



Prenatal particulate matter exposure and wheeze in Mexican children: effect modification by prenatal psychosocial stress

Maria José Rosa, DrPH^{*}; Allan C. Just, PhD^{*}; Itai Kloog, PhD[†]; Ivan Pantic, BSc[‡]; Lourdes Schnaas, PhD[§]; Alison Lee, MD, MS^{||}; Sonali Bose, MD, MPH^{||}; Yueh-Hsiu Mathilda Chiu, ScD^{*}; Hsiao-Hsien Leon Hsu, ScD^{*}; Brent Coull, PhD[¶]; Joel Schwartz, PhD[#]; Sheldon Cohen, PhD^{**}; Martha María Téllez Rojo, PhD^{††}; Robert O. Wright, MD, MPH^{*,††}; Rosalind J. Wright, MD, MPH^{*,††}

^{*} Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, New York

[†] Department of Geography and Environmental Development, Ben-Gurion University of the Negev, Beer Sheva, Israel

[‡] Department of Developmental Neurobiology, National Institute of Perinatology, Mexico City, Mexico

[§] Division of Research in Community Interventions, National Institute of Perinatology, Mexico City, Mexico

^{||} Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, New York

[¶] Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts

[#] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts

^{**} Department of Psychology, Carnegie Mellon University, Pittsburgh, Pennsylvania

^{††} Center for Nutrition and Health Research, National Institute of Public Health, Ministry of Health, Cuernavaca, Morelos, Mexico

^{††} Institute for Exposomic Research, Icahn School of Medicine at Mount Sinai, New York, New York

ARTICLE INFO

Article history:

Received for publication April 13, 2017.

Received in revised form June 23, 2017.

Accepted for publication June 28, 2017.

ABSTRACT

Background: Air pollution exposure in childhood is associated with greater incidence and exacerbation of asthma, particularly in children whose parents report high levels of psychological stress. However, this interaction has not been completely elucidated in pregnancy.

Objective: To examine whether the association between prenatal exposure to particulate matter no larger than 2.5 μm in diameter ($\text{PM}_{2.5}$) and wheeze in children is modified by prenatal stress.

Methods: Mexican women were recruited during pregnancy ($N = 552$). Residential prenatal daily exposure to $\text{PM}_{2.5}$ was estimated using a satellite-based spatiotemporally resolved prediction model and averaged over trimesters. Maternal stress was indexed by maternal negative life events (NLE) score (range 0–11) ascertained during mid to late pregnancy. NLE scores were dichotomized at the median as low (NLE score ≤ 3) and high (NLE score > 3) stress. Reports of ever wheeze and wheeze in the past 12 months (current wheeze) for children were obtained using the International Study of Asthma and Allergies in Childhood survey at 48 months. The association between prenatal $\text{PM}_{2.5}$ and wheeze was analyzed using a modified Poisson regression and stratified by low vs high stress.

Results: Greater $\text{PM}_{2.5}$ exposure during the first trimester was associated with increased risk of current wheeze among children with mothers reporting high prenatal stress (relative risk 1.35, 95% confidence interval 1.00–1.83, per interquartile range increase 3.8 $\mu\text{g}/\text{m}^3$) but not among those reporting low stress (relative risk 0.84, 95% confidence interval 0.61–1.16, per interquartile range increase 3.8 $\mu\text{g}/\text{m}^3$; P for interaction = .04).

Conclusion: Increased prenatal stress enhanced the association between $\text{PM}_{2.5}$ exposure in early pregnancy, and child wheeze at 48 months of age. It is important to consider chemical and nonchemical stressors together to more comprehensively characterize children's environmental risk.

© 2017 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Reprints: Rosalind J. Wright, MD, MPH, One Gustave L. Levy Place, Box 1198, New York, NY 10029; E-mail: rosalind.wright@mssm.edu.

Disclosures: Authors have nothing to disclose.

Funding Sources: The PROGRESS project has been funded by grants R01 ES021357 and R01 ES013744 (R.O. Wright, principal investigator). Phenotyping and

biostatistical support was funded by grant P30 ES023515. During the preparation of this article, Dr Rosa was supported by grant T32 HD049311-09; Dr Lee was supported by grant K23 HL135349; and Dr Just was supported by grant R00 ES023450. This study was supported and funded in part by the National Institute of Public Health, Ministry of Health of Mexico.

