ORIGINAL ARTICLE

Prenatal Particulate Air Pollution and Asthma Onset in Urban Children

Identifying Sensitive Windows and Sex Differences

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Abstract

Rationale: The influence of particulate air pollution on respiratory health starts *in utero*. Fetal lung growth and structural development occurs in stages; thus, effects on postnatal respiratory disorders may differ based on timing of exposure.

Objectives: We implemented an innovative method to identify sensitive windows for effects of prenatal exposure to particulate matter with a diameter less than or equal to 2.5 μm ($PM_{2.5}$) on children's asthma development in an urban pregnancy cohort.

Methods: Analyses included 736 full-term (⩾37 wk) children. Each mother's daily $PM_{2.5}$ exposure was estimated over gestation using a validated satellite-based spatiotemporal resolved model. Using distributed lag models, we examined associations between weekly averaged $PM_{2.5}$ levels over pregnancy and physician-diagnosed asthma in children by age 6 years. Effect modification by sex was also examined.

Measurements and Main Results: Most mothers were ethnic minorities (54% Hispanic, 30% black), had 12 or fewer years of education (66%), and did not smoke in pregnancy (80%). In the sample as a whole, distributed lag models adjusting for child age, sex, and maternal factors (education, race and ethnicity, smoking, stress, atopy, prepregnancy obesity) showed that increased $PM_{2.5}$ exposure levels at 16–25 weeks gestation were significantly associated with early childhood asthma development. An interaction between $PM_{2.5}$ and sex was significant ($P = 0.01$) with sex-stratified analyses showing that the association exists only for boys.

Conclusions: Higher prenatal $PM_{2.5}$ exposure at midgestation was associated with asthma development by age 6 years in boys. Methods to better characterize vulnerable windows may provide insight into underlying mechanisms.

Keywords: fine particulate matter; asthma; prenatal exposure; sensitive windows; sex difference

Toxic exposures in critical developmental windows may result in permanently altered changes in respiratory and interrelated systems (e.g., immune, autonomic, neuroendocrine) at the cellular, structural, and/or functional level that manifest in childhood disorders (e.g., asthma) (1, 2). The fetus is particularly vulnerable because of immature immune, neuroendocrine, and xenobiotic detoxification systems and antioxidant defenses (3–6). Prenatal development of the respiratory system is a multievent process progressing sequentially from early gestation (7), thus toxins may have variable impact depending on timing of exposure (1).

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At a Glance Commentary

Scientific Knowledge on the Subject: The influence of ambient fine particulate matter ($PM_{2.5}$) on respiratory health starts *in utero* and may be sex specific. Fetal lung growth and structural development occurs in stages. Thus, effects on early childhood respiratory disorders may differ based on timing of exposure, albeit the effect of exposure timing remains poorly understood in human studies.

What This Study Adds to the Field: This is the first study to leverage weekly $PM_{2.5}$ exposure estimates over gestation combined with data-driven statistics to characterize susceptibility windows, removing the subjectivity that currently guides the decision of when to assess exposure effects. These data demonstrate that increased prenatal $PM_{2.5}$ exposure at mid-gestation (16–25 wk gestation) was associated with asthma development by age 6 years in boys. A more definitive understanding of the temporal effects of *in utero* toxins on outcomes in early childhood may provide clues as to the underlying mechanisms being perturbed based on current understanding of the cellular differentiation, proliferation, or physiologic function changes occurring progressively over pregnancy that impact respiratory outcomes.

Air pollution exposure impacts the developing respiratory system, with evidence particularly implicating prooxidants, such as particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$). Epidemiologic studies link prenatal particulate air pollution with childhood wheeze, asthma, and altered lung function (4, 8–10). Animal studies link prenatal PM with cytokine disruption, increased IgE, impaired lung growth, and airway hyperresponsiveness in offspring (11–14). Gestational exposure to PM may enhance maternal systemic oxidative stress and proinflammatory cytokine production (15) resulting in placental and endothelial dysfunction, and increased fetal oxidative stress with consequent effects on fetal immune and lung development (7, 14, 16–18).

