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Prenatal Particulate Air Pollution and Neurodevelopment in Urban Children: Examining Sensitive Windows and Sex-specific Associations

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Abstract

Background—Brain growth and structural organization occurs in stages beginning prenatally. Toxicants may impact neurodevelopment differently dependent upon exposure timing and fetal sex.

Objectives—We implemented innovative methodology to identify sensitive windows for the associations between prenatal particulate matter with diameter $2.5\mu\text{m}$ ($\text{PM}_{2.5}$) and children's neurodevelopment.

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Methods—We assessed 267 full-term urban children’s prenatal daily PM_{2.5} exposure using a validated satellite-based spatio-temporally resolved prediction model. Outcomes included IQ (WISC-IV), attention (omission errors [OEs], commission errors [CEs], hit reaction time [HRT], and HRT standard error [HRT-SE] on the Conners’ CPT-II), and memory (general memory [GM] index and its components - verbal [VEM] and visual [VIM] memory, and attention-concentration [AC] indices on the WRAML-2) assessed at age 6.5±0.98 years. To identify the role of exposure timing, we used distributed lag models to examine associations between weekly prenatal PM_{2.5} exposure and neurodevelopment. Sex-specific associations were also examined.

Results—Mothers were primarily minorities (60% Hispanic, 25% black); 69% had 12 years of education. Adjusting for maternal age, education, race, and smoking, we found associations between higher PM_{2.5} levels at 31–38 weeks with lower IQ, at 20–26 weeks gestation with increased OEs, at 32–36 weeks with slower HRT, and at 22–40 weeks with increased HRT-SE among boys, while significant associations were found in memory domains in girls (higher PM_{2.5} exposure at 18–26 weeks with reduced VIM, at 12–20 weeks with reduced GM).

Conclusions—Increased PM_{2.5} exposure in specific prenatal windows was associated with poorer function across memory and attention domains with variable associations based on sex. Refined determination of time window- and sex-specific associations may enhance insight into underlying mechanisms and identification of vulnerable subgroups.

Keywords

air pollution; prenatal exposure; particulate matter; neurodevelopment; sensitive windows; sex-specific associations

1. INTRODUCTION

Cognitive impairment and behavioral problems affect up to 20% of U.S. children, placing an enormous burden on the education and healthcare systems (Boulet et al. 2009; Costello et al. 2003; Froehlich et al. 2007; Leonard and Wen 2002; Montes et al. 2012; Perou et al. 2013). As loss of early functioning may result in diminished academic and economic productivity that persists over the life span, understanding how maladaptive trajectories are set in early life and identifying environmental influences amenable to intervention are research priorities. Growing evidence implicates ambient air pollution (e.g., traffic-related pollutants, particulate matter) as a developmental neurotoxicant (Block and Calderon-Garciduenas 2009; Genc et al. 2012; Liu and Lewis 2014; Zanchi et al. 2010). Animal, experimental, and epidemiological studies demonstrate that effects of air pollution on neurodevelopment likely begin *in utero* (Genc et al. 2012; Zanchi et al. 2010).

While mechanisms are not completely understood, prenatal pollutant-induced oxidative stress and inflammatory processes that disrupt differentiation and organization of the fetal brain and central nervous system (CNS) may play a key role (Block and Calderon-Garciduenas 2009; Block et al. 2012). The CNS develops sequentially with different anatomic regions forming at different life stages and specific processes occurring in a timed cascade. Beginning *in utero*, the brain forms a network of interconnected cells (i.e. neurons) that stretch across different anatomic regions as well as connecting to peripheral tissues (Lavenex and Banta Lavenex 2013; Tau and Peterson 2010). The various structural

components of this network may be differentially vulnerable to environmental toxins depending on the timing of exposure and anatomic region of the brain affected which are linked to specific neurodevelopment function domains (Rodier 2004). Subtle disturbances in development, even slight disruption, at an early stage may affect later developmental processes by offsetting the normal trajectory (Weiss 2000).

