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Maternal exposure to $PM_{2.5}$ during pregnancy and asthma risk in early childhood

Consideration of phases of fetal lung development

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Background: Increasingly studies suggest prenatal exposure to air pollution may increase risk of childhood asthma. Few studies have investigated exposure during specific fetal pulmonary developmental windows.
Objective: To assess associations between prenatal fine particulate matter exposure and asthma at age 4.
Methods: This study included mother–child dyads from two pregnancy cohorts—CANDLE and TIDES—within the ECHO-PATHWAYS consortium (births in 2007–2013). Three child asthma outcomes were parent-reported: ever asthma, current asthma, and current wheeze. Fine particulate matter ($PM_{2.5}$) exposures during the pseudoglandular (5–16 weeks gestation), canalicular (16–24 weeks gestation), saccular (24–36 weeks gestation), and alveolar (36+ weeks gestation) phases of fetal lung development were estimated using a national spatiotemporal model. We estimated associations with Poisson regression with robust standard errors, and adjusted for child, maternal, and neighborhood factors.
Results: Children (n = 1,469) were on average 4.3 (SD 0.5) years old, 49% were male, and 11.7% had ever asthma; 46% of women identified as black and 53% had at least a college/technical school degree. A 2 $\mu g/m^3$ higher $PM_{2.5}$ exposure during the saccular phase was associated with 1.29 times higher risk of ever asthma [95% confidence interval (CI): 1.06, 1.58]. A similar association was observed with current asthma (risk ratio 1.27, 95% CI: 1.04, 1.54), but not current wheeze (risk ratio 1.11, 95% CI: 0.92, 1.33). Effect estimates for associations during other developmental windows had CIs that included the null.
Conclusions: Later phases of prenatal lung development may be particularly sensitive to the developmental toxicity of $PM_{2.5}$.

Keywords: Air pollution; Particulate matter; Child asthma; $PM_{2.5}$; prenatal; Developmental Origins of Health and Disease

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Introduction

The prenatal period is a critical exposure window when the developing respiratory and immune systems are susceptible to damaging impacts of environmental toxicants. Several reviews have suggested adverse effects of prenatal exposure to nitrogen dioxide (NO_2) and particulate matter less than 10 μm in diameter (PM_{10}) on child airway health, though notable limitations, including suboptimal exposure assessment, were identified.[1,2] More recent studies found an increased risk of childhood asthma with elevated prenatal fine particulate matter ($PM_{2.5}$) exposure.[3–5] The mechanisms through which air pollution may contribute to the development of asthma include increased maternal systemic inflammation, endothelial changes, and oxidative stress; reduced placental growth and nutrient transport; epigenetic changes; and direct effects of particles crossing the placental barrier.[2] Factors that may amplify risk have been identified, including male fetal sex, maternal history of asthma, and high prepregnancy body mass index (BMI).[3,4,6,7]

What this study adds

We investigated the relationship between maternal exposure to air pollution during pregnancy and early childhood asthma risk in a large, diverse multicity US sample. We used a novel approach to estimate prenatal exposure to $PM_{2.5}$ during well-recognized windows of key fetal lung developmental phases. Prenatal air pollution exposure was associated with a higher risk of child asthma in early childhood and our results suggest that the saccular phase (24–36 weeks gestation) may be a critical window for exposure. Furthermore, these adverse associations were observed at fairly low concentrations, within current regulatory thresholds for ambient air.

To date, studies have largely assessed exposures as averages within trimesters or across the whole pregnancy period. Maturational phases with distinct morphological lung development are well recognized: terminal bronchioles are formed during the pseudoglandular phase; the canalicular phase includes distal airway formation, differentiation of epithelial cells, angiogenesis, and vascular development; formation of terminal sacs, thinning of the alveolar walls, and maturation of the pulmonary surfactant system occur during the saccular phase; and alveolarization and microvasculature maturation occur during the prenatal alveolar phase.[8] However, such developmentally relevant windows of vulnerability have not been explicitly examined in previous studies of $PM_{2.5}$ and pediatric lung health.

We utilized finely spatiotemporally resolved exposures to examine associations between exposure to $PM_{2.5}$ during established morphogenic phases of prenatal lung development and child asthma in 2 pregnancy cohorts.

Methods

Study population

The sample of participants included in this analysis was drawn from two pregnancy cohorts of the ECHO-PATHWAYS consortium: (1) the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study and (2) The Infant Development and the Environment Study (TIDES). CANDLE study procedures were approved by the University of Tennessee Health Science Center Institutional Review Board (IRB), TIDES study procedures were approved by IRBs at each local institution, and all ECHO-PATHWAYS research activities were approved by the University of Washington IRB.