Human studies have not extensively elucidated sensitive windows, largely because of variable methods for exposure assignment and lack of temporal resolution. Epidemiologic studies have historically used more crude and less time resolved indices (e.g., "high polluted" vs. "low polluted" areas, levels at closest monitor, proximity to roads, traffic density), because it is cost prohibitive to collect repeated exposure data over pregnancy using personal monitoring (19–21). Thus studies have considered relatively arbitrary assignment of exposure windows (e.g., averaged over pregnancy, within clinically defined trimesters, personal monitoring at discrete time points) rather than being grounded in an understanding of developmental processes relevant to the respiratory system. Because the processes involved in programming respiratory outcomes do not necessarily occur within clinically defined trimesters and sensitive periods remain largely unknown (7), research that allows flexibility in identifying sensitive windows may be particularly informative. More recently developed approaches (e.g., spatiotemporal land-use regression [LUR], multiscale air quality deterministic chemistry models, and so forth) for deriving spatiotemporally resolved exposure profiles (22–24) allow researchers to estimate exposure patterns at a higher temporal resolution.

Overlapping animal and human research suggest that prenatal air pollution exposure may have sex-specific effects. Animal studies demonstrate sex differences in lung growth and airway development (25, 26). In humans, females display earlier fetal breathing and surfactant production, which may in part be the basis for the reduction in forced expiratory flow rates that predispose males to airway diseases in early childhood (27, 28). Prenatal air pollution induces fetal oxidative stress (29), and in turn influences gene expression and physiologic events crucial for lung maturation (30). Boys may be more vulnerable to prenatal oxidant injury (31) and thus may have an exaggerated response to *in utero* air pollution exposure.

To address these research gaps, we leveraged daily prenatal $PM_{2.5}$ measures available over pregnancy and applied advanced statistical methods (e.g., distributed lag models [DLMs]) to more precisely identify sensitive windows in relation to childhood asthma onset by age 6 years in an ethnically mixed lower socioeconomic status urban pregnancy cohort. Effect modification by sex was also examined. Findings from these analyses have been previously reported in the form of an abstract (32).

Methods

Participants were from the Asthma Coalition on Community, Environment and Social Stress (ACCESS) project, a pregnancy cohort designed to examine the effects of perinatal exposure to physical toxins and psychosocial stress on urban childhood respiratory health (33). In brief, English- or Spanish-speaking pregnant women (⩾18 yr old) receiving care at Brigham and Women's Hospital, Boston Medical Center, and affiliated community health centers were enrolled at 28.4 ± 7.9 weeks gestation between August 2002 and July 2009. Among pregnant women approached who were eligible, 989 (78.1%) agreed to enroll. Based on screening data, mothers who declined versus enrolled were slightly less likely to be ethnic minorities (78.9% and 81.5% Hispanic or African American, respectively) or to have a high school education or less (57.7% vs. 60.6%, respectively) and slightly more likely to report an income level less than $20,000 annually (37.7% vs. 35.2%, respectively); there were no significant differences between groups on these covariates. Of those enrolled, 955 gave birth to a singleton live born infant and continued follow-up. Procedures were approved by human studies committees at the Brigham and Women's Hospital and Boston Medical Center; written consent was obtained in the subject's primary language.

Daily Prenatal $PM_{2.5}$ Levels

Mothers' prenatal exposure to $PM_{2.5}$, an index of ambient pollution from traffic and other sources, was estimated based on residence over the pregnancy (i.e., at enrollment and updated if they moved) using a novel spatiotemporal model incorporating moderate resolution imaging spectroradiometer satellite-derived aerosol optical depth (AOD) measurements at a 10 × 10 km spatial resolution and layering this remote sensing data with

traditional LUR predictors to yield residence-specific estimates of daily $PM_{2.5}$ as detailed previously (22). The model was run using day-specific calibrations of AOD data using ground $PM_{2.5}$ measurements from 78 monitoring stations covering New England and LUR and meteorologic variables (temperature, wind speed, visibility, elevation, distance to major roads, percent open space, point emissions, and area emissions). This approach incorporates highly resolved spatial information from the LUR data and important spatiotemporal data from the remote sensing satellite data.