To date, human studies have mostly considered subjective assignment of exposure timing, either assessing air pollution at a specific prenatal time point in a trimester or using exposure averaged over the entire pregnancy. A meta-analysis of six European birth cohorts linked nitrogen dioxide (NO₂) and PM_{2.5} levels averaged over pregnancy with delayed psychomotor development in 1–6 year olds (Guxens et al. 2014). Guxens et al. (Guxens et al. 2012) found that NO₂ levels averaged over the pregnancy were associated with decreased mental development index scores on the Bayley Scales of Infant Development (BSID) in 14 month olds. Kim et al. (Kim et al. 2014) linked higher prenatal PM₁₀ levels averaged over the pregnancy estimated by inverse distance weighting modeling with delayed mental and psychomotor development in 6–24 month olds. Perera et al. measured polycyclic aromatic hydrocarbons (PAHs) using 48-hour personal sampling in the third trimester and found associations with mental developmental delays on BSID in 3 year olds (Perera et al. 2006), lower full-scale IQ at age 5 years (Perera et al. 2009), and increased attention problems in 6–7 years olds (Perera et al. 2012). Edwards et al. (Edwards et al. 2010) linked PAHs measured by 48-hour personal sampling at mid-to-late pregnancy with lower IQ scores at age 5 years. While extant data collectively suggest an association between prenatal exposure to air pollution and children's neurodevelopment, it is difficult to compare the results between studies as well as tease out the critical windows affecting fetal programming. Measuring exposure in a less relevant susceptibility window may lead to underestimated or even missed associations; yet, the exact windows are often unknown while evidence suggests that clinically defined trimesters may not necessarily correspond to relevant vulnerable periods of brain development (Tau and Peterson 2010). Therefore, implementing methods to objectively identify windows of susceptibility for neurotoxicants and the neurodevelopmental domains being impacted may enhance insight into underlying mechanisms and/or the processes being disturbed.

Further, several lines of evidence suggest effects may be sex specific. Research has identified morphological (i.e. volume, shape, thickness), physiological (i.e. variation in circuits), and chemical (i.e. abundance, type, and metabolism of neurotransmitters) differences between boys and girls in relation to neurodevelopment; a recent review suggests that differences extend to a range of phenotypic domains of memory and learning (Andreano and Cahill 2009). Overlapping research documents complex sex-specific early neurodevelopmental effects related to other chemicals (e.g., mercury, lead, bisphenol A) that vary by exposure timing (Braun et al. 2011; Engel et al. 2010; Hamadani et al. 2011; Sagiv et al. 2012; Tatsuta et al. 2014). Recent animal studies demonstrate sex differences in the association between prenatal air pollution and offspring neurodevelopment (Bolton et al. 2014; Dada et al. 2014). Other evidence shows sex-specific vulnerability to prenatal oxidant injury (Minghetti et al. 2013) suggesting that the male and female fetus may be differentially impacted by *in utero* exposures. Sex-specific effects of prenatal air pollution exposure on

neurodevelopmental outcomes in early childhood have not been examined in humans to date.

To begin to address these gaps, we leveraged data on daily exposure to particulate matter with a diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) measured over gestation and applied advanced statistical methods to more precisely identify the sensitive windows of prenatal particulate air pollution exposure on a range of children's neurodevelopmental outcomes (IQ, attention, and memory) in an ethnically mixed lower-SES inner city population, and also examined effect modification by sex. We hypothesized that the sensitive windows would vary relative to the different neurodevelopmental domains and that there would be sex-specific associations.

2. MATERIALS AND METHODS

Participants were from the Asthma Coalition on Community, Environment and Social Stress (ACCESS) project, a pregnancy cohort originally funded to recruit 500 mother-child pairs and designed to examine independent and interactive effects of early life stress and physical toxins on childhood respiratory health (Wright et al. 2008). In brief, English- or Spanish-speaking pregnant women (≥ 18 years old) receiving care at Brigham & Women's Hospital (BWH), Boston Medical Center (BMC), and affiliated community health centers were enrolled at 28.4 ± 7.9 weeks gestation between August 2002 and January 2007. Research assistants approached women receiving prenatal care on select clinic days, 78% of those approached who were eligible agreed to enroll. There were no significant differences on race/ethnicity, education, and income between women enrolled and those who declined; $n=455$ gave birth to a live born infant and continued follow-up. Neurodevelopmental testing in children was conducted between March 2012 to February 2014 during which time $n=310$ families were re-contacted and agreed to participate. Among these families, $n=9$ were unable to be scheduled despite an average of 11 attempts, $n=5$ children were unable to adequately cooperate with the testing protocol, $n=28$ were born pre-term (<37 weeks), and $n=1$ was *a priori* excluded from analyses given an IQ score more than two standard deviations below the mean, resulting in $n=267$ included in our analysis. Characteristics of included (maternal age 26 ± 5 years, 69% with high school education or less, 25% black, 60% Hispanic, and 55% male) versus excluded (maternal age 27 ± 6 years, 62% with high school education or less, 29% black, 55% Hispanic, and 52% male) participants were not significantly different. Procedures were approved by the human studies committees at BWH and BMC. Written consent was obtained from mothers; assent was obtained for children ≥ 7 years old.

