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Prenatal $PM_{2.5}$ Exposure and Infant Temperament at Age 6 Months: Sensitive Windows and Sex-Specific Associations

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Abstract

Background: Prenatal exposure to fine particulate matter with a diameter of ≤2.5 microns ($PM_{2.5}$) has been linked to adverse neurodevelopmental outcomes in later childhood, while research on early infant behavior remains sparse.

Objectives: We examined associations between prenatal $PM_{2.5}$ exposure and infant negative affectivity, a stable temperamental trait associated with longer-term behavioral and mental health outcomes. We also examined sex-specific effects.

Methods: Analyses included 559 mother-infant pairs enrolled in the PRogramming of Intergenerational Stress Mechanisms (PRISM) cohort. Daily $PM_{2.5}$ exposure based on geocoded residential address during pregnancy was estimated using a satellite-based spatiotemporal model. Domains of negative affectivity (Sadness, Distress to Limitations, Fear, Falling Reactivity) were assessed using the Infant Behavior Questionnaire-Revised (IBQ-R) when infants were 6 months old. Subscale scores were calculated as the mean of item-specific responses; the global Negative

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Affectivity (NA) score was derived by averaging the mean of the four subscale scores. Bayesian distributed lag interaction models (BDLIMs) were used to identify sensitive windows for prenatal $PM_{2.5}$ exposure on global NA and its subscales, and to examine effect modification by sex.

Results: Mothers were primarily racial/ethnic minorities (38% Black, 37% Hispanic), 40% had ≤12 years of education; most did not smoke during pregnancy (87%). In the overall sample, BDLIMs revealed that increased $PM_{2.5}$ at mid-pregnancy was associated with higher global NA, Sadness, and Fear scores, after adjusting for covariates (maternal age, education, race/ethnicity, sex). Among boys, increased $PM_{2.5}$ at early pregnancy was associated with decreased Fear scores, while exposure during late pregnancy was associated with increased Fear scores (cumulative effect estimate=0.57, 95% CI: 0.03–1.41). Among girls, increased $PM_{2.5}$ during mid-pregnancy was associated with higher Fear scores (cumulative effect estimate=0.82, 95% CI: 0.05–1.91).

Conclusions: Prenatal $PM_{2.5}$ exposure was associated with negative affectivity at age 6 months, and the sensitive windows may vary by subdomains and infant sex.

Keywords

prenatal air pollution exposure; infant temperament; negative affectivity; fear; sex difference; developmental origins of health and disease

1. INTRODUCTION

There has been increased research focused on the health effects of ambient air pollution over the past decade, in part due to anticipated exposure increases and changing distribution patterns related to human activities and climate change. A review from a National Institute of Environmental Health Sciences expert panel highlighted evidence linking outdoor air pollution to central nervous system (CNS) disorders (Block et al., 2012) with growing evidence that the developing fetus may be especially vulnerable (Johnson et al., 2021). Our group and others have reported associations between ambient air pollution exposure in pregnancy, especially fine particulate matter with a diameter of ≤2.5 micrometers ($PM_{2.5}$), and a range of adverse neuropsychological and behavioral disorders in older children (Block et al., 2012; Bose et al., 2019; Chiu et al., 2013; Chiu et al., 2016; Cowell et al., 2015; Johnson et al., 2021; McGuinn et al., 2020; Payne-Sturges et al., 2019; Sunyer and Dadvand 2019). However, associations with early behavioral outcomes are less well understood.

Temperament comprises variations in behavioral tendencies of emotional responses and reactions to stimuli and includes various domains that reflect relatively stable traits over an individual's lifespan. Infant temperament has significant long-term consequences for life course development, including influencing later personality and psychosocial development and risk for emotional and behavioral problems (Gartstein and Rothbart 2003). Domains of negative affectivity (e.g., fear, sadness, distress reactivity and recovery) seem to have particular import for longer-term developmental outcomes (Bosquet Enlow et al., 2017; Gartstein and Rothbart 2003; Tang et al., 2020; Toffol et al., 2019). In addition, negative affectivity has been demonstrated to be a particularly stable trait across the life course, based on the measures of negative affectivity from infancy to later childhood as well as the adult personality factor of neuroticism. Thus, identifying potentially modifiable environmental

risk factors for early precursor behaviors so that interventions can be applied early, to promote optimal development, could have significant implications for prevention of chronic psychopathology.