Introduction

Emerging evidence has linked exposure to ambient air pollution during the prenatal period to increased respiratory morbidity later in childhood.^{1,2} In addition, increased prenatal maternal stress and stress correlates (eg, maternal anxiety) have been independently associated with early asthma phenotypes in many prospective epidemiologic studies.^{3–8} Other data have suggested that lower socioeconomic status populations are more susceptible to the health effects of air pollution, potentially because of concomitant increased psychosocial stress.^{9,10}

Epidemiologic studies have begun to document synergistic effects between stress and ambient air pollution exposure in early childhood on the incidence and exacerbation of asthma and decrements in lung function.^{11–16} For example, in a 3-year follow-up study of children enrolled at 5 to 9 years of age in Southern California, annual residential exposure to oxides of nitrogen was associated with greater asthma incidence in children whose parents also reported higher perceived stress.¹² In this same study, exposure to nitric oxide, nitrogen dioxide (NO₂), and total oxides of nitrogen estimated at children's residences and schools also was associated with greater decrements in lung function among children whose parents reported high perceived stress compared with parents who reported low stress.¹¹ Our group previously reported that higher lifetime exposure to ambient NO₂, estimated using land use regression, in urban children followed to approximately 7 years of age was associated with increased risk of asthma diagnosis only among children also exposed to higher levels of community violence in the neighborhood.¹³ Our team also reported that prenatal exposure to black carbon and particulate matter no larger than 2.5 μm in diameter (PM_{2.5}) was associated with increased odds of repeated wheeze at 2 years of age with an additive effect of concurrent prenatal community violence exposure.¹⁵ Data on the potential synergistic effects of increased ambient particulate air pollution exposure and psychosocial stress starting in utero on children's respiratory health remain sparse.

Moreover, fetal lung development occurs through a complex orchestration of sequential biologic events and there might be periods when the fetus is more sensitive to pro-oxidant exposures. Recent epidemiologic evidence has shown that exposure to ambient air pollution at different periods in pregnancy is associated with respiratory outcomes in childhood.^{2,17,18} Our group showed that PM_{2.5} exposure during the second trimester was associated with asthma at 6 years of age in children in Boston, Massachusetts.² A study in China reported varying periods of importance for outdoor prenatal exposure to NO₂ and allergic or respiratory outcomes, with first-trimester exposure associated with eczema, second-trimester exposure associated with asthma, and third-trimester exposure linked with allergic rhinitis.¹⁸ In a study in Spain, second-trimester NO₂ exposure estimated using land use regression was associated with decreased lung function at 4.5 years of age and increased risk of low lung function (<80% of predicted forced expiratory volume in 1 second).¹⁷ Therefore, there is reason to expect that the particular timing of exposure during the prenatal period might be of importance. We leveraged existing data from an established population-based prenatally enrolled longitudinal cohort in Mexico City, Mexico to examine the association between prenatal PM_{2.5} averaged over trimesters and report of wheeze in children followed to 48 months of age. We examined whether these associations were modified by prenatal psychosocial stress.

Methods

Study Population

Pregnant women who were receiving health services and prenatal care through the Mexican Social Security System (Instituto

Mexicano del Seguro Social) were recruited into the Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) study from July 2007 through February 2011. Women were eligible to participate if they were at less than 20 weeks of gestation, at least 18 years old, planned to stay in Mexico City for the next 3 years, had telephone access, and reported no medical history of heart or kidney disease, no daily alcohol consumption, and no use of any steroid or antiepilepsy medications. After birth, 815 mother-child dyads had at least 1 follow-up visit and 552 had completed the visit at 48 months of age and had all the necessary covariates for these analyses. Procedures were approved by institutional review boards at the Harvard School of Public Health (Boston, Massachusetts), the Icahn School of Medicine at Mount Sinai (New York, New York), and the Mexican National Institute of Public Health (Mexico City, Mexico). Women provided written informed consent.

Prenatal PM_{2.5} Levels

Our group developed a hybrid satellite-based method to estimate daily PM_{2.5} levels across Mexico City for 2004 through 2014. Daily exposures to PM_{2.5} were estimated for each participant during pregnancy using a novel spatiotemporal model that incorporates moderate resolution imaging spectroradiometric satellite-derived aerosol optical depth measurements from the multi-angle implementation of atmospheric correction at a 1- $\times$ 1-km spatial resolution.¹⁹ These remote sensing data are calibrated with data from 12 municipal ground-level monitors of PM_{2.5}, roadway density, and meteorologic data (temperature, relative humidity, planetary boundary layer, and daily precipitation) to yield estimates of daily residential PM_{2.5} levels for each participant. Mixed-effect models with spatial and temporal predictors and day-specific random effects were used to account for temporal variations in the relation between PM_{2.5} and aerosol optical depth. For days without aerosol optical depth data, the model was fit with a seasonal smooth function of latitude and longitude and time-varying average incorporating local monitoring. Model performance was assessed using monitor-level leave-1-out cross-validation with an R^2 of 0.724. For more in-depth model details, please refer to Just et al.¹⁹

Each woman's daily exposure to PM_{2.5} across the pregnancy was estimated based on the gestational age and residential address during the pregnancy. Because ultrasounds were not routinely performed as standard of care, gestational age at birth was estimated based on the mother's report of her last menstrual period and by a standardized physical examination.²⁰ If the physical examination assessment of gestational age differed by more than 3 weeks from the gestational age based on the last menstrual period, then the physical examination was used instead of the gestational age determined by the last menstrual period. We calculated the average PM_{2.5} over clinically defined trimesters (first trimester 1–13 weeks, second trimester 14–27 weeks, third trimester 28 weeks to delivery).