2.1 Prenatal $\text{PM}_{2.5}$ Levels

Individuals' prenatal exposure to $\text{PM}_{2.5}$, an index of ambient pollution from traffic and other sources, was estimated based on residence over the duration of pregnancy (i.e., at enrollment and updated if they moved) using a hybrid satellite based spatio-temporal prediction model. The model incorporated Moderate Resolution Imaging Spectroradiometer (MODIS) derived aerosol optical depth (AOD) measurements at a 10 km spatial resolution. The model combines the AOD data with traditional land-use regression (LUR) predictors to yield residence-specific estimates of daily $\text{PM}_{2.5}$ as detailed elsewhere (Kloog et al. 2011). The model was run using day-specific AOD data calibrated against ground monitor-based $\text{PM}_{2.5}$

measurements derived from 78 monitoring stations covering New England. The model incorporated traditional LUR (traffic density, point sources, etc) and meteorological variables (temperature, wind speed, visibility, elevation, distance to major roads, percent of open space, point emissions and area emissions). The AOD-PM_{2.5} relationship was calibrated daily using data from grid cells with both monitor and AOD values using mixed models with random slopes for day, nested within regions. For locations on days without AOD data (due to cloud coverage, snow, etc.), the model was fit with a thin plate spline of latitude and longitude and a random intercept for each cell (similar to universal kriging) to impute predictions at these missing locations. The “out of sample” ten-fold cross validation R² for daily values were 0.83 and 0.81 for days with and without available AOD data, respectively. To reduce potential noise caused by day-to-day variation of PM_{2.5}, exposure levels for each participant were aggregated into weekly averages for each week during gestation.

2.2 Neurodevelopmental Measurements

All neurodevelopmental tests were administered on children at age 6.5 ± 0.98 years. As working memory and executive attention are dependent on many overlapping brain structures and circuits (Fougnie 2008) and it is not yet clear which processes are influenced by particulate matter exposure in fetal development, we examined a global cognitive measure (IQ) as well as a range of sub-domains related to memory and attention.

2.2.1 Intelligence quotient (IQ)—Child intelligence was assessed using the full-scale IQ score on the Wechsler Intelligence Scale for Children (WISC)-IV (Wechsler 2003), which can be completed without reading or writing skills in children at ages 6–16 years. The WISC-IV standardization sample is representative of the March 2000 U.S. Census data based on age, sex, race, ethnicity, parent education level, and geographic location (Wechsler 2003), and has been widely used in culturally diverse populations.

2.2.2 Attention and Response Inhibition—Children also completed the Conners’ Continuous Performance Test-II (CPT-II) (Conners 2000) which does not have reading or literacy requirements and can be administered to children as young as age 6 years. The test consists of letters flashing in succession and at variable rates on the screen. The child was instructed to push the space bar as quickly as possible in response to each letter except for “X”. Outcomes included hit reaction time (HRT; mean reaction time for all target responses), HRT standard error (HRT-SE; standard error of reaction time, a measure of response speed consistency throughout the test), total omission errors (OEs; failing to respond to a target), and total commission errors (CEs; erroneously responding to a non-target) expressed as standardized percentiles representing the performance of the study subject relative to the performance by children in the same age and sex group in the normative sample (Conners 2000). Higher percentiles indicate more errors (for CEs and OEs), slower reaction time (for HRT), or greater variability in HRT (for HRT-SE). Inattention is reflected through a higher number of OEs and longer HRTs as well as higher reaction time variability (HRT-SE), and poorer response inhibition is reflected by a higher number of CEs. The CPT has been widely used and prior studies have found that reaction times are particularly sensitive indicators of exposures to toxicants (White et al. 2009).

2.2.3 Memory—We assess memory with the Wide Range Assessment of Memory & Learning, 2nd Edition (WRAML-2) (Sheslow and Adams 2003), a widely used standardized test normed for children aged 5–17 years among racially diverse groups. This test evaluates immediate and delayed memory ability along with the acquisition of new learning. The WRAML-2 yields an overall composite general memory index (GM) and its components (verbal memory index [VEM], visual memory index [VIM], and attention/concentration index [AC]). All measures are expressed as age-standardized scores. Lower percentiles indicate poorer memory functioning.

2.3 Covariates

Maternal age, race, and educational status were ascertained at enrollment; information about child's sex, date of birth, parity, gestational age at birth, and birth weight were obtained by medical record review. Women reported on smoking at enrollment and in the third trimester and were classified as prenatal smokers if they reported smoking at either visit; postnatal smoking was recorded at each 3-month postpartum interview. Duration of breast feeding was also ascertained by postpartum interviews. Children's blood lead levels were assessed using a portable blood lead analyzer (LeadCare® II, Magellan Diagnostics, Inc.) on the day of neurodevelopment testing.