The AOD-$PM_{2.5}$ relationship was calibrated for each day using data from grid cells with both monitor and AOD values using mixed models with random slopes for day, nested within region. For days without AOD data (because of cloud coverage, snow, and so forth), the model was fit with a smooth function of latitude and longitude and a random intercept for each cell (similar to universal Kriging). The "out of sample" 10-fold cross validation R^2 for daily values was 0.83 and 0.81 for days with and without available AOD data, respectively. For use in the health effect models, to reduce potential noise caused by day-to-day $PM_{2.5}$ variation, daily levels were averaged into weekly exposure profiles. Predicted overall prenatal $PM_{2.5}$ levels at participant's residence in relation to the 10×10 km grids for which AOD data were available are shown in Figure 1. Although levels were higher around major roadways as anticipated, there was reasonable heterogeneity.

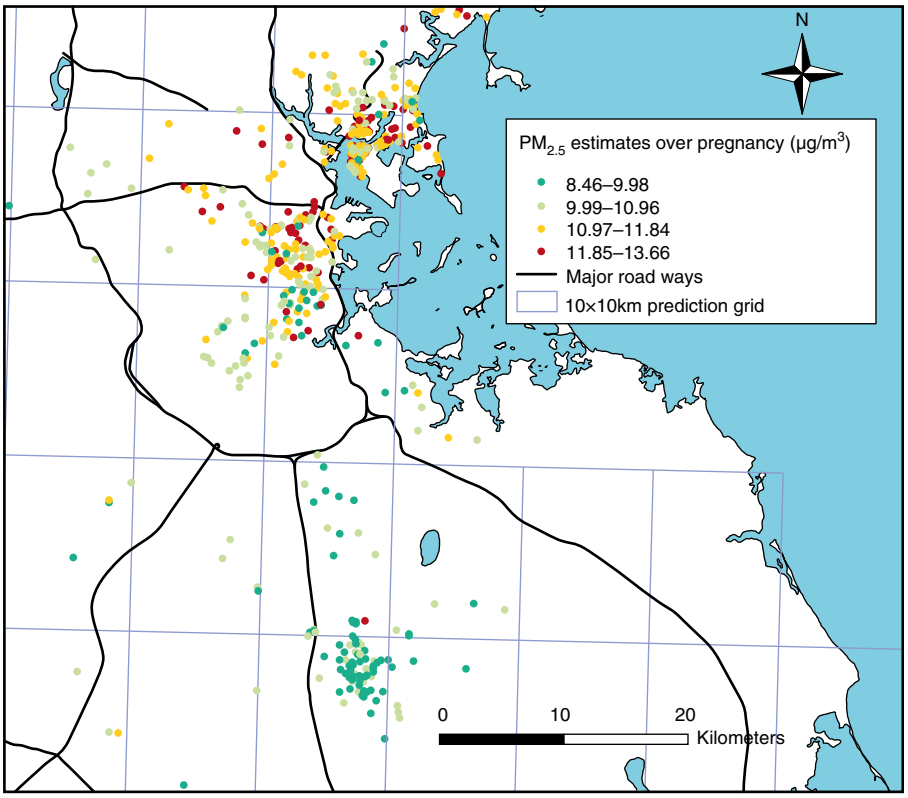

Figure 1. Predicted daily particulate matter with a diameter less than or equal to 2.5 μm ($PM_{2.5}$) levels for Asthma Coalition on Community, Environment and Social Stress participants averaged over pregnancy. This figure demonstrates predicted daily $PM_{2.5}$ levels for study participants based on residence and averaged throughout the gestation period. The 10×10 km aerosol optical depth grid used to predict daily $PM_{2.5}$ levels is also depicted.

Asthma

Maternal-reported clinician-diagnosed asthma was ascertained from birth up to age 6 years through telephone and face-to-face interviews at approximately 3-month intervals for the first 24 months then annually thereafter. Mothers were asked, "Has a doctor or nurse ever said that your child had asthma?" Most of these children were given a diagnosis of asthma after the age of 3 years (78.6%) (*see* Figure E1 in the online supplement).