The CANDLE cohort is located in Memphis, TN; women were recruited from an urban hospital obstetric clinic, community obstetric practices, and general community recruitment in 2006–2011 during the second trimester of pregnancy.[9] The original aim of this cohort was to identify early-life determinants of neurocognitive development and eligibility criteria included planning to deliver at 1 of 5 hospitals in Memphis, age 16–40 years, residence in Shelby County, and having a low-medical-risk pregnancy at enrollment. Mother–child pairs were followed up at regular intervals, including a clinic visit at age 4–6 years.

TIDES is a pregnancy cohort with four sites across the United States, in San Francisco, CA; Minneapolis, MN; Rochester, NY; and Seattle, WA.[10] Women were recruited in 2010–2012 during the first trimester of pregnancy from obstetrical clinics affiliated with academic medical centers. The initial aim of this cohort was to examine associations of prenatal phthalate and other environmental chemical exposures with early life reproductive development. Inclusion criteria included being at least 18 years old, planning to deliver at one of the study hospitals, and having a low-medical-risk pregnancy at enrollment. Mother–child pairs were followed up with questionnaires and a clinic visit at age 4 years.

Participants were included in this analysis if they completed questions relating to child asthma and wheeze at the age 4–6 study visits and had a valid geocoded address at enrollment. Preterm births (<37 weeks gestation, n = 153) were excluded because preterm birth is a strong risk factor for the development of asthma and because we were interested in assessing risk associated with maternal exposure through the later weeks of fetal lung development.

Prenatal air pollution exposures

The primary exposure of interest, fine particulate matter ($PM_{2.5}$), was estimated at each participant's enrollment address using a national spatiotemporal model.[11] Briefly, the model uses pollutant concentration data from over 900 research monitors and 1500 regulatory agency monitors across the United States, as well as satellite-derived $PM_{2.5}$ measurements, and a large (>200) suite of geographic covariates. This modeling approach accounts for complex spatiotemporal dependencies in a land use and spatial smoothing framework, and produces 2-week average pollutant concentrations at the geospatial point for each participant residential address, following principles described previously.[12,13] The 2-week $PM_{2.5}$ concentrations were averaged across 4 prenatal phases of lung development: the pseudoglandular (5–16 weeks gestation), canalicular (16–24 weeks gestation), saccular (24–36 weeks), and alveolar (36+ weeks gestation) phases. This approach, defining exposure windows by fetal lung developmental phases, was specified *a priori*. In sensitivity analyses, exposures were averaged across each trimester of pregnancy and over the entire pregnancy period for comparison with prior literature. In further sensitivity analyses, an estimate of postnatal exposure, defined as $PM_{2.5}$ concentrations averaged over the year before the age 4 study visit at the single address that was reported at the age 4 study visit, was included as a covariate.

Child airway outcomes

Child asthma was reported via the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire and other study questionnaires that assessed respiratory health at the age 4–6 study visit in each cohort.[14,15] The primary outcome, ever asthma, reflected an affirmative response to the question "Has your child ever had asthma?" Two secondary outcomes were also examined: current wheeze and current asthma. Current wheeze was defined as an affirmative response to "Has your child had wheezing or whistling in the chest in the last 12 months?" Current asthma was defined as having at least 2 of the following 3: ever asthma, current wheeze, and asthma-specific medication use. To maximize the use of available data, participants who were missing data for asthma-specific medication use and did not indicate yes to both ever asthma and current wheeze questions were considered not to have current asthma. In CANDLE, asthma medication use was defined as an affirmative response to the question "In the past 12 months has your child used any medications for asthma or wheeze?" In TIDES, free-text responses reporting any serious health conditions (asthma or asthma symptoms) and medications for those conditions (beta-2-agonist or an inhaled or oral corticosteroid) in the prior 24 months were used to define asthma medication use.

Covariates

Confounders were selected *a priori* based on literature review. Maternal characteristics included age at delivery (years), race (Black/African-American or other), education (less than high school, high school degree, graduated college or technical school, or some graduate work or a graduate or professional degree), history of asthma (yes/no asked at the age 4–6 year visit), prepregnancy BMI (kg/m^3), maternal report of smoking during pregnancy (yes/no), and prior live births (0 or 1+). Characteristics of the household during the postnatal period included the secondhand smoke exposure in the household (yes/no) and dog or cat in the household (yes/no), assessed at age 4. Neighborhood socioeconomic conditions were included as the Childhood Opportunity Index socioeconomic subscale at the census tract level for the enrollment address.[16] Date of birth was modeled as cubic splines with 1 degree of freedom per year. Season of birth was also included as an indicator variable, defined as either cold (October through March) or warm (April through September) season. An indicator term for the study site was also included as a proxy for unmeasured confounders that likely vary strongly by site.