Research indicates that environmental exposures during pregnancy, particularly those known to influence brain development, can influence temperament outcomes in infants (Takegata et al., 2021). Studies to date have primarily considered maternal stress and prenatal psychological functioning (Bosquet Enlow et al., 2017; Van den Bergh et al., 2020) and exposure to substances including tobacco, alcohol and other drugs (Clark et al., 2016; Froggatt et al., 2020; Guille and Aujla 2019). To our knowledge, no prior study has examined associations between prenatal exposure to $PM_{2.5}$ and infant temperament.

While mechanisms linking prenatal $PM_{2.5}$ and neurodevelopment are not completely understood, pollutant-induced systemic and placental oxidative stress and inflammatory processes that disrupt differentiation and organization of the fetal CNS may play a key role (Sunyer and Dadvand 2019). The CNS develops sequentially with different anatomic regions forming at different life stages and specific processes occurring in a timed cascade (Andersen 2003; Sunyer and Dadvand 2019). Beginning *in utero*, a network of interconnected cells (i.e., neurons) forms in the brain, which stretch across different anatomic regions as well as connecting to peripheral tissues (Lavenex and Banta Lavenex 2013; Tau and Peterson 2010). It has been suggested that several structural components of this network may be differentially susceptible to environmental toxicants depending on exposure timing and the anatomic region of the brain impacted, which have been linked to different domains of neurodevelopment (Rodier 2004). However, both animal and human studies to date have mostly used subjective assignment of exposure timing, either measuring air pollution exposure at a convenient or pre-determined time point, such as trimester-specific averages or exposure averaged over the entire pregnancy, which may be potentially prone to missed or biased associations (Wilson et al., 2017b). Furthermore, studies examining a range of environmental exposures (e.g., toxic metals, bisphenol A, phthalate, organochlorines) (Braun et al., 2011; Engel et al., 2010; Hamadani et al., 2011; Sagiv et al., 2012; Tatsuta et al., 2014), as well as air pollutants (Bolton et al., 2014; Chiu et al., 2013; Chiu et al., 2016; Sentís et al., 2017; Wang et al., 2021), have shown complex sex-specific effects on early childhood neurodevelopment, with these effects also depending on exposure timing.

In this study, we applied advanced statistical methods to objectively identify the sensitive windows of prenatal particulate air pollution exposure on infant negative affectivity and its subdomains (Sadness, Distress to Limitation, Fear, Falling Reactivity/Recovery from Distress) assessed at age 6 months, utilizing highly temporally resolved data on daily exposure to $PM_{2.5}$ measured across pregnancy in a lower-SES ethnically mixed inner-city pregnancy cohort. We hypothesized that increased exposure to fine particulate matter would be associated with higher global negative affectivity. We also hypothesized that the sensitive prenatal exposure windows may be domain-specific and that the associations would vary by sex.

2. METHODS

2.1. Study Participants

Participants were from the PRogramming of Intergenerational Stress Mechanisms (PRISM) project, an ongoing longitudinal pregnancy cohort designed to examine relationships of prenatal stress and other environmental factors with child developmental outcomes. The study recruited n=1110 women receiving prenatal care from the Beth Israel Deaconess Medical Center and East Boston Neighborhood Health Center in Boston, MA (from March 2011–December 2013) and Mount Sinai Hospital in New York City, NY (from April 2013–April 2020). Eligibility criteria included English- or Spanish-speaking, ≥18 years of age, and singleton pregnancy. Exclusions included maternal intake of ≥7 alcoholic drinks/week prior to pregnancy recognition or any after pregnancy recognition, HIV positive status, and congenital abnormalities that could impact participation. Supplemental funding supported the assessment of infant temperament at age 6 months after study initiation. The analytic sample includes n=559 mother-child dyads (enrolled at 23.0±8.9 weeks gestation) with data on both prenatal ambient $PM_{2.5}$ exposure levels and infant temperament. Most of the basic characteristics of those enrolled and those who were included in the analysis were similar (including maternal age at delivery, maternal education, maternal smoking status, and child sex; all p-values>0.1), except that the composition of maternal race/ethnicity was different with the analytic sample having slightly more Hispanic (36.7% vs. 33.5%) and White (19.9% vs. 14.0%) than the full sample (p=0.03, Online Supplement, Table S1). When comparing to those excluded from the analysis (due to assessments for infant temperament and/or $PM_{2.5}$ exposure data not available), the analytic sample also appears to be slightly older (median 29.9 vs. 28.1 years; p=0.01) with more non-smokers (87.5% vs. 79.3%; p=0.04). Procedures were approved by the relevant institutions' human studies committees; mothers provided written consents in their primary language.