Covariates

Maternal age, race, education, and prepregnancy height and weight, and child's sex were ascertained by questionnaire; date of birth, gestational age, and birth weight were obtained by medical record review. A validation analysis on a subset of 121 ACCESS women showed no difference in the level of agreement/disagreement for height and weight when comparing values measured early in pregnancy (<10 wk) with self-report (34). Women were asked about smoking at enrollment and in the third trimester and classified as prenatal smokers if smoking at either visit. Mothers reported postnatal smoking and whether others smoked in the home at each postpartum interview. Household crowding was calculated by dividing the number of persons living in the home by the number of rooms based on maternal report in pregnancy. Maternal atopy was defined by self-reported doctor-diagnosed asthma, eczema, and/or hay fever. Body mass index was calculated by dividing weight by height squared (kg/m^2); obesity was defined as body mass index greater than or equal to 30 kg/m^2 (35).

Because prenatal stress may covary with pollution and has been associated with asthma (36), this was also considered as a confounder. We measured stress using the Crisis in Family Systems-Revised survey administered prenatally within 2 weeks of enrollment (37, 38). This survey assesses life events experienced across 11 domains (e.g., financial, relationships, violence, housing, discrimination/prejudice). Mothers endorsed events experienced in the past 6 months and rated each as positive, negative, or neutral. The number of domains with one or more negative event was summed to create a continuous negative life events (NLEs) domain score, with higher scores indicating greater stress. Because birth weight and gestational age may be on the pathway between prenatal PM and asthma risk, birth weight for gestational age *z* score (39) was considered in sensitivity analyses.

Statistical Analysis

Analyses included 736 singleton full-term (gestational age ⩾37 wk) children with two or more postnatal interviews followed up to age 6 years and air pollution exposure

data. Table E1 shows that there were no differences across covariates when comparing those included in the analysis with the whole sample. To explore sensitive windows, we constructed an exposure lag space (40) incorporating weekly averages of daily $PM_{2.5}$ predictions at each subject's residence throughout the gestational period. We fit DLMs to estimate the time-varying association between the probability of child's asthma onset and the estimated $PM_{2.5}$ level during a given week in pregnancy. Specifically, we fit the logistic regression DLM:

$$logit(\pi_i) = \beta_0 + \sum_{j=1}^{n}\left[\alpha_j AP_{ij}\right] + \beta_1 x_{1i} + \ldots + \beta_p x_{pi},$$

where π_i is the probability of a report of clinician diagnosed asthma, AP_{ij} is the estimated $PM_{2.5}$ level for week j of pregnancy, and $x_{1i}, \ldots, x_{pi}$ are confounders for subject i. Models included maternal age, race and ethnicity, education, prepregnancy obesity, prenatal and postnatal tobacco smoke exposure, prenatal NLEs, and child's sex. Without additional structure on the α_j coefficients, the estimates of the week-specific effects are typically unstable because of collinearity among the weekly pollution averages. Therefore, we fit constrained DLMs that assume these effects α_j are a smooth function of j (wk), such $\alpha_j = h(j)$. We modeled this smooth function using b-splines. A sensitive window was identified when the pointwise 95% confidence bands did not contain zero.

Next, to assess whether the sensitive window of prenatal $PM_{2.5}$ exposure on childhood asthma onset was different between boys and girls, sex-stratified DLMs were performed, adjusting for maternal age, race and ethnicity, education, prepregnancy obesity, prenatal and postnatal smoking status, and prenatal NLEs. We then constructed a difference curve by subtracting the effect estimates of the DLM curve for the girls from the effect estimates of the DLM curve for the boys ([log odds of boys] − [log odds of girls]), and calculated the associated pooled standard error to derive the 95% pointwise confidence interval of the difference curve. For additional sensitivity analyses, we also examined sex-specific associations between prenatal $PM_{2.5}$ levels averaged across the DLM-identified sensitive windows using multivariable-adjusted logistic regression models, and fitting the interaction model using the following equation:

