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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 μm ($PM_{2.5}$) and children's neurodevelopment.
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 may be 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.

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.

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 ≤ 2.5 μm; AOD, aerosol optical depth; LUR, land-use regression; DLM, distributed lag model.

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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 (NO_2) 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 NO_2 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 PM_{10} 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 year 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 ≤ 2.5 μm ($PM_{2.5}$) 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 ($\geq$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 $\pm$ 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 $\pm$ 5 years, 69% with high school education or less, 25% black, 60% Hispanic, and 55% male) versus excluded (maternal age 27 $\pm$ 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 $\geq$7 years old.

2.1. Prenatal $PM_{2.5}$ levels

Individuals' prenatal exposure to $PM_{2.5}$, 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 $PM_{2.5}$ as detailed elsewhere (Kloog et al., 2011). The model was run using day-specific AOD data calibrated against ground monitor-based $PM_{2.5}$ measurements derived from 78 monitoring stations covering New England. The model incorporated traditional LUR (traffic density, point sources, etc.) and