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

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Keywords

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Introduction

Emerging evidence links exposure to ambient air pollution during the prenatal period to increased respiratory morbidity later in childhood.[1, 2] Additionally, increased prenatal maternal stress and stress correlates (e.g., maternal anxiety) have been independently associated with early asthma phenotypes in a number of prospective epidemiological studies.[3–8] Other data suggests that lower socio-economic status populations are more susceptible to air pollution related health effects, potentially due to concomitant increased psychosocial stress.[9, 10]

Epidemiological studies have begun to document synergistic effects between stress and ambient air pollution exposure in early childhood on 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 age 5–9 years in Southern California, annual residential exposure to NOx was associated with greater asthma incidence in children whose parents also reported higher perceived stress.[12] In this same study, exposure to nitric oxide (NO), nitrogen dioxide (NO$_2$), and total oxides of nitrogen (NOx) estimated at children's residences and schools was also associated with greater decrements in lung function among children whose parents reported high perceived stress when compared to parents who reported low stress.[11] Our group previously reported that higher lifetime exposure to ambient NO$_2$, estimated using land use regression (LUR), in urban children followed to approximately age 7 years 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 has also reported that prenatal exposure to black carbon (BC) and particulate matter 2.5 microns in diameter (PM$_{2.5}$) was associated with increased odds of repeated wheeze at age 2 years 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 may be periods of time in which the fetus is more sensitive to pro-oxidant exposures. Recent epidemiological evidence demonstrates 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 age 6 in children in Boston.[2] A study in China reported varying periods of importance for outdoor prenatal exposure to NO$_2$ and allergic or respiratory outcomes, with first trimester exposure associated with eczema, exposure in the second trimester associated with asthma, and third trimester exposure linked with allergic rhinitis.[18] In a study in Spain, second trimester NO$_2$ exposure estimated using LUR was associated with reduced lung function at age 4.5 years and increased risk of low lung function (<80% of predicted forced expiratory volume in 1 second [FEV$_1$]).[17] Therefore, there is reason to

expect that the particular timing of exposure during the prenatal period may be of importance. We leveraged existing data from an established population-based prenatally enrolled longitudinal cohort in Mexico City 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 service and prenatal care through the Mexican Social Security System (Instituto Mexicano del Seguro Social –IMSS) were recruited into the Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) study between July 2007 and February 2011. Women were eligible to participate if they were less than 20 weeks gestation, at least 18 years old, planned to stay in Mexico City for the next 3 years, had telephone access, reported no medical history of heart or kidney disease, no daily alcohol consumption, and of no use any steroid or anti-epilepsy medications. Following birth, 815 mother-child dyads had at least one follow-up visit and 552 had completed the 48 months of age visit and had all the necessary covariates for these analyses. 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.

Prenatal PM$_{2.5}$ Levels

Our group has developed a hybrid satellite-based method to estimate daily $PM_{2.5}$ levels across Mexico City for the years 2004–2014. Daily exposures to $PM_{2.5}$ were then estimated for each participant during pregnancy using a novel spatio-temporal model that incorporates Moderate Resolution Imaging Spectroradiometer (MODIS) satellite-derived Aerosol Optical Depth (AOD) measurements from the Multiangle Implementation of Atmospheric Correction (MAIAC) at a 1×1 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 meteorological 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 $PM_{2.5}$-AOD relationship. For days without AOD 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 one-out cross-validation with an R^2 of 0.724. For more in depth model details please refer to Just et al, 2015.[19] Each woman's individual daily exposure to $PM_{2.5}$ across the pregnancy was estimated based on their 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 mother's report of her last menstrual period (LMP) 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 LMP, the physical exam was used instead of the gestational age determined by LMP. We

calculated the average $PM_{2.5}$ over clinically defined trimesters (1st trimester: 1–13 weeks, 2nd trimester: 14–27 weeks, 3rd trimester: 28 weeks-delivery).

Measures of psychosocial stress

The validated[21] Spanish version of the Crisis in Family Systems-Revised (CRISYS) 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 one or more 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 measures

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 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 was obtained from mother's report and delivery records. Mother's age at delivery was calculated by subtracting child's birthdate from 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 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. Thirteen variables derived from prenatal questionnaire results were used to classify study participant families into six levels based on the socioeconomic status (SES) index created by the Asociación Mexicana de Agencias de Investigación de Mercados y Opinión Pública (AMAI).[23] These levels were then collapsed into low, medium, and high socioeconomic status.

Statistical Analyses

In order to obtain risk ratios for our prospectively measured dichotomous outcomes, data were analyzed using a modified Poisson regression approach that allows 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. SES and NLE scores at 48 months of age were also examined as

potential confounders, but were not independently associated with the outcome nor did they significantly affect the estimate, thus they were excluded from 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 multiplicativity. Models were then stratified by low and high stress with adjustment for other covariates. Generalized additive models (GAMs) were used to model NLE scores as numeric measures. Because research links prenatal air pollution to preterm birth[25] and in turn, preterm birth is 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 version 3.2.3 (Vienna, Austria) [27] and SPSS version 23 (Chicago, IL).