$$\begin{aligned}\text{logit(asthma)} = \text{intercept} &+ \beta_1(PM_{2.5}) \\ &+ \beta_2(\text{male}) \\ &+ \beta_3(\text{male} \times PM_{2.5}) \\ &+ \beta_4 x_{1i} + \beta_5 x_{2i},\end{aligned}$$

where $x_{1i}, x_{2i}, \ldots$ are covariates. Finally, because prenatal and postnatal $PM_{2.5}$ levels were correlated (Spearman $r = 0.82$), we performed sensitivity analyses by including postnatal $PM_{2.5}$ levels in the models. We also fit models including birth weight adjusted for gestational age. DLMs were implemented using the *dlnm* package in *R* version 3.0.1 (Vienna, Austria) (40), and other analyses were performed in SAS version 9.1.3 (SAS Institute, Inc., Cary, NC).

Results

Most mothers were ethnic minority (54% Hispanic, 30% African American), had less than or equal to 12 years of education (66%), and did not smoke in pregnancy (80%); the distribution of these covariates did not differ by sex (Table 1). There

Table 1. ACCESS Participant Characteristics

	All Children (*n* = 736)	Boys (*n* = 374)	Girls (*n* = 362)
Ever had asthma up to 6 yr old, n (%)			
No	626 (85.0)	307 (82.1)	319 (88.1)
Yes	110 (15.0)	67 (17.9)	431 (1.9)
Race/ethnicity, n (%)			
Black	218 (29.6)	119 (31.8)	99 (27.4)
Hispanic	395 (53.7)	191 (51.1)	204 (6.4)
White/other	123 (16.7)	64 (17.1)	59 (16.3)
Maternal education, n (%)			
>12 yr	251 (34.1)	128 (34.2)	123 (34)
⩽12 yr	485 (65.9)	246 (65.8)	239 (66.0)
Maternal smoking status, n (%)			
Never smoked	590 (80.2)	303 (81)	287 (79.0)
Smoked prenatally, but not postnatally	36 (4.9)	19 (5.1)	17 (4.7)
Did not smoke prenatally, but smoked postnatally	42 (5.7)	19 (5.1)	23 (6.4)
Smoked both prenatally and postnatally	68 (9.2)	33 (8.8)	13 (9.7)
Maternal atopy, n (%)*	262 (35.6)	131 (35.0)	131 (36.2)
Maternal obese, n (%)†	205 (27.9)	97 (26.0)	108 (30.0)
Maternal age at enrollment, yr, median (IQR)	25.5 (22.3–30.7)	25.6 (22.4–31.3)	25.4 (22.2–30.3)
Birth weight for gestational age *z* score, mean ± SD	−0.16 ± 1.06	−0.07 ± 1.09	−0.26 ± 1.03
Averaged prenatal $PM_{2.5}$ level, $\mu g/m^3$, median (IQR)	11.2 (10.2–11.8)	11.2 (10.2–11.9)	11.0 (10.2–11.7)
Prenatal negative life events score, mean ± SD‡	2.40 ± 2.00	2.37 ± 1.99	2.43 ± 2.03
Household crowding, median (IQR)§	1 (0.60–1.25)	1 (0.60–1.25)	1 (0.67–1.25)

Definition of abbreviations: ACCESS = Asthma Coalition on Community, Environment and Social Stress; IQR = interquartile range; $PM_{2.5}$ = particulate matter with a diameter less than or equal to 2.5 μm.
*Ever self-reported doctor-diagnosed asthma, eczema, and/or hay fever.
†Prepregnancy obesity: body mass index ⩾ 30 kg/m^2.
‡Assessed using Crisis in Family Systems-Revised survey (37, 38), a multiitem survey summarized into a continuous score.
§Household crowding indexed as number of people in the home divided by number of rooms in the home (person per room).

