life event exposure is associated with reduced cortisol levels in pregnant women⁵³ and may have a protective function.^{54, 55} We calculated a positive life event score (summing those 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 (e.g., stress hormones, autonomic reactivity, etc.), examine more definitive outcomes including physician diagnosed asthma or lung function as these children continue to be followed. It is also possible that women experiencing higher stress might underreport their child's symptoms, due to being overwhelmed or not aware of the child but this would lead to an underestimation of the true relationship. Conversely, women experiencing higher stress might overreport symptoms if they are more attentive to their children's health.⁵⁶ Mothers in the study were not aware of the hypothesis linking stress to wheeze in their children. Also, it is reassuring that other variables in the model (maternal asthma, sex) were associated with wheeze in the same direction reported by previous studies.^{57, 58}

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 first 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.^{59, 60} 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 etiology and natural history. Future interventions should consider stress reduction modalities in pregnant women and the early postpartum period.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CRISYS	Crisis in Family Systems-Revised questionnaire
HPA	hypothalamic-pituitary-adrenocortical
ISAAC	International Study of Asthma and Allergies in Childhood
NLE	Negative Life Events
PM_{2.5}	Particulate matter <2.5 microns in diameter

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Figure 1. Exposure-response relationship between prenatal and postnatal NLE domain scores and ever wheeze a) overall, b) in boys and c) in girls

For overall results, generalized additive models (GAM) were adjusted for child's sex, maternal asthma, maternal age at delivery, average $PM_{2.5}$ during pregnancy, average $PM_{2.5}$ postnatal year one, report of a smoker in the home prenatally and at 48 months. Stratified models adjusted for maternal age at delivery, average $PM_{2.5}$ during pregnancy, average $PM_{2.5}$ postnatal year one, report of a smoker in the home prenatally and at 48 months.

Figure 2. Exposure-response relationship between prenatal and postnatal NLE domain scores and current wheeze a) overall, b) in boys and c) in girls

For overall results, generalized additive models (GAM) were adjusted for child's sex, maternal asthma, maternal age at delivery, average $PM_{2.5}$ during pregnancy, average $PM_{2.5}$ postnatal year one, report of a smoker in the home prenatally and at 48 months. Stratified models adjusted for maternal age at delivery, average $PM_{2.5}$ during pregnancy, average $PM_{2.5}$ postnatal year one, report of a smoker in the home prenatally and at 48 months.

Table 1

Sample characteristics

Characteristic	Overall n=417	Boys n=211	Girls n=206	p-value ^a
Maternal asthma, n (%)	7 (1.7)	6 (2.8)	1 (0.5)	0.12
Prenatal ETS [*] exposure, n (%)	160 (38.4)	78 (37)	82 (39.8)	0.55
Postnatal ETS exposure, n (%)	53 (13)	24 (11.4)	29 (14.1)	0.41
Mother's age at delivery, median (25 th –75 th)	28 (24–32)	27 (23–31)	27 (23–31)	0.30
Average prenatal PM _{2.5} µg/m ³ , median (25 th –75 th)	23 (21–24)	23 (21–24)	23 (20–24)	0.23
Average PM _{2.5} µg/m one year postnatal, median (25 th –75 th)	23 (20–24)	23 (20–24)	23 (20–24)	0.53
Prenatal NLE domain score, median, (range)	3 (0–11)	3 (0–11)	3 (0–10)	0.93
Postnatal NLE domain score, median, (range)	3 (0–9)	3 (0–8)	3 (0–9)	0.51
Ever wheeze, n (%)	107 (26)	63 (29.9)	44 (21.4)	0.05
Current wheeze, n (%)	55 (13)	36 (17.1)	19 (9.2)	0.02

^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.

* ETS: Environmental tobacco smoke

Table 2
Spearman correlations between prenatal and postnatal stress and ambient air pollution concentrations

	Prenatal NLE score		Postnatal NLE score		Prenatal PM _{2.5} concentration	
	ρ	P	ρ	P	ρ	P
Postnatal NLE score	0.45	<0.001				
Prenatal PM _{2.5} concentration	-0.01	0.77	-0.01	0.77		
Postnatal year 1 PM _{2.5} concentration	0.02	0.64	0.06	0.18	0.31	<0.001

Table 3

Sex-stratified associations between maternal stress and wheeze outcomes

NLE Domain Score	Boys N=211	Girls N=206	p-value for interaction
<u>Ever wheeze</u>			
Prenatal	1.12 (1.02, 1.24)	1.03 (0.92, 1.15)	0.25
Postnatal	1.09 (0.99, 1.20)	1.16 (1.03, 1.30)	0.48
<u>Current wheeze</u>			
Prenatal	1.11 (0.96, 1.28)	1.11 (0.93, 1.34)	0.81
Postnatal	1.11 (0.97, 1.27)	1.35 (1.13, 1.61)	0.04

Overall models adjusted for child's sex, maternal asthma, maternal age at delivery, average PM_{2.5} during pregnancy, average PM_{2.5} postnatal year one, report of a smoker in the home prenatally and at 48 months. Stratified models adjusted for maternal age at delivery, average PM_{2.5} during pregnancy, average PM_{2.5} postnatal year one, and report of a smoker in the home prenatally and at 48 months.