Results

Table 1 shows 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 higher percentage of participants reporting a smoker in the home in the high stress group when compared to the low stress group (43% vs. 33%, respectively). Overall 25% of the children had ever wheezed and 12% had report of wheeze in the past 12 months. Supplemental Table 1 shows 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, NLE score or prenatal ETS exposure. Participants in the remainder of 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 prior to stratification. Table 2 shows 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 interaction between $PM_{2.5}$ and NLE scores independent of the stratum specific RRs shown. RRs are shown for an IQR 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 the children in the high stress stratum. The dose response relationships between first trimester $PM_{2.5}$ and each wheeze outcome are also depicted using generalized additive models (GAM) in Figures 1 and 2, stratified by low/high stress. As shown in Figures 1 and 2 we see increasing odds of ever wheeze and current wheeze with increasing $PM_{2.5}$ concentrations during the first trimester only in the 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 between 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 saw 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 to 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 age 4, specifically in participants concurrently exposed to higher prenatal stress.

Evidence from both animal and human studies suggests that pregnancy may be a particular vulnerable period for ambient air pollution exposure for the developing fetus. Increased maternal systemic oxidative stress and production of pro-inflammatory cytokines due to air pollution exposure may 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 show greater airway inflammation and lung hyperresponsiveness when compared to non-pregnant controls.[28] Mouse pups exposed to $PM_{2.5}$ perinatally had decreased alveolarization and reduced lung volumes when compared to unexposed controls.[29] In humans, Janssen and colleagues reported that prenatal PM_{10} was associated with significantly lower mitochondrial DNA content in placenta, an indicator of enhanced placental oxidative stress.[30] Prenatal $PM_{2.5}$ levels have also been associated with significantly lower mitochondrial DNA content in cord blood.[31] Placental 3-nitrotyrosine (3-NTp), 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 PM_{10} prior to delivery has been associated with elevated fetal C-reactive protein, a marker of systemic inflammation.[33] Psychosocial stress during pregnancy may also disrupt maternal systems like the hypothalamic-pituitary-adrenocortical (HPA) axis, the sympathetic-adrenal-medullary system and immunomodulation which may lead to a potentiation of the fetal immune system through the upregulation of maternal and fetoplacental cytokine or IgE production.[34, 35]

Previous research has demonstrated variability in downstream effects like 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 pseudo-glandular stage of fetal lung development. During this period budding and 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 can hypothesize that early toxicant exposure may impact 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 in order to better elucidate windows of susceptibility to these exposures.

Strengths of our study include the prospective design and a validated spatio-temporal 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 measure 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 in understudied population in Mexico City. We were also able to adjust for important covariates like 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 larger-sized epidemiological studies[38, 39] and this was assessed using a standardized measure 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 both chemical and non-chemical stressors together in order 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 age 4 years, particularly if their mothers also experienced more toxic levels of stress prenatally. Knowledge of interactions between chemical and non-chemical environmental toxins can better inform prevention and intervention strategies that may preclude persistence of symptoms or lung function deficits in later childhood. For example, these findings suggest that interventions aimed at reducing prenatal stress could mitigate the effects of chemical toxins such as air pollution which may 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 as well as her developing child. Notably, the modifying effect of stress considered women who were above the median as high stress compared to those below the median. This underscores that interventions do not need to eliminate stress altogether but rather they should be designed to reduce 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