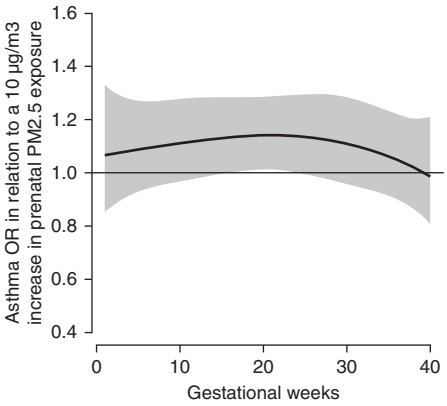

Figure 2. Association between weekly particulate matter with a diameter less than or equal to 2.5 μm ($PM_{2.5}$) levels over gestation and asthma onset. This figure demonstrates the association between $PM_{2.5}$ over gestation and asthma onset by age 6 years using a distributed lag model assuming week-specific effects, adjusting for child's sex, maternal age at enrollment, race and ethnicity, education, prepregnancy obesity, prenatal and postnatal smoking, and prenatal stress. The *y*-axis shows the odds ratio (OR) of asthma in relation to a 10 $\mu g/m^3$ increase in prenatal $PM_{2.5}$ exposure; the *x*-axis depicts gestational age in weeks. The *solid line* shows the predicted OR, and the *gray area* indicates the 95% confidence interval. A sensitive window is identified when the estimated pointwise 95% confidence interval does not include zero.

were 110 asthma cases among the 736 children included in the final analysis. We present the distribution of asthma cases relative to all ACCESS participants in the online supplement (*see* Figure E2). There were also no significant sex difference in terms of gestational age at birth, maternal age, atopy, obesity, prenatal stress, and $PM_{2.5}$ exposure. Boys were more likely to be diagnosed with asthma compared with girls (18% vs. 12%; chi-square test, $P = 0.02$). Birth weight for gestational age *z* score was significantly lower in girls than boys (Wilcoxon rank sum test, $P = 0.003$).

Distributed Lag Models

Figure 2 shows the association between prenatal $PM_{2.5}$ and children's asthma onset using DLMs, adjusting for maternal age, race and ethnicity, education, prepregnancy obesity, prenatal and postnatal tobacco smoke exposure, prenatal NLEs, and child's sex. We observed a significant sensitive window of $PM_{2.5}$ exposure around mid-pregnancy on asthma onset by age 6 years, specifically during 16–25 weeks gestation (Figure 2). Sensitivity analyses additionally including averaged postnatal $PM_{2.5}$ levels and birth weight adjusted for gestational age did not materially change these results (data not shown).

Figure 3 demonstrates the sex-specific association between prenatal $PM_{2.5}$ and children's asthma onset using DLMs, adjusting for maternal age, race and ethnicity, education, prepregnancy obesity, prenatal and postnatal tobacco smoke exposure, and prenatal NLEs. When stratified by sex, we observed a significant sensitive exposure window between 12 and 26 weeks gestation among boys but not girls (Figure 3). To examine the interaction between prenatal $PM_{2.5}$ and sex, we also constructed a DLM demonstrating the difference between boys and girls; the difference curve showed that associations were significantly stronger in boys from 14–20 weeks gestation compared with girls (Figure 4). Finally, we fit a multivariable logistic regression model including a $PM_{2.5} \times$ sex interaction term using $PM_{2.5}$ level averaged over this identified sensitive window, and found a significant interaction between $PM_{2.5}$ and sex ($P = 0.01$). Details on the full regression model can be found in the online supplement (*see* Tables E2A and E2B).

Discussion

These data add to a growing literature linking prenatal particulate air pollution exposure to children's respiratory health. This is the first study to leverage weekly $PM_{2.5}$ exposure estimates over gestation combined with data-driven statistics to characterize susceptibility windows, removing the subjectivity that currently guides the decision of when to assess exposure effects. These data demonstrate that increased prenatal $PM_{2.5}$ exposure in mid-gestation (16–25 wk gestation) was associated with development of childhood asthma in these urban children, but only in boys.