Statistical analysis

Study sample characteristics were explored using descriptive statistics. We examined correlations between each of the $PM_{2.5}$ exposures using Pearson correlations. For associations between prenatal air pollution and child airway outcomes, Poisson regression with robust standard errors was used to estimate the risk ratio (RR). A minimally adjusted model included study site, child age and sex, a cold versus warm season indicator for date of birth, and cubic splines with 1 degree of freedom per year based on the date of birth. The fully adjusted main model additionally included maternal age at delivery, race, education, maternal history of asthma, prepregnancy BMI, prenatal smoking, and parity; child exposure to secondhand smoke and pets in the home; and neighborhood opportunity index. Effect modification by child sex, maternal history of asthma, and prepregnancy BMI were each separately tested using a multiplicative interaction term.

Sensitivity analyses included estimation of RRs based on exposure to $PM_{2.5}$ by trimester (1–13, 14–27, and 28+ weeks, separately) to facilitate comparisons with the existing literature. To assess potential confounding by $PM_{2.5}$ exposure during other prenatal and postnatal time periods, we conducted several sensitivity analyses. We used a mutually adjusted model in which exposures during all prenatal fetal lung developmental phases were included in the same model. We also adjusted the primary models for postnatal exposure, estimated as the average across the year prior to outcome assessment. Additionally, we used a series of exploratory constrained distributed lag models with 2-week $PM_{2.5}$ exposures across the entire prenatal period and either 4 or 5 degrees of freedom in the splines for the lag effect in each model.[17] To further examine the robustness of the results, we also performed sensitivity analyses by removing portions of the analytic sample based on region of residence. We ran 6 iterations of the analysis of $PM_{2.5}$ exposures, with participants from each of the cities and cohorts left out of each analysis in turn. We also ran a set of sensitivity analyses to examine the impact of covariate adjustment. A reduced model was run without adjustment for study site, season, or splines for date of birth. A second reduced model was run without adjustment for the covariates assessed at the time of the outcome assessment: secondhand smoke exposure and pets in the home. In extended models, exact gestational age at birth and birthweight were each added as covariates because these could be on the causal pathway. All analyses were conducted in R 3.6 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1.

Characteristics of the study population (N = 1,469)

	Pooled sample[a]	
Maternal age (years), mean (SD)	28.1	(5.8)
Maternal education, n (%)		
Less than high school	142	(10)
High school completion	545	(37)
College or technical school degree	446	(30)
Some graduate work or graduate/professional degree	332	(23)
Maternal race, n (%)		
Black/African American	669	(46)
White or other	795	(54)
Maternal history of asthma, n (%)		
Yes	240	(17)
No	1212	(83)
Prior live births, n (%)		
1+	824	(56)
0	639	(44)
Prepregnancy BMI, mean (SD)	27.3	(7.4)
Prenatal smoking, n (%)		
Yes	115	(8)
No	1349	(92)
Postnatal secondhand smoke, n (%)		
Yes	328	(23)
No	1098	(77)
Pets in the home, n (%)		
Yes	654	(45)
No	811	(55)
Child sex, n (%)		
Male	718	(49)
Female	751	(51)
Child airway outcomes		
Ever asthma, n (%)		
Yes	172	(11.7)
No	1292	(88.3)
Current wheeze, n (%)		
Yes	229	(15.6)
No	1236	(84.4)
Current asthma,[b] n (%)		
Yes	178	(12.1)
No	1291	(87.9)

[a]Number missing for individual variables include: education (4), maternal race (5), maternal history of asthma (17), prior live birth (6), prepregnancy BMI (5), prenatal smoking (5), postnatal smoke exposure (43), and pets in the home (4).

[b]In TIDES, reported asthma medications in a free-text response that were used to define current asthma included Albuterol, Q-Var, Flovent, Pulmicort, Ventolin, Advair, Dulera, prednisone, steroids, inhaler, and/or nebulizer.

Results

In this pooled analytic sample (n = 1,469 in Table 1; n = 1,009 in CANDLE and n = 460 in TIDES in Table S1; http://links.lww.com/EE/A117), 53% of the women had at least a college or technical school degree and 46% identified as Black or African-American; 49% of children were male and 11.7%, 15.6%, and 12.1% were defined as having ever asthma, current wheeze, or current asthma, respectively.

City-specific mean (SD) $PM_{2.5}$ concentrations across pregnancy ranged from 5.3 (0.9) $\mu g/m^3$ in Seattle, WA to 10.7 (0.9) $\mu g/m^3$ in Memphis, TN (Table 2). Eighty-nine percent of all observations were below 12 $\mu g/m^3$, the current standard for annual average exposures in the United States.[18] Exposures during prenatal periods closer in time or during overlapping windows were more correlated with each other than those further apart (Table S2; http://links.lww.com/EE/A117).