2.2. Prenatal $PM_{2.5}$ Exposure

Individual level prenatal daily exposure to $PM_{2.5}$ for each woman was derived based on the residential address across each woman's pregnancy period and updated if the participant moved. Exposure levels of ambient $PM_{2.5}$ were estimated using a hybrid satellite-based spatio-temporal prediction model, as detailed previously (Just et al., 2020). Briefly, we regressed daily surface $PM_{2.5}$ measurements (obtained by U.S. Environmental Protection Agency Air Quality System and Interagency Monitoring of Protected Visual Environments Network) on satellite-derive aerosol optical depth (AOD) measurements (1 km^2 spatial resolution). To determine residence-specific daily $PM_{2.5}$, we included meteorological variables and land-use terms in machine learning algorithms, which helped to minimize the prediction error and accurately estimate the daily exposures (Just et al., 2020). We calibrated our daily prediction models and validated the estimates with a robust out of sample 10-fold cross-validation (R^2=0.87). For infants born prior to 40 weeks gestation, exposure estimates for the remaining weeks were based on postnatal $PM_{2.5}$ estimates corresponding to this time.

2.3. Infant Negative Affectivity

Mothers completed the Infant Behavior Questionnaire-Revised (IBQ-R) during an in-person interview when infants were 6.3±1.2 months old (Gartstein and Rothbart 2003). The IBQ-R

is a widely used tool to assess temperament in infants aged 3–12 months with demonstrated validity in English and Spanish samples (Gartstein et al., 2006; Gonzalez-Salinas et al., 2000; Parade and Leerkes 2008). Mothers reported on the frequency of 191 specific infant behaviors as well as reactions to concrete situations within the prior two weeks. A trained research assistant read each item to the mother and recorded her response on a 7-point scale (1=never, 7=always). Scores were calculated, including the four scales (Sadness, Distress to Limitations, Fear, and Falling Reactivity/Rate of Recovery from Distress) that have been found to load on the global dimension of Negative Affectivity in previous factor analysis studies (Gartstein and Rothbart 2003) and confirmed in our sample (Bosquet Enlow et al., 2016). In brief, the Sadness scale is based on 14 items examining lowered mood and activity in relation to personal suffering, physical state, object loss, or inability to perform a desired action; the Distress to Limitations scale includes 16 items assessing the infant's tendency to being distressed (i.e., fussing, crying) during caretaking activities like bathing, being unable to perform a certain action or when put in confined places or positions like a playpen or a car seat; the Fear scale consists of 16 items on the IBQ-R, assessing an inhibited approach to novelty, or being startled or distressed to sudden changes in physical or social stimuli; and the Falling Reactivity/Rate of Recovery from Distress scale includes 13 items assessing an infant's ease at falling asleep, or their recovery from being distressed or excited. The Falling Reactivity / Recovery from Distress scale was reversed coded so that all the subscale scores reflect the same directionality (i.e., a higher score indicates greater negative affect). Each scale's score was calculated by taking the mean of the participant's item-specific responses. The global Negative Affectivity (NA) factor score was derived by averaging the mean of the four subscale scores.

2.4. Covariates

Women reported age, race/ethnicity, and education level at enrollment; child's sex and date of birth were extracted from medical records. Gestational age at birth was extracted from a mother's medical record; if not available via medical records, it was then derived based on: (1) difference between date of delivery and self-reported last menstrual period, and (2) ultrasound estimates from the first-trimester examination. Maternal prenatal smoking status was classified based on a mother's affirmative response to "do you currently smoke cigarettes?" and/or "do you currently smoke pipes or cigars?", and/or "how many cigarettes do you smoke per day" in any prenatal visits, as well as mother's recall at postnatal 1-month visit to these questions: "did you use any cigarettes at any point during your pregnancy?" and/or "on average, how many cigarettes did you smoke per day during pregnancy?". Women reported on postnatal smoking at postnatal 1-month visit as well as each telephone follow-up visit starting at 2 months postpartum with 4-month intervals. Secondhand smoke exposure was ascertained by collecting the information on environmental exposure to cigarette, cigar, or pipe smoke at home, work, and restaurants during pregnancy; women were classified as exposed to secondhand smoke if they were living with smoker(s) at home, or exposed to environmental tobacco smoke for at least one hour per week during pregnancy. Race/ethnicity was categorized as Black/Hispanic-Black, non-Black Hispanic, non-Hispanic White, and Other in the analysis.