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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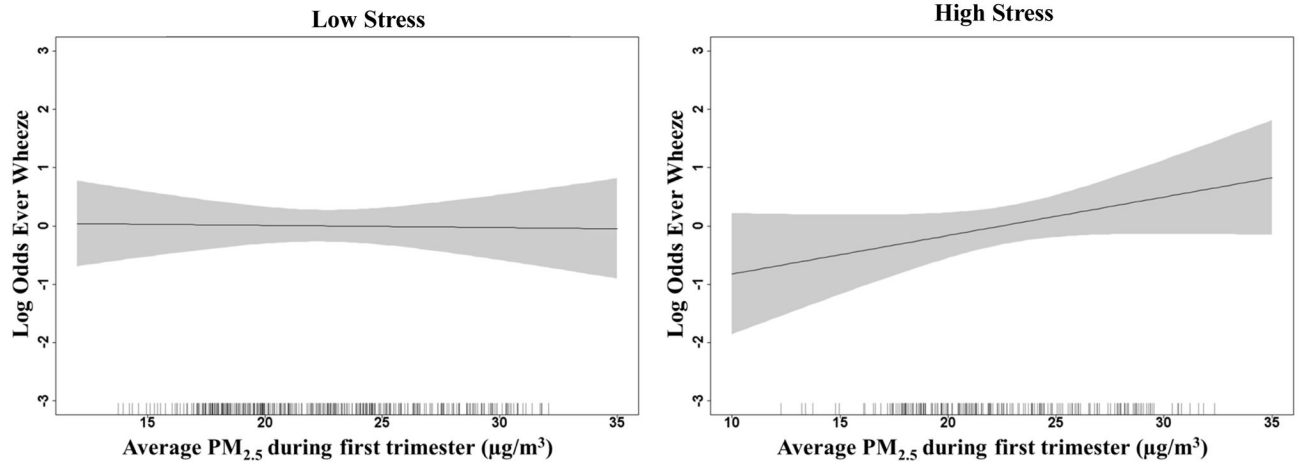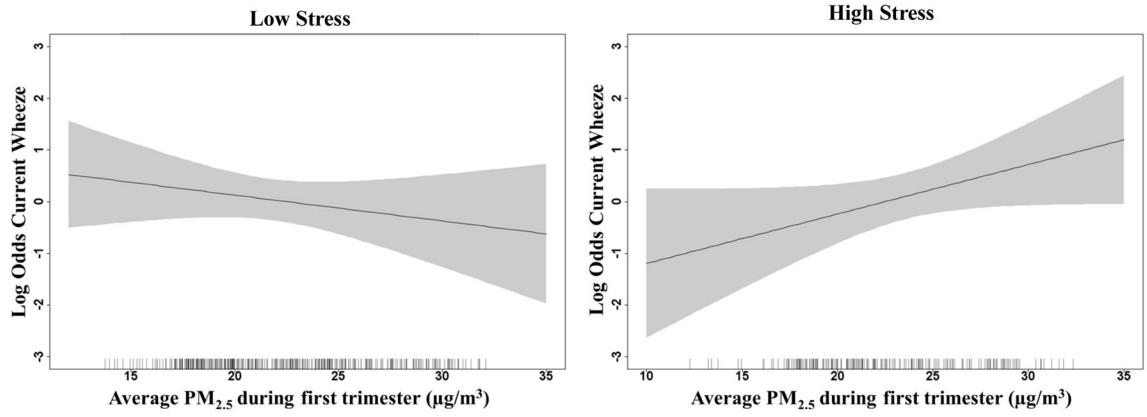
Low Stress   **High Stress**

Figure 1.

Figure 2.

Table 1

Sample characteristics

Characteristic	Overall n=552	Low Stress (3) n=349	High Stress (>3) n=203	p-value[a]
Male sex, n (%)	279 (51)	168 (48)	111 (55)	0.14
Maternal asthma, n (%)	7 (1.2)	5 (1.4)	2 (1.0)	0.65
Prenatal ETS, n (%)	202 (37)	114 (33)	88 (43)	
Postnatal ETS, n (%)	79 (14)	48 (14)	31 (15)	0.62
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)	0.65
Average 1st trimester $PM_{2.5}\mu g/m^3$, median (IQR)	22.0 (18,9, 25.7)	22.2 (18.9, 25.6)	21.6 (18.9, 25.9)	0.99
Average 2nd trimester $PM_{2.5}\mu g/m^3$, median (IQR)	21.1 (18.8, 25.6)	21.0 (18.6, 25.4)	21.2 (19.2, 25.7)	0.23
Average 3rd trimester $PM_{2.5}\mu g/m^3$, median (IQR)	22.5 (19.0, 27.3)	22.7 (18.8, 27.3)	22.2 (19.1, 27.2)	0.68
Ever wheeze, n (%)	136 (25)	77 (22)	59 (29)	0.07
Current wheeze, n (%)	66 (12)	35 (10)	31 (15)	0.07

Abbreviations: ETS, Environmental tobacco smoke; IQR, interquartile range; $PM_{2.5}$, particulate matter 2.5 microns and less in diameter.

[a] Differences in categorical variables tested using Fisher's Exact test or Pearson Chi-Square test. Differences in continuous variables tested using Mann Whitney U test.

Table 2

Interaction models and stress-stratified associations between prenatal $PM_{2.5}$ concentrations and wheeze outcomes and RRs shown for an average pregnancy IQR (3.8 μg/m^3) increase in $PM_{2.5}$. Models adjusted for child's sex, maternal asthma, maternal age at delivery, prenatal ETS exposure, ETS exposure at 48 months of age, other trimester $PM_{2.5}$ concentrations and postnatal year 1 average $PM_{2.5}$.

	RR (95% CI)		
	Low Stress (≤3) Stratum N=349	High Stress (>3) Stratum N=203	Combined data N=552
			p-value for interaction between $PM_{2.5}$ and stress
Ever Wheeze			
1st trimester $PM_{2.5}$	0.99 (0.83, 1.18)	1.18 (0.97, 1.43)	0.19
2nd trimester $PM_{2.5}$	0.92 (0.76, 1.12)	1.06 (0.85, 1.32)	0.32
3rd trimester $PM_{2.5}$	0.96 (0.82, 1.13)	0.94 (0.78, 1.15)	0.66
Current wheeze			
1st trimester $PM_{2.5}$	0.84 (0.61, 1.16)	1.35 (1.00, 1.83)	0.04
2nd trimester $PM_{2.5}$	0.74 (0.54, 1.04)	0.99 (0.71, 1.38)	0.22
3rd trimester $PM_{2.5}$	0.96 (0.74, 1.26)	0.83 (0.61, 1.13)	0.28

Abbreviations: CI, confidence interval; RR, relative risk.