Associations are reported per 2 $\mu g/m^3$ higher $PM_{2.5}$, which is approximately the interquartile range of exposure averaged across pregnancy in this sample. In the primary analysis (Figure 1), we observed an elevated risk of ever asthma with 2 $\mu g/m^3$ higher $PM_{2.5}$ exposure during the saccular period [RR 1.29, 95% confidence interval (CI): 1.06, 1.58]. A similar association with $PM_{2.5}$ during the saccular period was observed for current asthma (RR 1.27, 95% CI: 1.04, 1.54), but not for current wheeze (RR 1.11, 95% CI: 0.92, 1.33). Effect estimates for earlier in pregnancy during the pseudoglandular phase tended to be less than one, although the CIs included the null. Effect estimates for the canalicular and alveolar periods tended to be greater than one, suggesting an adverse association between air pollution and child asthma, though confidence intervals for these estimates also included the null. When exposures were averaged across the entire pregnancy, adverse associations were observed for the ever asthma and current asthma outcomes, although the confidence intervals were wide and included the null (Table S3; http://links.lww.com/EE/A117).

No effect modification by child sex or prepregnancy BMI was observed (Figure 2 and Figure S1; http://links.lww.com/EE/A117). Associations between $PM_{2.5}$ during the saccular phase and ever asthma were observed among children without a maternal history of asthma (RR 1.42, 95% CI: 1.14, 1.76), whereas no evidence of an association was observed among those with maternal history of asthma (RR 1.00, 95% CI: 0.72, 1.39; $P_{interaction} = 0.05$; Figure 3). Similar patterns of interaction by maternal asthma history, with associations between

Table 2.

Mean (SD) of $PM_{2.5}$ exposures (μg/m³) during each fetal lung development window, overall and by city

$PM_{2.5}$ exposure window	Full cohort (n = 1,469)		Memphis, TN (n = 1,009)		San Francisco, CA (n = 125)		Minneapolis, MN (n = 128)		Rochester, NY (n = 117)		Seattle, WA (n = 90)	
Pseudoglandular phase: 5–16 weeks	9.71	(2.12)	10.54	(1.50)	8.93	(2.01)	8.65	(1.60)	7.95	(1.36)	5.25	(1.58)
Canalicular phase: 16–24 weeks	9.78	(2.23)	10.64	(1.57)	8.75	(2.51)	8.58	(1.47)	8.23	(1.71)	5.32	(1.88)
Saccular phase: 24–36 weeks	9.87	(2.18)	10.80	(1.52)	8.82	(2.08)	8.27	(0.94)	8.08	(1.22)	5.40	(1.78)
Alveolar phase: 36+ weeks	9.94	(2.62)	10.80	(2.13)	9.25	(2.93)	8.57	(1.91)	8.34	(1.67)	5.30	(1.97)
Entire pregnancy	9.81	(1.75)	10.68	(0.91)	8.96	(1.36)	8.51	(0.62)	8.05	(0.78)	5.33	(0.91)

$PM_{2.5}$ during the saccular phase and child asthma found only within the group without maternal history of asthma, were also observed for current asthma ($RR_{\text{no maternal asthma}}$ 1.41, 95% CI: 1.13, 1.75; $RR_{\text{with maternal asthma}}$ 0.95, 95% CI: 0.67, 1.36; $P_{\text{interaction}}$ = 0.04) and current wheeze ($RR_{\text{no maternal asthma}}$ 1.19, 95% CI: 0.98, 1.45; $RR_{\text{with maternal asthma}}$ 0.89, 95% CI: 0.66, 1.20; $P_{\text{interaction}}$ = 0.07).

When models included mutual adjustment for all prenatal windows or for postnatal $PM_{2.5}$ exposure, results for the current asthma and current wheeze outcomes were similar to those obtained in the primary analysis (Table S3; http://links.lww.com/EE/A117). In particular, the effect observed for exposure during the saccular phase and current asthma in the mutually adjusted model remained similar to that in the primary analysis (RR 1.27, 95% CI: 1.01, 1.60), whereas the association was slightly attenuated for ever asthma (RR 1.24, 95% CI: 0.99, 1.55). When adjusted for postnatal exposure, effect estimates for ever asthma and current asthma remained consistent with the primary analysis (RR 1.25, 95% CI: 1.01, 1.54 and RR 1.33, 95% CI: 1.08, 1.63, respectively). In additional sensitivity analyses using trimester-specific exposure windows, $PM_{2.5}$ during the third trimester was associated with a higher risk of ever asthma and a lower risk of current wheeze was observed for exposure during the first trimester (Table S3; http://links.lww.com/EE/A117).