2.5. Statistical Analysis

First, we derived the frequencies and distributions of the sociodemographic variables, including maternal age at delivery, maternal education, maternal race/ethnicity, and tobacco smoke exposure, as well as prenatal $PM_{2.5}$ exposure levels averaged at each trimester and the Infants' IBQ-R scores. Participant characteristics were derived for the sample as a whole, as well as based on child sex. Wilcoxon rank sum test and χ^2 test were used as appropriate to compare the difference in these variables between boys and girls.

For the primary analyses, we estimated the overall and sex-specific time-varying associations between daily $PM_{2.5}$ exposure during pregnancy and infant temperament scale scores using Bayesian distributed lag interaction models (BDLIMs) (Wilson et al., 2017a). This approach assumes that $PM_{2.5}$ effects in any given exposure window is linear but allows the effects to vary nonlinearly across exposure windows. We first fit models assuming a common distributed lag effect for all subjects in the data, and then fit distributed lag interaction models to the sample to examine differences in both the magnitude and timing of effects by infant sex. The BDLIM for child i (i = 1, …, n) who is sex j (j = 0 for female and j = 1 for male) is $E\left(Y_i\right) = a_j + \beta_j \sum_{t=1}^{T} w_{jt} X_{it} + Z_i' \gamma$, where a_j is a fixed sex-specific intercept, β_j is the regression coefficient characterizing the sex-specific association between weighted $PM_{2.5}$ exposure and infants' temperament scores, $\sum_{t=1}^{T} w_{jt} X_{it}$ is the weighted exposure, with T denoting the number of timepoints, and $Z_i' \gamma$ is the covariate regression term. The w_{jt} (weights) identifies critical windows of susceptibility while β_j identifies the within window effect. When weights are constant across time, this is equivalent to using mean exposure. However, when the weight varies by the time the model assigns greater relative weight to some periods. Time periods with weights substantially different from zero identify critical windows. The model uses a smooth orthonormal basis based on the joint distribution of the time-resolved exposure data to smooth the w_{jt} terms. Four patterns of effect modification by child sex was examined by allowing β_j (effect magnitude) and/or the weights w_{jt} (critical window) to be sex-specific or the same for both sexes: 1) boys and girls have different critical windows and the within-window association between prenatal $PM_{2.5}$ and infant temperament also differs by sex; 2) boys and girls have different critical windows but the same magnitude of within-window association; 3) boys and girls have the same critical window but different magnitude of within-window association; and 4) boys and girls have the same critical window and within-window association (i.e., no modification). Posterior model probability and deviance information criterion (DIC) were used to determine the model that best fit the data.

In secondary analyses, we conducted multivariable-adjusted linear regression models using trimester-averaged exposures (TAEs) as previously described (Wilson et al., 2017b), for comparison with BDLIM results (detailed in Online Supplement). Stratified analyses were also conducted to examine effect modification by child sex in these secondary analyses. All models were adjusted for maternal age at delivery, race/ethnicity, and education, as well as child sex for the overall sample. Finally, sensitivity analyses were conducted by additionally adjusting for maternal perinatal smoking status and secondhand smoke exposure during pregnancy, as well as additionally adjusting for calendar year at childbirth to account

for potential temporal trends in the exposure and outcome measurements. Analyses were conducted using the "*regimes*" package (Wilson et al., 2017a) in *R* (v4.0.3, Vienna, Austria), as well as SAS statistical software (v9.4, SAS Institute Inc., Cary, NC).

3. RESULTS

Descriptive characteristics for the sample overall as well as stratified by infant sex are shown in Table 1. The majority of women were ethnic minorities (37.6% Black, 36.7% Hispanic) and more than one third had ≤12 years of education (40.4%); most women did not smoke during pregnancy (87.5%). Sociodemographic characteristics of the mothers were mostly similar between infant sex (all p-values>0.2), except that mothers of male infants on average had higher education level (p=0.04). For infant temperament, boys and girls on average had similar global NA factor and subscale scores, except that girls had higher Fear scale scores compared to boys (p=0.01). Prenatal $PM_{2.5}$ exposure levels were similar between mothers of male infants and mothers of female infants across trimesters. The $PM_{2.5}$ exposures across trimesters were weakly correlated (Spearman correlation coefficient r=0.09 (p=0.05), r=0.19 (p<0.01), and r=0.14 (p=0.002) between 1st and 2nd trimesters, 2nd and 3rd trimesters, and 1st and 3rd trimesters, respectively).