Measurements of Psychosocial Stress

The validated Spanish version of the Crisis in Family Systems–Revised (CRISYS)²¹ survey was administered by a trained psychologist during the second or third trimester of pregnancy and during the 48-month follow-up postnatal 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.^{3,8,22} Therefore, domains with at least 1 negative life event were summed into a negative life event

(NLE) domain score, with higher scores indicating greater stress. The range of NLE score in our sample was 0 to 11 for prenatal NLE and 0 to 9 for 48-month NLE. Prenatal stress was dichotomized as low stress (NLE scores = 0–3) and high stress (NLE scores > 3) based on the median value.

Outcome Measurements

The validated Spanish version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was administered at the 48-month visit. Ever wheeze was defined as the caregiver's 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 the response to "Has your child had wheezing or whistling of the chest in the past 12 months?"

Covariates

Child's sex was obtained from the mother's report and delivery records. Mother's age at delivery was calculated by subtracting the child's birthdate from the mother's birthdate collected at enrollment. Mother's report of ever having asthma was collected through questionnaires at enrollment (second or third trimester). Exposure to environmental tobacco smoke (ETS) was ascertained during pregnancy (during the second or third trimester) and during the 48-month visit through the report of any smoker in the home during these periods. Thirteen variables derived from prenatal questionnaire results were used to classify study participant families into 6 levels based on the socioeconomic status index created by the Asociación Mexicana de Agencias de Investigación de Mercados y Opinión Pública.²³ These levels were collapsed into low, medium, and high socioeconomic status.

Statistical Analyses

To obtain risk ratios for our prospectively measured dichotomous outcomes, data were analyzed using a modified Poisson regression approach that allowed us to estimate risk ratios instead of odds ratios.²⁴ Models were adjusted for child's sex, report of any smoker in the home during pregnancy and at 48 months, mother's age at delivery, and maternal ever asthma. Co-exposures for every trimester and postnatal year 1 exposures were included in final models. Low stress (NLE scores 0–3) and high stress (NLE scores > 3) groups were based on the median split. Socioeconomic status and NLE scores at 48 months of age also were examined as potential confounders but were not independently associated with the outcome and did not significantly affect the estimate, so they were excluded from the final analyses. Statistical interactions between prenatal stress and PM_{2.5} levels were determined by including a product term between average PM_{2.5} levels and the dichotomized NLE score to test for a departure in multiplicative property. Then,

models were stratified by low and high stress with adjustment for other covariates. Generalized additive models were used to model NLE scores as numeric measurements. Because research has linked prenatal air pollution to preterm birth²⁵ and in turn preterm birth has been linked to childhood respiratory disease,²⁶ we also carried out sensitivity analyses by restricting the analyses to only full-term children (gestational age ≥ 37 weeks). Analyses were performed in R 3.2.3 (R Project for Statistical Computing, Vienna, Austria)²⁷ and SPSS 23 (SPSS, Inc, Chicago, Illinois).

Results

Table 1 presents the distribution of covariates, exposure, and outcomes across the sample as a whole and then stratified by low and high stress. Sample characteristics did not differ significantly by stress except for prenatal ETS, with a larger percentage of participants reporting a smoker in the home in the high stress group compared with the low stress group (43% vs 33%, respectively). Overall, 25% of children had ever wheezed and 12% had report of wheeze in the past 12 months. As presented in Supplemental eTable 1, there were no significant differences between participants who had all necessary covariates compared with those who did not by mother's age at delivery, maternal asthma, child's sex, NLE score, or prenatal ETS exposure. Participants in the remainder of the cohort did not vary by trimester exposure to PM_{2.5}, except for slightly higher exposure during the first trimester, with borderline significance.