We conducted another set of sensitivity analyses in which covariates were either removed from or added to the model to assess the impact of adjustment for those covariates (Table S4; http://links.lww.com/EE/A117). Removal of site, season, and year of birth resulted in larger estimates of adverse associations with all 3 airway outcomes for all developmental phases. Removing covariates assessed at the age 4 study visit (secondhand smoke exposure and pets in the child's home) did not substantively change the results. In extended models that additionally adjusted for birthweight or exact gestational age at birth, results for the saccular phase were similar to those from the primary models.

Excluding participants at any one of the TIDES sites from the analysis did not alter the results (Table S5; http://links.lww.com/EE/A117). When Memphis (all CANDLE participants) was excluded, effectively restricting the analysis to the TIDES cohort, estimates for exposure during each fetal lung development period are null. When we excluded all 4 TIDES sites at the same time, we observed larger point estimates for associations between exposure in the saccular period and the ever asthma and current asthma outcomes in the CANDLE cohort (ever asthma RR 1.36, 95% CI: 1.10, 1.67; current asthma RR 1.35, 95% CI: 1.09, 1.66).

Discussion

This study implemented a novel developmental biology-informed approach to investigate prenatal developmental windows of susceptibility to air pollution. In this pooled analysis of two pregnancy cohorts, higher exposure to $PM_{2.5}$ during the saccular phase of fetal lung development was associated with a higher risk of asthma. These associations were stronger among those without a maternal history of asthma. We did not observe differences in these associations by child sex or pre-pregnancy BMI.

Only a small number of prior studies have investigated multiple prenatal exposure windows when estimating associations with child asthma. Hsu et al., using a data-driven, hypothesis generating approach examining weekly exposures throughout pregnancy in a cohort of 736 children in Boston, MA, found that an increase of 10 μg/m³ prenatal $PM_{2.5}$ exposure during weeks 16–25 of pregnancy was associated with child asthma.[4]

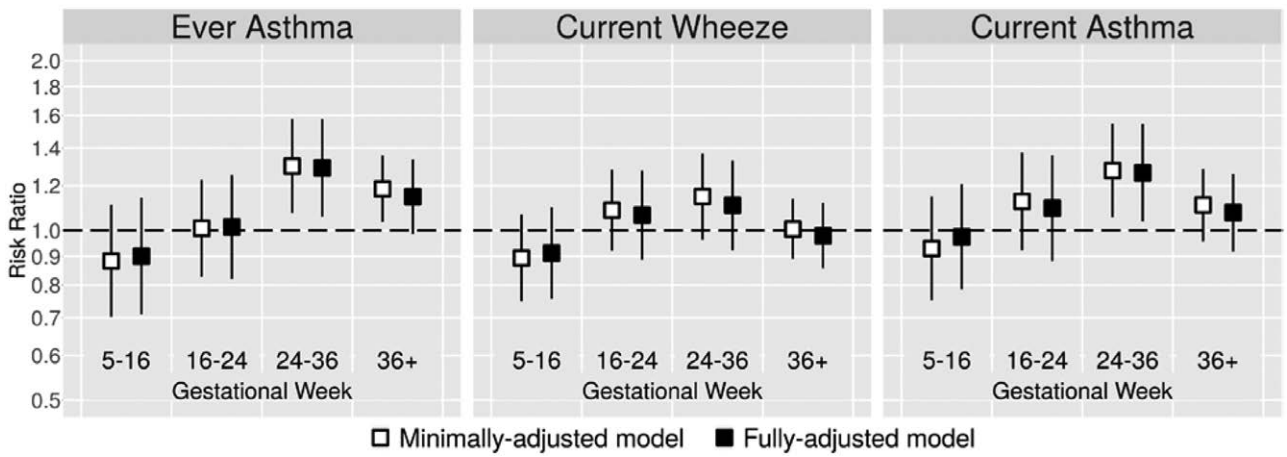

Figure 1. Associations between prenatal $PM_{2.5}$ exposure during phases of fetal lung development and child asthma at age 4. Risk ratios (95% confidence intervals) per 2 μg/m³ higher $PM_{2.5}$ exposure during each window. Fully adjusted models included child age, sex, birth in warm versus cold season, cubic splines for date of birth (1 degree of freedom/year), study site, maternal age, maternal race, maternal education, prepregnancy BMI, prenatal smoking, parity, postnatal secondhand smoke, pets in the home, and Childhood Opportunity Index.