Although previous studies link higher prenatal exposure to PM with adverse pulmonary outcomes, such as asthma (41–43), the sensitive window with the greatest impact has not been well elucidated. A more definitive understanding of the temporal effects of toxins on outcomes in the offspring may provide clues as to the underlying mechanisms being perturbed based on current understanding of the cellular

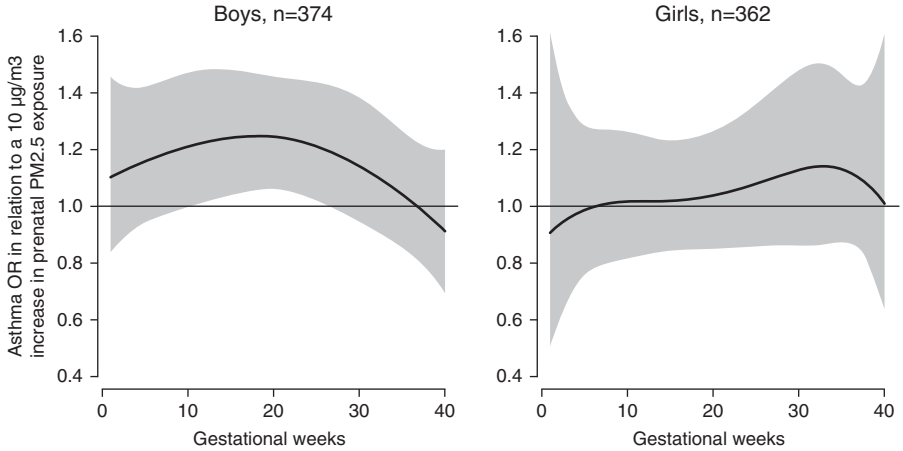

Figure 3. Association between weekly particulate matter with a diameter less than or equal to 2.5 μm ($PM_{2.5}$) levels over gestation and asthma onset. This figure demonstrates the association between $PM_{2.5}$ over gestation and asthma onset by age 6 years using distributed lag models assuming week-specific effects, stratified by sex. The models adjusted for maternal age at enrollment, race and ethnicity, education, prepregnancy obesity, prenatal and postnatal smoking status, and prenatal stress. The *y*-axis shows the odds ratio (OR) of asthma in relation to a 10 $\mu g/m^3$ increase in prenatal $PM_{2.5}$ exposure; the *x*-axis depicts gestational age in weeks. The *solid line* shows the predicted OR, and the *gray area* indicates the 95% confidence interval. A sensitive window is identified when the estimated pointwise 95% confidence interval does not include zero.

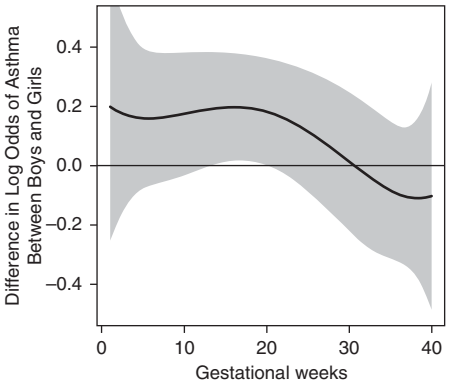

Figure 4. Association between weekly particulate matter with a diameter less than or equal to 2.5 μm ($PM_{2.5}$) levels over gestation and the difference in asthma onset between boys and girls. This figure demonstrates the association between $PM_{2.5}$ over gestation and the difference in asthma onset between sex using a distributed lag model assuming week-specific effects, adjusting for maternal age at enrollment, race and ethnicity, education, prepregnancy obesity, prenatal and postnatal smoking status, and prenatal stress. The *y*-axis shows the differences in log odds of asthma between boys and girls ([log odds of boys] − [log odds of girls]) in relation to a 10 $\mu g/m^3$ increase in prenatal $PM_{2.5}$ exposure; the *x*-axis is gestational age in weeks. The *solid line* shows the predicted odds ratio, and the *gray area* indicates the 95% confidence interval.

differentiation, proliferation, or physiologic function changes occurring progressively over pregnancy. This study demonstrates the applicability of advanced statistical modeling to illustrate the pattern of associations throughout the pregnancy based on the data *per se* rather than assigning *a priori* exposure time points relevant to the exposure of interest. The identified sensitive window coincides with the late pseudoglandular and canalicular phases of fetal lung development (7). Several essential tissues and their functions are shaped during these lung development phases. During the pseudoglandular stage (5–17 wk), the conducting airways develop smooth muscle, mucous glands form, and acinar outlines appear (44).