Time-weighted cumulative effect estimates across the entire pregnancy estimated by BDLIMs were in the hypothesized direction for the global NA factor as well as subscale scores although none reached statistical significance in the sample overall (Figure 1). Sex-specific time-weighted cumulative effects across the entire pregnancy were significantly associated with increased Fear scores in both boys (cumulative effect estimate=0.57, 95% CI: 0.03–1.41, corresponding to per 10 $\mu g/m^3$ increase in $PM_{2.5}$) and girls (cumulative effect estimate=0.82, 95% CI: 0.05–1.91) (Figure 2). We did not find evidence of significant sex-specific time-weighted cumulative effects for other subscales or global NA scores, although the effect estimates were generally more suggestive in girls (Figure 2).

In the sample overall, we found time-varying associations with significant sensitive windows between prenatal $PM_{2.5}$ exposure and infant outcomes, including global NA factor, Sadness, and Fear scale scores (Figure 3). In adjusted analyses, the BDLIM identified that increased daily $PM_{2.5}$ exposure from 14–20 weeks gestation and towards the end of gestation were significantly associated with an increased global NA factor. Increased daily $PM_{2.5}$ exposure from 15–19 weeks gestation was also significantly associated with the Sadness subscale score. Increased daily $PM_{2.5}$ exposure during weeks 2–4 gestation was significantly associated with decreased Fear scores, while increased daily $PM_{2.5}$ exposure in from 37–40 weeks gestation was significantly associated with increased Fear scores. As seen in Figure 3(C), exposure in mid-pregnancy was also suggestively associated with increased Fear scores but it did not reach statistical significance at α=0.05 level. We did not find any significant exposure windows for Distress of Limitations or Recovery from Distress scales (Online Supplement, Figure S1).

When examining effect modification by infant sex, BDLIMs demonstrated that the significant windows of exposure were different in boys and girls for the Fear subscale (Figure 4). Based on the posterior model probability and DIC, the model indicated that

the magnitude of the time-varying association between prenatal $PM_{2.5}$ exposure and Fear scores was similar in boys and girls, but the sensitive windows differed. The normalized posterior density of 0.76 supported this model (common effect magnitude, but different sensitive window) as the best-fitting pattern of effect modification by fetal sex. Among boys, increased daily $PM_{2.5}$ exposure in early pregnancy (1–4 weeks gestation) was significantly associated with decreased Fear scores, while increased daily $PM_{2.5}$ exposure in late pregnancy (35–40 weeks gestation) was significantly associated with elevated Fear scores. Among girls, increased daily $PM_{2.5}$ exposure in mid-pregnancy (20–24 weeks gestation) was significantly associated with elevated Fear scores.

Results from multivariable-adjusted linear regression models using trimester-specific exposure averages were generally consistent albeit less significant given reduced power that resulted from averaging exposure over periods of time inside and outside of the estimated sensitive windows (Online Supplement, Table S1). Results from sensitivity analyses additionally adjusting for maternal perinatal smoking and secondhand smoke exposure during pregnancy (Online Supplement, Table S2), as well as calendar year at childbirth (Online Supplement, Figure S2), were materially unchanged.

4. DISCUSSIONS

To our knowledge, this is the first epidemiological study to investigate the association between maternal $PM_{2.5}$ exposures across gestation and early infant negative affectivity. We found that sensitive prenatal exposure windows varied for different subscales comprising the global NA factor score, with increased $PM_{2.5}$ exposure being most significantly associated with higher fearful behaviors in both boys and girls at age 6 months. However, the sensitive windows for prenatal $PM_{2.5}$ effects differed based on infant sex.