2.4 Statistical Analysis

Analyses included 267 singleton full-term (> 37 weeks gestation) children. Prior research links prenatal air pollution exposure to preterm birth (Backes et al. 2013) and in turn, preterm birth is linked to poor neurodevelopmental outcomes in children (Sutton and Darmstadt 2013). Thus, we restrict to infants born at > 37 weeks to minimize over-adjustment for a pathway variable. In order to identify sensitive windows for effects of prenatal PM_{2.5} in relation to neurodevelopmental outcomes, we constructed a conceptualized model that takes into account the effects and correlations among exposures at different time points by creating an exposure lag space (Gasparrini et al. 2010) using weekly averages of each participant's daily exposures (predicted by our spatio-temporal PM_{2.5} prediction model described above) throughout that participant's gestational period (Hsu et al. 2015). We fit distributed lag models (DLMs) to estimate the time-varying association between a given neurodevelopmental outcome and estimated PM_{2.5} level during a given week in pregnancy. Specifically, we fit the linear distributed lag model

$$Y_i = \beta_0 + \sum_{j=1}^n [\alpha_j AP_{ij}] + \beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \varepsilon_i$$

where AP_{ij} is the estimated PM_{2.5} level in week j of pregnancy and $x_{1i}, \dots, x_{pi}$ are the confounders for subject i . Confounders included maternal age, race, education, smoking status, parity, and blood lead level at neurodevelopmental testing in all models, as well as child's sex in models not stratified by sex. Without additional structure on the α_j coefficients, the estimates of the week-specific effects are typically unstable due to collinearity among the weekly pollution averages. Therefore, we fit constrained DLMs that assume these effects α_j are a smooth function of j (week), such that $\alpha_j = h(j)$. Thus, the model incorporates the data from all timepoints simultaneously and assumes that the association between the outcome and exposure at a given timepoint, controlling for exposure at all other timepoints, varies smoothly as a function of time. We modeled this smooth function using b-splines (Gasparrini 2011;

Gasparrini et al. 2010) with 4 degrees of freedom. A sensitive window is identified when the estimated pointwise 95% confidence bands do not include zero. Next, to assess whether the sensitive window of prenatal PM_{2.5} exposure on childhood neurodevelopment was different between boys and girls, sex-stratified DLMs were run. To compare how the estimate of an association between PM_{2.5} exposure and outcome would have differed from analyses examining exposures based on the entire pregnancy or trimesters, we also estimated sex-specific associations between prenatal PM_{2.5} levels averaged across the sensitive windows identified by the DLMs and neurodevelopmental outcomes using multivariable linear regression models, adjusting for maternal age, education, race, prenatal/postnatal maternal smoking, parity, and blood lead level. Sensitivity analyses further adjusted for postnatal daily PM_{2.5} levels predicted by the spatio-temporal model averaged over the first 2 years of life (which were correlated with prenatal exposure levels; Spearman's $r=0.82$, $p<0.001$), birth weight for gestational age, and breast feeding for 6 months were also performed. DLMs were implemented using *dlm* package in *R* (v3.1.0, Vienna, Austria) (Gasparrini 2011), and other analyses were performed in SAS (v9.3, SAS Institute Inc., Cary, NC).

3. RESULTS

3.1 Participant characteristics

Most mothers were ethnic minority (60% Hispanic, 25% African American), had 12 years of education (69%), and did not smoke during pregnancy (81%); the distribution of covariates did not differ by children's sex (Table 1). Table 2 summarizes the distribution of the neurodevelopmental domain scores and PM_{2.5} exposure by sex. Prenatal PM_{2.5} levels were similar for boys and girls and there were also no significant sex differences in terms of gestational age at birth, maternal age at enrollment, parity, and children's age at neurodevelopmental testing (Tables 1–2).

3.2 Identification of sensitive windows using distributed lag models (DLMs)

The associations between prenatal PM_{2.5} and child IQ were examined by DLMs, adjusting for maternal age, race/ethnicity, education, pre- and postnatal maternal smoking. “Sensitive windows” graphically appear as a bump during which exposure is significantly associated with the respective neurophenotypes. For both IQ and attention domains, we did not find significant associations with prenatal PM_{2.5} when models included boys and girls together (Figures 1 and 2). However, when stratified by sex, we did observe sexually dimorphic associations. We observed a significant association between increased PM_{2.5} exposure in late pregnancy (31–38 weeks of gestation) and lower IQ scores in boys, but not in girls (Figure 1). Significant associations were also observed between higher PM_{2.5} levels in mid-pregnancy (20–26 weeks of gestation) and increased omission errors, between higher PM_{2.5} exposure in late pregnancy (32–36 weeks of gestation) and slower HRT, as well as between higher exposure in mid-to-late pregnancy (22–40 weeks of gestation) and increased variability in response time across the test (HRT-SE) among boys; no association was found with commission errors (Figure 2; higher percentiles of attention domains indicate less favorable performance). On the other hand, we observed significant associations between higher PM_{2.5} levels in early-to-mid pregnancy and adverse memory performances only among girls. Specifically, higher exposure to PM_{2.5} was associated with reduced VIM (18–

27 weeks gestation), AC (8–18 weeks gestation), and GM (12–20 weeks gestation) scores among girls; no association was found with VEM (Figure 3).