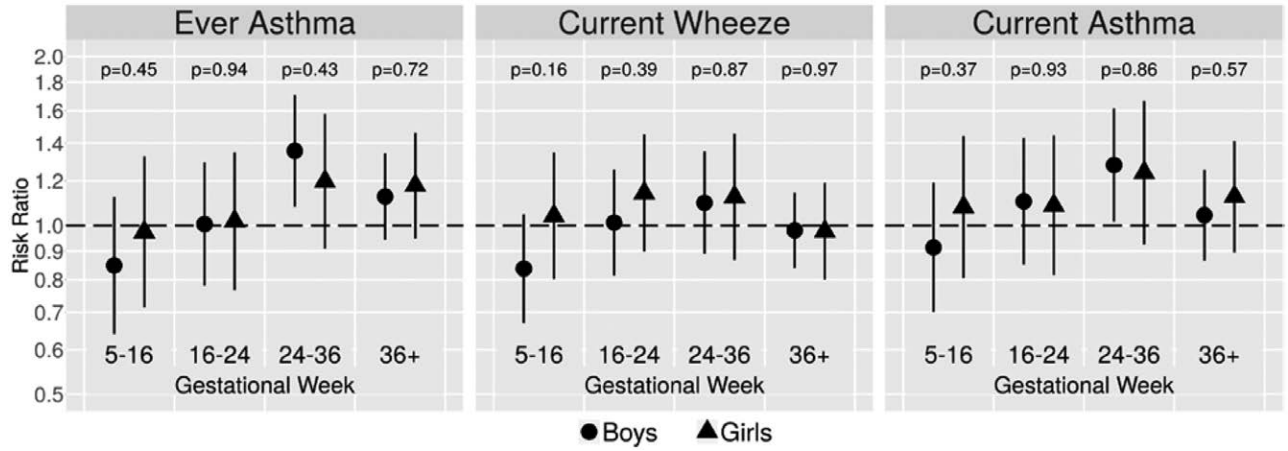

Figure 2. Sex-specific associations between prenatal $PM_{2.5}$ exposure during phases of fetal lung development and child asthma at age 4. Risk ratios (95% confidence intervals) shown for a 2 μg/m³ higher $PM_{2.5}$ exposure during each phase of fetal lung development. Models include child age, birth in warm versus cold season, cubic splines for date of birth (1 degree of freedom/year), study site, maternal age, maternal race, maternal education, prepregnancy BMI, prenatal smoking, parity, postnatal secondhand smoke, pets in the home, Childhood Opportunity Index, sex, and a multiplicative interaction term for $PM_{2.5}$ by sex. *P* values are shown for the multiplicative interaction term. No statistically significant effect modification by child sex was observed.

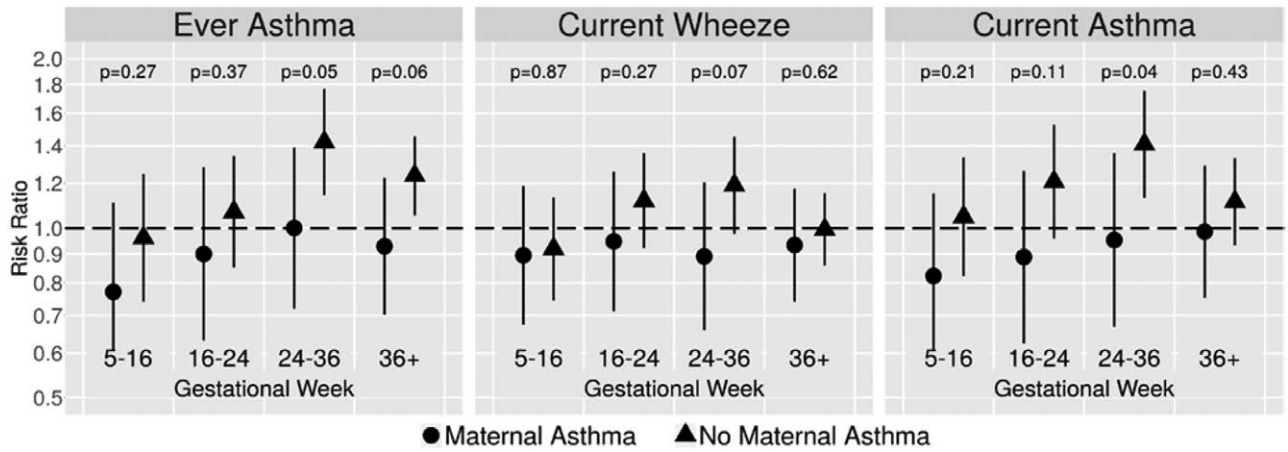

Figure 3. Effect modification of associations (risk ratios and 95% confidence intervals) between prenatal $PM_{2.5}$ exposure during fetal lung developmental windows and child airway outcomes at age 4, by maternal history of asthma. Risk ratios (95% confidence intervals) shown for a 2 μg/m³ higher $PM_{2.5}$ exposure during each phase of fetal lung development. Models are adjusted for child age, sex, birth in warm versus cold season, cubic splines for date of birth (1 degree of freedom/year), study site, maternal age, maternal race, maternal education, prepregnancy BMI, prenatal smoking, parity, postnatal secondhand smoke, pets in the home, and Childhood Opportunity Index. *P* values are shown for the multiplicative interaction term between $PM_{2.5}$ and maternal history of asthma.