We did not see any significant associations between any trimester PM_{2.5} levels and wheeze outcomes in adjusted models before stratification. Table 2 presents the results of adjusted models for the association between trimester PM_{2.5} concentrations and ever wheeze and current wheeze, stratified by low and high stress, with *P* values for interaction models when including a product term for PM_{2.5} and NLE score in the combined sample. The interaction *P* value represents the formal test for the interaction between PM_{2.5} and NLE scores independent of the stratum-specific risk ratios listed. Risk ratios are shown for an interquartile range increase in PM_{2.5} levels during each trimester. For the current wheeze outcome, we found a significant interaction between first-trimester PM_{2.5} and prenatal stress on current wheeze. There was a positive association between first-trimester PM_{2.5} concentrations and current wheeze only among children born to mothers who also reported experiencing higher stress during pregnancy. We did not find significant interactions for the ever wheeze outcome, although we saw a similar pattern for first-trimester PM_{2.5} concentrations and higher risk of ever wheeze only in children in the high stress stratum. The dose-response relations between first-trimester PM_{2.5} and each wheeze outcome also are depicted using generalized additive models, stratified by low and high stress, in Figures 1 and 2. As shown in Figures 1 and 2, increasing odds of ever

Table 1
Sample Characteristics

Characteristic	Overall (N = 552)	Low stress (≤3; n = 349)	High stress (>3; n = 203)	<i>P</i> value ^a
Boys, n (%)	279 (51)	168 (48)	111 (55)	.14
Maternal asthma, n (%)	7 (1.2)	5 (1.4)	2 (1.0)	.65
Prenatal ETS, n (%)	202 (37)	114 (33)	88 (43)	.01
Postnatal ETS, n (%)	79 (14)	48 (14)	31 (15)	.62
Mother's age at delivery, median (IQR)	27.6 (23.6–31.8)	27.5 (23.5–31.6)	27.7 (24.2–32.0)	.65
Average first-trimester PM _{2.5} (μg/m ³), median (IQR)	22.0 (18.9–25.7)	22.2 (18.9–25.6)	21.6 (18.9–25.9)	.99
Average second-trimester PM _{2.5} (μg/m ³), median (IQR)	21.1 (18.8–25.6)	21.0 (18.6–25.4)	21.2 (19.2–25.7)	.23
Average third-trimester PM _{2.5} (μg/m ³), median (IQR)	22.5 (19.0–27.3)	22.7 (18.8–27.3)	22.2 (19.1–27.2)	.68
Ever wheeze, n (%)	136 (25)	77 (22)	59 (29)	.07
Current wheeze, n (%)	66 (12)	35 (10)	31 (15)	.07

Abbreviations: ETS, environmental tobacco smoke; IQR, interquartile range; PM_{2.5}, particulate matter no larger than 2.5 μm in diameter.

^aDifferences in categorical variables were tested using Fisher exact test or Pearson χ^2 test. Differences in continuous variables were tested using Mann-Whitney *U* test.

Table 2
Interaction Models and Stress-stratified Associations Between Prenatal PM_{2.5} Concentrations and Wheeze Outcomes^a

	RR (95% CI)		P value for interaction between PM _{2.5} and stress for combined sample (N = 522)
	Low stress (≤ 3) stratum (n = 349)	High stress (> 3) stratum (n = 203)	
Ever wheeze			
First-trimester PM _{2.5}	0.99 (0.83–1.18)	1.18 (0.97–1.43)	.19
Second-trimester PM _{2.5}	0.92 (0.76–1.12)	1.06 (0.85–1.32)	.32
Third-trimester PM _{2.5}	0.96 (0.82–1.13)	0.94 (0.78–1.15)	.66
Current wheeze			
First-trimester PM _{2.5}	0.84 (0.61–1.16)	1.35 (1.00–1.83)	.04
Second-trimester PM _{2.5}	0.74 (0.54–1.04)	0.99 (0.71–1.38)	.22
Third-trimester PM _{2.5}	0.96 (0.74–1.26)	0.83 (0.61–1.13)	.28

Abbreviations: CI, confidence interval; PM_{2.5}, particulate matter no larger than 2.5 μm in diameter; RR, relative risk.

^aRelative risks refer to an average pregnancy IQR (3.8- $\mu\text{g}/\text{m}^3$) increase in PM_{2.5}. Models were adjusted for child's sex, maternal asthma, maternal age at delivery, prenatal environmental tobacco smoke exposure, environmental tobacco smoke exposure at 48 months of age, other trimester PM_{2.5} concentrations, and postnatal year 1 average PM_{2.5}.

wheeze and current wheeze occurred with increasing PM_{2.5} concentrations during the first trimester only in children whose mothers reported higher stress during pregnancy.

In sensitivity analyses adjusting for NLE scores collected at 48 months, effect estimates remained virtually unchanged. Restricting the analyses to participants who were considered full term (≥ 37 weeks' gestation) also did not alter the results.

Discussion

This is the first study to prospectively demonstrate associations among prenatal PM_{2.5} concentrations, maternal stress in pregnancy, and wheeze outcomes among 4-year-old children in an urban population in Mexico City. In general, we found that increasing ambient PM_{2.5} exposure during the first trimester was associated with increased risk of wheeze outcomes in children whose mothers reported higher prenatal stress compared with children whose mothers reported low stress in pregnancy. Higher PM_{2.5} exposure during the first trimester was associated with increased risk of wheeze in the past 12 months at 4 years of age, specifically in participants concurrently exposed to higher prenatal stress.