3.3 Models using PM_{2.5} levels at identified sensitive windows vs. assigned exposure windows

To further assess associations over the “sensitive windows” identified by the DLMs, we also fit multivariable linear regression models using PM_{2.5} levels averaged over the time period when the association was significant based on the pointwise 95% CI bounds. These analyses were run using a more conventional linear regression approach. Given previously demonstrated sexual dimorphic results, these models were sex-stratified adjusting for maternal age, race, education, and prenatal/postnatal maternal smoking. Figure 4A shows results of the domains where the DLMs suggested a sensitive window among boys, including full-scale IQ and three attention domains (OEs, HRT, and HRT-SE; higher percentiles indicating less favorable performance). The effect estimates of PM_{2.5} averaged across the sensitive windows in multivariable-adjusted linear models were in a less favorable direction in boys for these domains with full-scale IQ exhibiting the strongest association; no significant associations were found in girls (Figure 4A). Figure 5A shows the results of the WRAML-2 memory domain subscales (VIM, AC, and GM; lower percentiles indicating poorer memory functioning) where the DLMs suggested a sensitive window among girls. Here associations were strongest in girls for the three memory domain subscales. While sex-stratified analyses suggested differences in these associations at the sensitive windows between boys and girls, the PM_{2.5} × sex interactions were not statistically significant in the interaction models ($p = 0.2$), likely due to the limited sample size.

In comparison, Figures 4B and 5B show the results from regression analyses using PM_{2.5} levels averaged over the entire pregnancy. No significant associations were found in relation to any neurodevelopmental measure, likely due to a loss of efficiency in health effect estimation that results from using PM_{2.5} averaged over the entire prenatal period as a predictor. Notably, the point estimates between the two analyses (Figures 4A/5A vs. Figures 4B/5B) were not very different but the uncertainties of the effect estimates are much larger for the analyses using exposure averaged over the entire pregnancy as compared to that using a more refined sensitive window. In analyses using PM_{2.5} averaged over clinically defined trimesters (Supplemental Material, Table S1), the direction of effect estimates were generally consistent with the DLM curves shown in Figures 1–3, but were only statistically significant for 2nd trimester exposure with VIM and GM in girls.

3.4. Sensitivity analyses

Finally, sensitivity analyses additionally including postnatal PM_{2.5} levels, birth weight for gestational age, and breast feeding for 6 months did not materially change these results (data not shown).

4. DISCUSSION

Our findings suggest that prenatal maternal particulate air pollution may be associated with IQ, attention and memory, and that the sensitive windows vary based on the

neurodevelopmental domain being examined and by sex. To our knowledge, this is the first study to leverage weekly address-specific PM_{2.5} exposure estimates and distributed lag models in order to objectively define prenatal windows of neurodevelopmental vulnerability, removing much of the subjectivity that currently guides the decision of when to measure environmental exposure. Moreover, while animal studies have suggested that there may be sex differences in the association between prenatal air pollution and neurodevelopment in offspring (Bolton et al. 2014; Dada et al. 2014), to our knowledge this is the first human study to examine sex-specific associations in this context.

The advantage of implementing a data-driven statistical method that resolves the pattern of associations across time is apparent. Our approach is based on the data *per se* rather than assigning *a priori* exposure time points arbitrarily (e.g., using clinically defined trimesters), in order to more definitively identify sensitive windows for effects on neurodevelopment. Our analyses suggest that the direction of the effect estimates using PM_{2.5} averaged over clinically defined trimesters were generally consistent with the results from DLMs, but the DLMs are more sensitive to the potential significant critical windows. This implies that analyses using exposure metrics arbitrarily defined *a priori*, such as clinical trimesters, may miss associations if the sensitive window crosses different trimesters (e.g., HRT-SE in the attention domain for boys, AC in the memory domain for girls) or only consists of a portion of a given trimester (e.g., OEs in the attention domain for boys).

More refined estimation of the time window in which air pollution has the greatest impact may enhance our insight into underlying mechanisms as well as the etiology of sex-specific neurotoxic effects. Animal studies demonstrate that particulate air pollution induces neuroinflammatory processes that may subsequently disrupt neurodevelopment in offspring (Allen et al. 2014; Bolton et al. 2014; Bolton et al. 2012; Hougaard et al. 2008). Neuroinflammation may disturb normal programmed cell death. Importantly, neuroapoptosis is part of normal neural differentiation, which occurs around mid-to-late pregnancy in multiple brain regions (Tau and Peterson 2010). Increased neuroinflammation from PM has been linked to structural changes in the brain in rodent studies with smaller brain volume and reduced thickness of the prefrontal cortex (Semmler et al. 2005), which in turn, has been linked to attention deficit disorders in humans (Hauser et al. 2014). Between 20–28 weeks, myelination (the maturation of nerve cells whereby a layer of myelin forms around the axons allowing nerve impulses to travel faster) begins first in white matter in subcortical and later in cortical regions gradually increasing during pregnancy (Tau and Peterson 2010). Studies also suggest that synaptogenesis (the formation of synapses between neurons in the nervous system) in the fetal brain begins in mid-pregnancy (Tau and Peterson 2010), and disruption in these processes has been linked with altered spatial and trace memory (Ramirez-Amaya et al. 2001; Shors 2004). Notably, we found a sensitive exposure window for PM_{2.5} for VIM around mid-to-late pregnancy. Disrupted myelination and synaptogenesis may also result from neuroimmune activation, which has also been linked to activation of memory related kinase (Yao et al. 2014) as well as neuroapoptosis in the hippocampus that is important to memory (Semmler et al. 2005; Stark et al. 2002). Neuroinflammation induced by air pollution may disrupt the development of hippocampus fields CA1-3 as well as the proliferation of granule neurons within the hippocampus (Bayer