These weeks correspond to the canalicular stage of lung morphological development. Median $PM_{2.5}$ exposure in this Boston cohort (11.2 μg/m³) was slightly higher than in our multicity cohort. In a Canadian cohort with lower average exposure (mean 7.3 μg/m³), assessing $PM_{2.5}$ exposure by trimester similarly suggested an increased susceptibility to exposures during mid-gestation. A hazard ratio for child asthma diagnosis of 1.04 (95% CI: 1.03, 1.05) was observed per 2 μg/m³ higher second trimester $PM_{2.5}$ exposure.[6]

However, not all prior work has identified the same critical window. Nitrate, a specific component of $PM_{2.5}$, during weeks 7–19 and 33–40 was found to be associated with child asthma in the same Boston cohort that observed an association with total $PM_{2.5}$ during mid-gestation.[19] In another cohort with higher levels of $PM_{2.5}$ (mean 36.2 μg/m³), associations with child asthma were observed per 10 μg/m³ higher exposures during gestational weeks 6–22, which includes portions of both the pseudoglandular and canalicular phases.[5] A study in Mexico City found an increased risk of child wheeze (RR 1.17, 95% CI: 1.00, 1.37) per 2 μg/m³ higher $PM_{2.5}$ during the first trimester, only among those also reporting high levels of maternal stressors.[20] Variability across studies may be attributed to numerous factors, including exposure levels, source contribution and related composition of PM, exposure assessment methods, and cohort characteristics.

Several mechanisms have been hypothesized for the effect of prenatal ambient air pollution exposures on fetal growth and development. Particulate matter may impact fetal morphological and immune system development through systemic inflammation and oxidative stress.[2] The accumulation of black carbon particulates on the fetal side of the placenta has also been identified, suggesting the potential for direct effects of these particles.[21]

Our study advances prior literature by utilizing exposure windows for $PM_{2.5}$ defined *a priori* based on phases of fetal lung development.[22,23] This approach improves upon prior trimester-based analyses, which may bias estimates when the developmental processes involved straddle trimesters. Based on findings reported in Hsu et al.,[4] we had hypothesized that the canalicular phase may be sensitive to air pollution exposures. Effects during early pregnancy might suggest an impact of pollutants

on branching morphogenesis.[2] Results from the current study, however, suggest that exposure windows later in pregnancy may be important. One explanation for this result may be related to the role of the immune system in the development of asthma. Some epidemiologic work supports the hypothesis that air pollution impacts immune system development based on observed alterations in several biomarkers, including epithelial cell derived cytokines and lymphocytes.[24,25] Herr et al.[26] identified months 6 and 7 of pregnancy as a critical window for associations between $PM_{2.5}$ and elevated cord serum total IgE, a measure of infant atopy and a strong risk factor for asthma. Much of immune development occurs later in gestation,[27] which may explain why we see increased risk with higher $PM_{2.5}$ exposures during later pregnancy if exposure is operating more significantly through disruptions to immune development compared with morphological airway development.

In an exploratory sensitivity analysis, we used a distributed lag model similar to several prior studies of prenatal $PM_{2.5}$ exposure (Figure S2; http://links.lww.com/EE/A117). However, the critical window identified using this approach changed when minor changes in the model specification were made and this instability suggests that these models should be interpreted cautiously. These sensitivity analyses did allay concern regarding cross-period confounding because even in the case where we observed an association in a different window in the distributed lag model than in our primary analysis, the critical window identified was entirely contained within a single fetal lung development phase. Had this association spanned more than one of the predefined exposure windows, we might then be concerned about confounding by other prenatal exposures; our sensitivity analyses do not provide evidence for this specific type of confounding.[28] For both current wheeze and current asthma outcomes, apparent protective associations were observed for exposures at the beginning of the prenatal period in several sensitivity analyses. Such effects may indicate selection bias in pregnancy cohorts such as this one, in which participants were enrolled in the study during mid-pregnancy.[29] Such bias may arise because inclusion in an analysis of a postnatal outcome is conditioned on live birth, which may result in the selection of a group in which those with higher exposure to air pollution have potentially lower susceptibility to the effects of other risk factors compared with those with lower air pollution exposures. Prior studies of other pediatric health outcomes diagnosed during childhood suggest this type of bias may result in inconsistent protective associations with air pollution exposure in early pregnancy.[30]