Evidence from animal and human studies has suggested that pregnancy could be a particularly vulnerable period for effects of ambient air pollution exposure on the developing fetus. Increased maternal systemic oxidative stress and production of proinflammatory cytokines from air pollution exposure could lead to placental and endothelial dysfunction and increased fetal oxidative

stress affecting fetal immune and lung development. Pregnant mice challenged with airborne and inert particles showed greater airway inflammation and lung hyperresponsiveness compared with nonpregnant controls.²⁸ Mouse pups exposed to PM_{2.5} perinatally had decreased alveolarization and smaller lung volumes compared with unexposed controls.²⁹ In humans, Janssen et al³⁰ reported that prenatal PM₁₀ was associated with significantly lower mitochondrial DNA content in the placenta, an indicator of enhanced placental oxidative stress. Prenatal PM_{2.5} levels also have been associated with significantly lower mitochondrial DNA content in cord blood.³¹ Placental 3-nitrotyrosine, another biomarker of oxidative stress, was positively associated with prenatal PM_{2.5} concentrations, particularly during the first and third trimesters.³² In the Generation R study, increased PM₁₀ before delivery was associated with increased fetal C-reactive protein, a marker of systemic inflammation.³³ Psychosocial stress during pregnancy also can disrupt maternal systems such as the hypothalamic-pituitary-adrenocortical axis, the sympathetic-adrenal-medullary system, and immunomodulation, which can lead to a potentiation of the fetal immune system through the upregulation of maternal and fetoplacental cytokine or immunoglobulin E production.^{34,35}

Previous research has demonstrated variability in downstream effects such as eczema, allergic rhinitis, and asthma in offspring depending on the trimester during which exposure to air pollution occurs.^{18,36} In our study, we report associations only during the first trimester of pregnancy, which corresponds to the pseudoglandular stage of fetal lung development. During this period, budding and

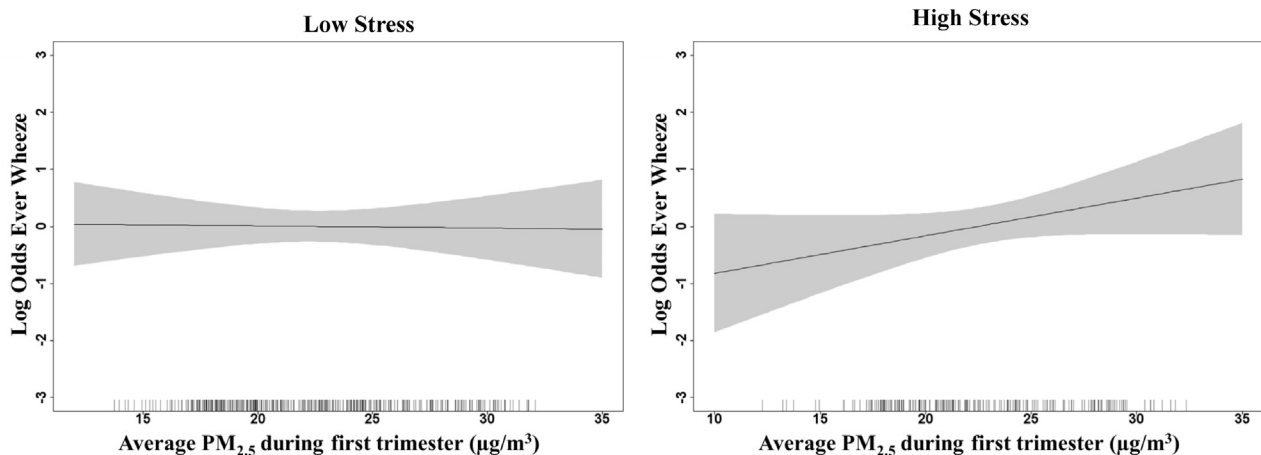


Figure 1. Exposure-response relation between average first-trimester PM_{2.5} and ever wheeze stratified by low stress (negative life events score ≤ 3) and high stress (negative life events score > 3). Models were adjusted for sex, maternal asthma, maternal age at delivery, prenatal environmental tobacco smoke exposure, environmental tobacco smoke exposure at 48 months, average second- and third-trimester PM_{2.5} and average postnatal year 1 PM_{2.5}. PM_{2.5}, particulate matter no larger than 2.5 μm in diameter.