The airways continue to develop during the canalicular stage (17–26 wk) and capillaries, thin-walled terminal saccules, and alveolar epithelium begin to appear. Type II cells may undergo differentiation to type I cells in this period, with subsequent surfactant production (7, 42, 45). For example, the airway epithelium, formed during the canalicular phase, can secrete an array of innate immune molecules implicated in reactive airway disorders, such as asthma (46). Specifically, the airway epithelium may be a major source of IL-25, which regulates immune-mediated inflammatory airway diseases and the response to infections, and IL-33 and thymic stromal lymphopoietin, which also influence asthma development (47). Moreover, recent studies have found that epithelial barrier, epithelial mesenchymal transition, and mesenchymal phenotype are associated with lung function and allergic pulmonary diseases over the life course (47–50). Factors involved in airway epithelial function and migration have been increasingly implicated in the links between PM, impaired lung growth, and asthma risk (51, 52).

Previous human studies have suggested that sex differences in lung development may be related to differential maturation in males relative to females in terms of surfactant synthesis, airway size, and airway resistance, which also begin during the late pseudoglandular and canalicular phases (28, 53). Fetal breathing, a critical determinant of lung development, and surfactant production occur earlier in females as compared with males (54, 55). Sex differences result in lower specific airway resistance and higher size-corrected flow rates and specific airway conductance in female infants (56–59) and predispose male infants to childhood respiratory diseases including asthma (60, 61). Infant males, therefore, may have a pulmonary phenotype more susceptible to the deleterious effects of prenatal air pollution exposure.

Moreover, a leading mechanism underlying the link between prenatal $PM_{2.5}$ exposure and childhood asthma is thought to involve oxidative stress pathways and proinflammatory cytokine production (15, 62). The developing fetus is particularly vulnerable to oxidative stress because fetal antioxidant capabilities do not increase until the third trimester. Murine models of oxidative stress at embryonic Day 16, equivalent to the canalicular phase in human lung development, demonstrate reductions in peripheral airway number, branching complexity, and alveolarization (63). This coupled with evidence to support an increased susceptibility of the male fetus to maternal oxidative stress (31) may contribute to the observed greater risk in males. It is also possible that the antioxidant properties of female sex hormones (64, 65) may mitigate damaging effects of prenatal ambient PM exposure. Future studies are needed to corroborate our findings and further examine these mechanisms to better understand observed sex differences.

We note several strengths of this study. We assessed prenatal maternal daily particulate air pollution using a validated state-of-the-art hybrid spatiotemporal LUR model incorporating satellite-derived AOD measures based on mothers' residence during pregnancy. We then leveraged these exposure estimates to implement a data-driven, advanced statistical method to objectively identify susceptibility windows for PM. Also, these analyses included a lower socioeconomic status ethnically mixed inner-city cohort that may be more highly exposed to ambient pollution and be at greater risk for asthma. Finally, this is the first study to examine sex-specific effects of prenatal particulate air pollution on childhood asthma development.

We also acknowledge some limitations. Although we adjusted for several factors known to be important in asthma development, we did not have data on dietary and other environmental factors that may covary with air pollution, such as temperature. Further studies may therefore consider sex-specific joint or interactive associations among additional environmental factors. Children's doctor-diagnosed asthma was reported by mothers. Most of these children were given a diagnosis of asthma after the age of 3 years (78.6%) (*see* Figure E1), which reduces the likelihood that cases represented wheezing respiratory illnesses other than asthma (e.g., early transient wheeze), although this remains a possibility. As we follow this cohort it will be informative to see if similar associations hold for more objective measures including respiratory function (e.g., spirometry, airway reactivity). Finally, although we focused on a higher-risk sample, our results may not be generalizable to the overall U.S. population.

In summary, we demonstrate that advanced statistical methods when combined with highly temporally resolved exposure data can identify susceptibility windows to environmental exposures that

may enhance the ability to find effects and identify vulnerable groups. Increased PM exposure around mid-gestation may be particularly relevant to childhood asthma development, especially among boys. A more definitive characterization of vulnerable windows may provide insight into underlying mechanisms when coupled with the understanding of lung growth, airway structural and functional development, and asthma pathophysiology. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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