Limited prior evidence suggests an interaction between maternal history of asthma and prenatal air pollution. Maternal asthma may impact fetal development through impaired respiratory function, alteration of immune responses, or epigenetic pathways.[31] These effects may result in a synergistic elevation of asthma risk with air pollution exposure, or alternatively, the increase in risk due to air pollution may be small relative to the contribution of genetic factors. Prior studies have observed associations only among children of women without asthma, whereas others have found associations only among children of women with a history of asthma.[6,26] In our study, we observed significant effects of particulate matter only among the group without a maternal history of asthma. Women with more severe or poorly controlled asthma may possibly be more likely to modify their behaviors (reduce outdoor time, use air filters in their homes) or the contribution of air pollution may be relatively small compared to genetic factors. However, the small sample size in the group with a maternal history of asthma (N = 240) also limits interpretation of these results.

Pooling across 2 cohorts provides several important analytic advantages in this study, including increased power both in the main analysis as well as in several subgroup analyses of interest, by child sex, maternal asthma history, and prepregnancy BMI. Additionally, pooling produces a more heterogeneous sample and improves generalizability. In this study, sensitivity analyses suggest that the associations observed with exposure during the saccular period appear to be driven by the CANDLE sample, which is expected given that CANDLE participants comprise a majority of the pooled sample. The lack of evidence of an association when restricted to the TIDES sites may suggest a difference in susceptibility between the 2 populations. For example, prior work has identified associations between air pollution and child asthma only among women reporting high levels of stress during pregnancy and not among women reporting lower levels of stress.[3,19,20] Exposure concentrations were also higher on average for CANDLE participants and furthermore, the toxicity of $PM_{2.5}$ may also differ by geography due to variation in the composition and sources of $PM_{2.5}$ across the United States.[32] The decreased precision and null results observed in TIDES may simply be due to the reduced sample size or alternatively the findings in CANDLE may be due to Type 1 error.

Further sensitivity analyses, in which we removed adjustment for site and time, resulted in shifted point estimates consistent with adverse associations across all exposure windows. The width of the confidence intervals was only slightly narrower in these reduced models compared with the primary analysis. The changes in effect estimates in this sensitivity analysis support the inclusion of study site and time in primary models to address confounding, while consistency in the confidence intervals suggests a minimal loss of precision when reducing the exposure variability by including site and time as covariates.

Our study had several limitations. As is common in ambient air pollution research, we were unable to account for indoor exposures or exposures beyond the primary residence. The prenatal residential history was limited to a single address per participant, ascertained at enrollment during the second trimester in CANDLE and at enrollment during the first trimester in TIDES. Particularly in TIDES, this may result in exposure misclassification and an attenuated effect estimate due to participants moving between enrollment earlier in pregnancy and the saccular period. Furthermore, even in mutually adjusted models it is difficult to ascertain whether true effects are due to prenatal or postnatal exposures. We observed correlations between prenatal exposures during fetal lung development phases and the postnatal period (averaged over the year before airway outcome ascertainment exposures) that were between 0.54 and 0.65. Last, the measures of child asthma used in this study rely on maternal report rather than objective measures of asthma, such as measurement of obstruction or reversible airway reactivity. Furthermore, it can be challenging to diagnose asthma in young children. The clinical diagnosis in early life relies largely on symptom report consistent with recurrent episodes of airway obstruction which may overlap with nonasthma recurrent respiratory infection in early childhood. More objective measurements of airway hyperreactivity and obstruction using spirometry are difficult to conduct adequately in children before school age. Although there is no clear gold standard for defining asthma in early childhood, the ISAAC questionnaire is widely used in epidemiological studies of asthma and symptom based clinical history continues to be a core component of clinical diagnosis of early childhood asthma.[33]

Our study contributes to the existing literature by examining this question in a large, multicity sample with detailed covariate information and exposures estimated from well-validated air pollution models. Specifically, this study addresses several limitations highlighted in reviews of previous literature on this topic, including coarse spatial and temporal resolution of prior exposure assessments and health effects models with minimal covariate adjustment.[1,2] Furthermore, results from this study suggest that health effects may be occurring with exposures below the current regulatory standards of the US Environmental Protection Agency.

Future work in the ECHO-PATHWAYS Consortium will include examining the relationships between prenatal air pollution and other metrics of airway health such as measurements of

lung function as children age into middle childhood time periods, investigating other pollutants such as NO_2 using a newly developed spatiotemporal model, and assessing effect modification by other prenatal social and environmental factors.

Conflict of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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The data utilized for this study are not publicly available but de-identified data may be available on request, subject to approval by the internal review board and under a formal data use agreement. Contact the corresponding author for more information.

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