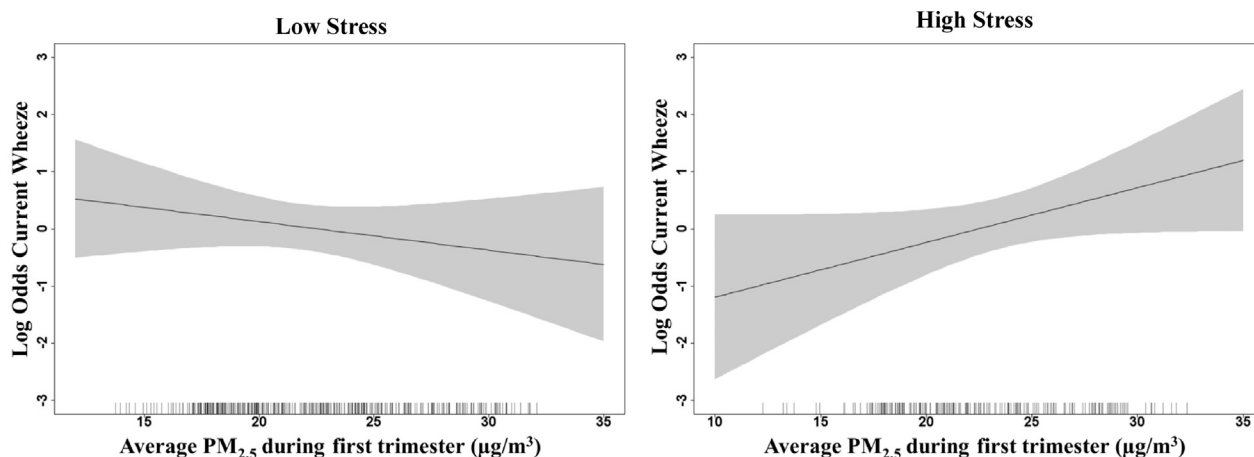


Figure 2. Exposure-response relation between average first-trimester $PM_{2.5}$ and current wheeze stratified by low stress (negative life events score ≤ 3) and high stress (negative life events score > 3). Models were adjusted for sex, maternal asthma, maternal age at delivery, prenatal environmental tobacco smoke exposure, environmental tobacco smoke exposure at 48 months, average second- and third-trimester $PM_{2.5}$ and average postnatal year 1 $PM_{2.5}$. $PM_{2.5}$, particulate matter no larger than $2.5 \mu m$ in diameter.

branching of the tracheobronchial tree is completed and further structural formation of the conducting airways such as vascular, smooth muscle, and mucosal glands formation occurs. We hypothesize that early toxicant exposure might affect the global transcriptional program of progenitor cells meant to differentiate into bronchial epithelium and other crucial components of future airway structure and defense.³⁷ However, further work is needed to better elucidate windows of susceptibility to these exposures.

Strengths of our study include the prospective design and a validated spatiotemporal satellite method of high spatial and temporal resolution to assign $PM_{2.5}$ exposure during pregnancy and postnatal year 1, allowing us to co-adjust for all trimester and postnatal year 1 $PM_{2.5}$ concentrations. Another strength of our study is the assessment of stress in pregnancy, a previously identified vulnerable developmental window for asthma risk and stress programming using a well-validated assessment of negative life events. Our study also adds to the growing area of study of environmental risk factors, by examining ambient air pollution and stress, for the development of childhood wheezing and asthma in Latin America by focusing on an understudied population in Mexico City. We also could be able to adjust for important covariates such as ETS exposure during the prenatal period, which was higher in the mothers who reported high stress, and concurrent with the administration of the ISAAC questionnaire. We also acknowledge some limitations. Children's wheeze was reported by mothers; however, caregiver-reported wheeze is commonly used in moderate to large epidemiologic studies^{38,39} and this was assessed using a standardized assessment validated for Spanish-speaking populations.³⁹ Future studies should aim to examine more definitive outcomes including physician-diagnosed asthma or lung function as these children continue to be followed.

Our prospective study adds to a growing literature underscoring the need to consider chemical and nonchemical stressors together to more comprehensively characterize children's environmental risk and is the first study to examine these associations in a Latin American sample. These data show that children born to mothers exposed to higher levels of particulate air pollution during pregnancy are at greater risk of wheeze at 4 years of age, particularly if their mothers also experienced more toxic levels of stress prenatally. Knowledge of interactions between chemical and nonchemical environmental toxins can better inform prevention and intervention strategies that might preclude persistence of symptoms or lung function deficits in later childhood. For example, these

findings suggest that interventions aimed at decreasing prenatal stress could mitigate the effects of chemical toxins such as air pollution, which might be harder to eliminate in the shorter term. A first step is to train clinicians to counsel pregnant women and young mothers on the important role of psychological stress in this context, validating for their patients that stress has medical implications for the mother and her developing child. Notably, the modifying effect of stress considered women who were above the median as having high stress compared with those below the median. This underscores that interventions do not need to eliminate stress altogether, but rather, they should be designed to decrease stress to more normative or manageable levels for pregnant women and young families. This is more practical and achievable when designing stress reduction strategies in the clinical setting.