et al. 1993). Brain inflammatory responses may reduce the capacity to provide brain-derived neurotrophic factor (BDNF) needed for memory-related plasticity processes at hippocampal synapses (Patterson 2014). Moreover, animal studies consistently demonstrate microglial activation in response to particle exposure. Microglia are resident macrophages in the CNS that play a critical role in neural development, synaptic plasticity, and neurobehavior. Morphological differences in neuronal dendritic spines (representing the number of synapses formed) and microglial colonization have been demonstrated in the hippocampus, frontal cortex, amygdala and pre-optic area during early development. Pro-inflammatory environmental toxins may activate microglia altering production of cytokines and chemokines that disrupt neurodevelopment. It is also possible that neuroinflammation during mid-to-late pregnancy may disrupt neuroapoptosis, myelination, as well as the synaptic pruning and maturation of the ventral tegmental area (VTA), which is the site of dopaminergic neuron cell bodies that project to the frontal and prefrontal cortex (Donev and Thome 2010; Gillies et al. 2014). The VTA is critical to reward behaviors, motivation and attention. Thus, PM effects on VTA development may, in part, explain our observed effects on attention in boys. More studies are needed to tease out the role of exposure timing and disruption of neuroinflammation, hippocampus and VTA development, and microglial activation.

Sex hormones may also influence these complicated processes and contribute to sex differences induced by pro-inflammatory triggers such as air pollution (Melcangi et al. 2008). For example, estrogens are known to have anti-inflammatory properties mediated by cytokine expression (Shivers et al. 2015). Sex differences in microglial colonization of the CNS have also been observed, with males generally showing a more activated morphology (Schwarz et al. 2012). The neuron-glial signaling cascade may respond to pro-inflammatory triggers such as particulate air pollution differently in males and females due to the bidirectional communication between the neuroendocrine (e.g., sex steroids) and immune systems during fetal development (Morale et al. 2001). These differences in immune response have been posited to explain differences in psychiatric disease prevalence by sex. Our findings suggest that associations with prenatal air pollution might be stronger in boys for attention domains and IQ. Notably, in another prospective urban Boston birth cohort, we previously reported an association between increased postnatal traffic-related air pollution exposure and attention problems that were more evident in school-aged boys compared to girls (Chiu et al. 2013).

In contrast, we found that associations between prenatal PM_{2.5} and memory domains were more evident in girls. To our knowledge, no previous studies have assessed sex differences on the association between prenatal air pollution and memory domains, and thus these findings warrant further replication. As mentioned above, the adverse association between prenatal PM_{2.5} and memory might be partially due to disruption in the development of hippocampal neurons (Bayer et al. 1993). Visual memory, a component of spatial memory, is a known sexually dimorphic trait and girls tend to have poorer performance in this domain than boys. Research suggests that testosterone may enhance hippocampal neurogenesis via increased cell survival in the dentate gyrus through an androgen-dependent pathway which suggests a protective mechanism for boys (Spritzer and Galea 2007). A recent animal study, however, has suggested that male mice might be more susceptible to loss of hippocampal

volumes (Dada et al. 2014). Further research in the role of PM-induced neuroinflammation on sexually dimorphic development is clearly needed.

This study has several strengths. First, we were able to estimate weekly address-specific particulate air pollution exposure for each woman over gestation using a validated state-of-the-art hybrid spatio-temporal LUR model incorporating satellite-derived AOD measures (Kloog et al. 2011). We then leveraged these exposure estimates to implement a data-driven advanced statistical method to objectively identify susceptibility windows for PM_{2.5}. Second, our study population consists of a lower-SES ethnically mixed inner-city cohort that may be more highly exposed to ambient pollution and also more likely to have poorer neurodevelopmental outcomes. That is, this is a more susceptible population in regards to the potential adverse impact of air pollution on neurodevelopment. Finally, this is the first study to examine sex-specific effects of prenatal particulate air pollution on a range of neurodevelopment domains including global intelligence, attention, and memory. We also acknowledge limitations. While results were significant in sex stratified analyses for several test outcomes, we did not find statistically significant interactions between sex and PM_{2.5}, which may be due to our sample size. However, the suggested sex-specific effects warrant future follow-up in larger cohorts. Also, while we were able to control for postnatal air pollution exposure as well as several factors known to be important in children's neurodevelopment, we did not have data on dietary and other environmental factors that may co-vary with air pollution, such as noise exposure. While maternal smoking status was adjusted for in all analyses, we were not able to obtain sufficient information on other source of household secondhand smoking. While we had information on breast feeding status, data on other parenting practices that may influence child neurobehavioral development were not available. However, we controlled for SES-related variables such as education and race, which are correlated with parenting practices. Finally, our results may be more applicable to lower SES racial/ethnic minority populations.