Acknowledgments

We thank the American British Cowdray Hospital in Mexico for providing research facilities.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2017.06.016>.

References

- [1] Clark NA, Demers PA, Karr CJ, et al. Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect.* 2010;118:284–290.
- [2] Hsu HHL, Chiu YHM, Coull BA, et al. Prenatal particulate air pollution and asthma onset in urban children identifying sensitive windows and sex differences. *Am J Resp Crit Care.* 2015;192:1052–1059.
- [3] Chiu YHM, Coull BA, Cohen S, et al. Prenatal and postnatal maternal stress and wheeze in urban children effect of maternal sensitization. *Am J Resp Crit Care.* 2012;186:147–154.
- [4] Hartwig IR, Sly PD, Schmidt LA, et al. Prenatal adverse life events increase the risk for atopic diseases in children, which is enhanced in the absence of a maternal atopic predisposition. *J Allergy Clin Immunol.* 2014;134:160–169.
- [5] Cookson H, Granell R, Joinson C, et al. Mothers' anxiety during pregnancy is associated with asthma in their children. *J Allergy Clin Immunol.* 2009;123:847–853.
- [6] Reyes M, Perzanowski MS, Whyatt RM, et al. Relationship between maternal demoralization, wheeze, and immunoglobulin E among inner-city children. *Ann Allergy Asthma Immunol.* 2011;107:42–49.
- [7] Guxens M, Sonnenschein-van der Voort AMM, Tiemeier H, et al. Parental psychological distress during pregnancy and wheezing in preschool children: the Generation R Study. *J Allergy Clin Immunol.* 2014;133:59–67.e1–12.

- [8] Rosa MJ, Just AC, Tamayo YOM, et al. Prenatal and postnatal stress and wheeze in Mexican children: sex-specific differences. *Ann Allergy Asthma Immunol*. 2016;116:306–312.e1.
- [9] Hajat A, Hsia C, O'Neill MS. Socioeconomic disparities and air pollution exposure: a global review. *Curr Environ Health Rep*. 2015;2:440–450.
- [10] Wright RJ. Moving towards making social toxins mainstream in children's environmental health. *Curr Opin Pediatr*. 2009;21:222–229.
- [11] Islam T, Urman R, Gauderman WJ, et al. Parental stress increases the detrimental effect of traffic exposure on children's lung function. *Am J Respir Crit Care Med*. 2011;184:822–827.
- [12] Shankardass K, McConnell R, Jerrett M, et al. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. *Proc Natl Acad Sci U S A*. 2009;106:12406–12411.
- [13] Clougherty JE, Levy JL, Kubzansky LD, et al. Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. *Environ Health Perspect*. 2007;115:1140–1146.
- [14] Jackson B, Kubzansky LD, Cohen S, et al. A matter of life and breath: childhood socioeconomic status is related to young adult pulmonary function in the CARDIA study. *Int J Epidemiol*. 2004;33:271–278.
- [15] Chiu YHM, Coull BA, Sternthal MJ, et al. Effects of prenatal community violence and ambient air pollution on childhood wheeze in an urban population. *J Allergy Clin Immunol*. 2014;133:713–722.e4.
- [16] van de Loo KF, van Gelder MM, Roukema J, et al. Prenatal maternal psychological stress and childhood asthma and wheezing: a meta-analysis. *Eur Respir J*. 2016;47:133–146.
- [17] Morales E, Garcia-Esteban R, de la Cruz OA, et al. Intrauterine and early postnatal exposure to outdoor air pollution and lung function at preschool age. *Thorax*. 2015;70:64–73.
- [18] Deng Q, Lu C, Li Y, et al. Exposure to outdoor air pollution during trimesters of pregnancy and childhood asthma, allergic rhinitis, and eczema. *Environ Res*. 2016;150:119–127.
- [19] Just AC, Wright RO, Schwartz J, et al. Using high-resolution satellite aerosol optical depth to estimate daily PM_{2.5} geographical distribution in Mexico City. *Environ Sci Technol*. 2015;49:8576–8584.
- [20] Capurro H, Konichevsky S, Fonseca D, Caldeyro-Barcia R. A simplified method for diagnosis of gestational age in the newborn infant. *J Pediatr*. 1978;93:120–122.
- [21] Berry CA, Quinn KA, Portillo N, et al. Reliability and validity of the Spanish version of the Crisis in Family Systems—Revised. *Psychol Rep*. 2006;98:123–132.
- [22] Myers HF. Ethnicity- and socio-economic status-related stresses in context: an integrative review and conceptual model. *J Behav Med*. 2009;32:9–19.
- [23] Carrasco AV. The AMAI system of classifying households by socio-economic level: ESOMAR2002. <https://www.esomar.org/>. Accessed April 13, 2017.
- [24] Zou GY. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159:702–706.
- [25] Stieb DM, Chen L, Eshoul M, et al. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. *Environ Res*. 2012;117:100–111.
- [26] Been JV, Lugtenberg MJ, Smets E, et al. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. *PLoS Med*. 2014;11:e1001596.
- [27] Gasparrini A. Distributed lag linear and non-linear models in R: the package dlnm. *J Stat Softw*. 2011;43:1–20.
- [28] Fedulov AV, Leme A, Yang Z, et al. Pulmonary exposure to particles during pregnancy causes increased neonatal asthma susceptibility. *Am J Respir Cell Mol Biol*. 2008;38:57–67.
- [29] Mauad T, Rivero DH, de Oliveira RC, et al. Chronic exposure to ambient levels of urban particles affects mouse lung development. *Am J Respir Crit Care Med*. 2008;178:721–728.
- [30] Janssen BG, Munters E, Pieters N, et al. Placental mitochondrial DNA content and particulate air pollution during in utero life. *Environ Health Perspect*. 2012;120:1346–1352.
- [31] Rosa MJ, Just AC, Guerra MS, et al. Identifying sensitive windows for prenatal particulate air pollution exposure and mitochondrial DNA content in cord blood. *Environ Int*. 2017;98:198–203.
- [32] Saenen ND, Vrijens K, Janssen BG, et al. Placental nitrosative stress and exposure to ambient air pollution during gestation: a population study. *Am J Epidemiol*. 2016;184:442–449.
- [33] van den Hooven EH, de Kluizenaar Y, Pierik FH, et al. Chronic air pollution exposure during pregnancy and maternal and fetal C-reactive protein levels: the Generation R Study. *Environ Health Perspect*. 2012;120:746–751.
- [34] Wright RJ, Visness CM, Calatroni A, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *Am J Respir Crit Care Med*. 2010;182:25–33.
- [35] Peters JL, Cohen S, Staudenmayer J, et al. Prenatal negative life events increases cord blood IgE: interactions with dust mite allergen and maternal atopy. *Allergy*. 2012;67:545–551.
- [36] Lu C, Deng L, Ou C, et al. Preconceptional and perinatal exposure to traffic-related air pollution and eczema in preschool children. *J Dermatol Sci*. 2017;85:85–95.
- [37] Carsin A, Mazenq J, Ilstad A, et al. Bronchial epithelium in children: a key player in asthma. *Eur Respir Rev*. 2016;25:158–169.
- [38] Akinbami LJ, Moorman JE, Garbe PL, et al. Status of childhood asthma in the United States, 1980–2007. *Pediatrics*. 2009;123:S131–S145.
- [39] Mallol J, Sole D, Baeza-Bacab M, et al. Regional variation in asthma symptom prevalence in Latin American children. *J Asthma*. 2010;47:644–650.

eTable 1

Sample Characteristics

Characteristic	Included in analyses (n = 552)	Remainder of base cohort (n = 263)	P value ^a
Mother's age at delivery, median (25th–75th percentiles)	27.6 (23.6–31.8)	27.4 (23.9–31.5)	.82
Maternal asthma, n (%)	7 (1.3)	7 (2.7)	.16
Boys, n (%)	279 (51)	151 (57)	.07
Prenatal ETS exposure, n (%)	202 (37)	89 (34)	.44
Average first-trimester PM _{2.5} (μg/m ³), median (25th–75th percentiles)	22.0 (18.9–25.7)	23.0 (19.3–26.9)	.05
Average second-trimester PM _{2.5} (μg/m ³), median (25th–75th percentiles)	21.1 (18.8–25.6)	21.4 (19.2–25.9)	.21
Average third-trimester PM _{2.5} (μg/m ³), median (25th–75th percentiles)	22.5 (19.0–27.3)	22.6 (19.2–27.9)	.31
Average postnatal year 1 PM _{2.5} (μg/m ³), median (25th–75th percentiles)	22.8 (20.6–23.9)	22.4 (20.1–23.7)	.08
NLE prenatal score, median (range)	3 (0–11)	3 (0–9)	.59

Abbreviations: ETS, environmental tobacco smoke; NLE, negative life events; PM_{2.5}, particulate matter no larger than 2.5 μm in diameter.

^aDifferences in categorical variables were tested using Pearson χ^2 test and differences in continuous variables were tested using Mann-Whitney *U* test. In the remainder of the base cohort, 197 of 263 had NLE prenatal scores and 260 of 263 had prenatal and postnatal PM_{2.5} measurements.