In summary, this study objectively elucidated sensitive prenatal windows and examined sex differences for the association between prenatal PM_{2.5} and neurodevelopmental outcomes in early childhood. Our findings suggest that increased exposure to prenatal particulate air pollution may have sex-specific time-dependent neurotoxic effects that may vary for different cognitive or behavioral domains, which likely reflect different underlying pathways. Advanced statistical methods combined with highly temporally resolved exposure data have great potential for the identification of susceptibility windows that may enhance our ability to find effects and identify vulnerable groups. Our approach is aided by an air pollution model with weekly temporal resolution across pregnancy; however, if other studies could generate similarly highly resolved temporal data on exposure metrics, these same techniques could also be applied to explore the most relevant critical windows.

More studies are needed to replicate these findings in other populations, particularly with respect to exposure timing, as well as to further elucidate underlying mechanisms. Susceptibility windows likely reflect several biological vulnerabilities within these anatomic regions, perhaps related to gene expression, disruption of hormone metabolism, protein modification, upstream DNA modifications or permeability of the blood brain barrier. Joint animal/epidemiologic research may be more efficient than isolated research approaches. For

example, by identifying susceptibility windows in epidemiological research, we may be able to inform the design of animal studies that can utilize this information to induce similar timed exposures while studying induced biological changes specific to the same functional domains.

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Abbreviations

WISC-IV	Wechsler Intelligence Scale for Children-IV
IQ	Intelligence quotient
Conner's CPT-II	Conners' Continuous Performance Test-II
OEs	omission errors
CEs	commission errors
HRT	hit reaction time
WRAML-2	Wide Range Assessment of Memory & Learning, 2nd Edition
GM	general memory index
VEM	verbal memory index
VIM	visual memory index
AC	attention/concentration index
PM_{2.5}	particulate matter with diameter 2.5µm
AOD	aerosol optical depth
LUR	land-use regression
DLM	distributed lag model

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Highlights

- We leverage weekly PM_{2.5} exposure during pregnancy combined with advanced statistics to objectively characterize susceptibility windows of childhood neurodevelopment.
- Increased PM_{2.5} exposure at specific prenatal windows was associated with poorer function across memory and attention domains at age 6–7 years with variable associations based on sex.
- A more definitive understanding of the temporal effects of *in utero* exposure to PM_{2.5} on early childhood outcomes may enhance our understanding of underlying mechanisms.

Figure 1. Sex-specific associations between weekly prenatal PM_{2.5} levels over gestation and full-scale IQ

This figure demonstrates PM_{2.5} exposure over pregnancy and full-scale IQ scores (WISC-IV) using distributed lag models assuming week-specific effects. Models were adjusted for maternal age, race, education, prenatal/postnatal maternal smoking, parity, and blood lead level at neurodevelopmental testing; child's sex was adjusted in the model not stratified by sex. The y-axis represents the change in full-scale IQ percentile associated with a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5}; the x-axis is gestational age in weeks. Lower IQ scores indicate less favorable functioning. Solid lines show the predicted change in the IQ percentile. Gray areas indicate 95% CIs. A sensitive window is identified for the weeks where the estimated pointwise 95% CI (shaded area) does not include zero.

Figure 2. Sex-specific associations between weekly prenatal PM_{2.5} levels over gestation and attention domains

This figure demonstrates PM_{2.5} exposure over pregnancy and attention domains (CPT-II) using distributed lag models assuming week-specific effects. Models were adjusted for maternal age, race, education, prenatal/postnatal maternal smoking, parity, and blood lead level at neurodevelopmental testing; child's sex was adjusted in models not stratified by sex. The y-axis represents the change in attention domain score percentile associated with a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5}; the x-axis is gestational age in weeks. Higher percentiles in attention domains indicate less favorable performance. Solid lines show the predicted change in each test score percentile. Gray areas indicate 95% CIs. A sensitive window is identified for the weeks where the estimated pointwise 95% CI (shaded area) does not include zero.

Figure 3. Sex-specific associations between weekly prenatal PM_{2.5} levels over gestation and memory domains

This figure demonstrates PM_{2.5} exposure over pregnancy and memory domains (WRAML-2) using distributed lag models assuming week-specific effects. Models were adjusted for maternal age, race, education, prenatal/postnatal maternal smoking, parity, and blood lead level at neurodevelopmental testing; child's sex was adjusted in models not stratified by sex. The y-axis represents the change in memory domain score percentile associated with a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5}; the x-axis is gestational age in weeks. Lower percentiles in memory domains indicate less favorable performance. Solid lines show the

predicted change in each test score percentile. Gray areas indicate 95% CIs. A sensitive window is identified for the weeks where the estimated pointwise 95% CI (shaded area) does not include zero.

Figure 4. Sex-specific associations between $PM_{2.5}$ exposure over gestation and attention domains and IQ: Comparing models based on levels averaged over pregnancy vs. identified sensitive windows

This figure demonstrates estimated sex-specific associations and 95% CIs between prenatal $PM_{2.5}$ levels and each attention related domain (CPT-II) and full-scale IQ (WISC-IV) percentiles, obtained from multivariate regression models in which the prenatal $PM_{2.5}$ levels were (A) averaged across the sensitive windows identified by DLMS as in Figures 1 and 2, and (B) averaged over gestation. Higher CPT-II measures (in percentiles) indicate more omission errors, slower HRT, and more variability in response time throughout the test (HRT-SE), whereas lower full-scale IQ (standardized IQ score) indicates poorer composite intellectual performance. Models were adjusted for maternal age, race, education, prenatal/postnatal maternal smoking, parity, and blood lead level at neurodevelopmental testing.

Figure 5. Sex-specific associations between $PM_{2.5}$ exposure over gestation and memory domains: Comparing models based on levels averaged over pregnancy vs. identified sensitive windows

This figure demonstrates estimated sex-specific associations and 95% CIs between prenatal $PM_{2.5}$ levels and each memory-related domain (WRAML-2) percentiles, obtained from multivariate regression models in which the prenatal $PM_{2.5}$ levels were (A) averaged across the sensitive windows identified by DLMs as in Figure 3, and (B) averaged over gestation. Lower percentiles of WRAML-2 measures indicate less favorable memory related performance. Models were adjusted for maternal age, race, education, prenatal/postnatal maternal smoking, parity, and blood lead level at neurodevelopmental testing.

Table 1

Participant characteristics: ACCESS study

	All children (n=267)	Boys (n=148)	Girls (n=119)
Race/Ethnicity			
Black	66	36	30
Hispanic	160	86	74
White/Other	41	26	15
Maternal education (n, %)			
>12 yrs	84	45	39
12 yrs	183	103	80
Maternal smoking status (n, %)			
Never smoked	215	121	94
Smoked prenatally, but not postnatally	14	8	6
Did not smoke prenatally, but smoked postnatally	14	8	6
Smoked both pre- and postnatally	24	11	13
Parity (n, %)			
0	123	67	56
1	144	81	63
Gestational age at birth (weeks; mean, SD)	39.0	38.9	39.1
Maternal age at enrollment (years; median, IQR)	26	23–31.3	27
Child's age at neurodevelopmental test (year; median, IQR)	6.5	6.0–7.1	6.5
Child's blood lead level at neurodevelopmental test ($\mu\text{g/dL}$; mean, SD)	2.25	1.16	2.28
Breast fed for 6 months (n, %)	168	90	78

Table 2

Neurodevelopmental test results and averaged prenatal PM_{2.5} exposure levels by sex

Variables	All children			Boys			Girls		
	Median	IQR	Median	Median	IQR	Median	Median	IQR	IQR
Averaged prenatal PM _{2.5} level (µg/m ³)	11.3	10.5–12.0	11.2	10.4–11.9	11.6	10.6–12.0			
Intelligence quotient; IQ (WISC-IV) ^a									
Full-scale IQ score	94	87–102	93	86–102	95	88–103			
Attention domains (CPT-II) ^b									
Omission errors (OEs) percentile	91.8	62.0–99.0	92.6	58.8–99.0	91.6	67.0–99.0			
Commission errors (CEs) percentile	70.9	45.9–86.5	77.8	52.1–88.1	68.5	44.2–85.4			
Hit reaction time (HRT) percentile	79.3	44.7–94.0	74.9	38.5–94.1	81.5	51.3–93.9			
Hit reaction time standard error (HRT-SE) percentile	91.9	71.3–98.2	91.6	67.1–97.5	92.9	75.2–98.8			
Memory domains (WRAML-2) ^c									
Verbal Memory Index (VEM) percentile	42	21–63	42	21–55	50	27–70			
Visual Memory Index (VIM) percentile	27	12–50	34	8–58	24	12–50			
Attention/Concentration Index (AC) percentile	50	27–73	50	24–73	50	27–73			
General Memory Index (GM) percentile	37	16–55	34	14–55	37	17–55			

^a Lower score in full-scale IQ indicates more adverse functioning

^b Higher percentile in CPT-II measures indicates worse performance

^c Lower percentile in WRAML-2 measures indicates poorer memory functioning