Infant temperament has been linked to lifetime consequences for neurobehavioral development, such as delayed personality and social development and increased risk of behavioral or emotional problems (Gartstein and Rothbart 2003). Negative affectivity involves the negative emotions (e.g., anger, fear, disgust, guilt, contempt, etc.) and low self-concept (Koch et al., 2013), and has been shown to be relatively stable throughout the life course and to play an important role in behavioral developmental outcomes (Tang et al., 2020; Toffol et al., 2019). Negative affectivity during infancy has been linked to negative affectivity during later childhood, as well as neuroticism in adulthood that leads to vulnerable personality traits including anger, anxiety and depression, irritability, and emotional instability (Gartstein and Rothbart 2003; Widiger and Oltmanns 2017). Internalizing problems, most prominently anxiety and depressive disorders, affect 400 million individuals globally (Beesdo et al., 2010) and share common features including negative affect (Feola et al., 2020). Negative affect in early childhood predicts internalizing disorders in adolescence and later life (Bould et al., 2014; Clauss et al., 2015) and fearful reactivity is believed to specifically tap infants' subsequent risk for anxiety problems (Chronis-Tuscano et al., 2009; Clauss and Blackford 2012). The IBQ-R Sadness scale captures general low mood, characterized by lowered mood and activity related to personal suffering, physical state, object loss, or inability to perform a desired action. The IBQ-R Fear scale reflects general behavioral inhibition, including startle or distress to sudden

changes in stimulation or novel physical objects or social stimuli leading to inhibited approach to novelty. Distinct circuitry in the brain has been linked to fear and sadness temperamental domains (Thomas et al., 2019). Pathological anxiety has been conceptualized as the hyperexcitability of fear circuits and sadness related circuitry plays a role in mood disorders (Rosen and Schulkin 1998). This circuitry starts to develop prenatally (Thomas et al., 2019). Thus, our findings are in line with a handful of studies demonstrating associations between prenatal air pollutant exposure and internalizing symptoms in later childhood. A rodent study reported that rats exposed to nanoscale particulate matter from gestation into the postnatal period showed elevated depressive behaviors (Woodward et al., 2018). In humans, a large nationwide population-based longitudinal study in Japan reported significant associations between prenatal air pollution exposure (including suspended particulate matter, nitrogen dioxide and sulfur dioxide) and emotional inhibition (unable to express emotions) at age 5.5 years (Yorifuji et al., 2016). In a birth cohort in New York City, increased prenatal exposure to polycyclic aromatic hydrocarbons (PAH) was associated with increased symptoms of anxiety and depression in children aged 6–7 years (Perera et al., 2012).

Our findings are also consistent with prior research in both animal (Bolton et al., 2014) and human (Chiu et al., 2013; Chiu et al., 2016; Sentís et al., 2017; Wang et al., 2021) demonstrating sex-specific associations between prenatal air pollution exposure and offspring neurodevelopment later in life. Notably, in distributed lag models, heightened exposure to $PM_{2.5}$ in mid-pregnancy was associated with increased global NA scores as well as higher sadness and fear scores in the sample overall. When also accounting for sex-specific effects, time-weighted cumulative effects over gestation were most significantly associated with increased fear scores in both boys and girls. While a sensitive window for effects of $PM_{2.5}$ on fear behaviors was identified in the second trimester (20 to 24 weeks gestation) in girls in subsequent distributed lag models, windows in early and late pregnancy were evident among boys. Indeed, taken together, these finding exemplify advantages of the BDLIMs. It is interesting that we saw similar significant time-weighted cumulative effect estimates and associated confidence bounds in the sex-specific estimates for Fear subscale from the BDLIMs (Figure 2). In a more standard statistical approach, one would expect that estimating the effect in the entire sample, where the sample size essentially doubled, would show approximately the same magnitude of effect but be more precise with a narrower confidence interval. However, as seen in Figure 1, while the cumulative effect estimate for the overall sample is about the same as the sex-specific estimates shown in Figure 2, it was less precise based on the wider confidence interval and nonsignificance. Presumably this shows the advantage of allowing different sensitive windows for different sexes (i.e., different exposure weightings at different timepoints), since the model for the overall sample constrained the same window for boys and girls and this misspecified assumption had resulted in less precise effect estimates.

These findings also suggest complex associations between prenatal exposure to fine particulate matter and fetal sex that likely reflect differences in underlying CNS structure and function as well as timing of neural circuitry development that may vary based on sex. While the underlying mechanisms are not well understood, a number of factors may play a role. In early development, differing structure volumes, neuronal morphology, and cascading

development of synaptic connections based on fetal sex lead to sexually dimorphic brain circuitry (Cosgrove et al., 2007; Sacher et al., 2013; Schwarz and McCarthy 2008). Glucocorticoids and sex steroids differentially influence kinetics and toxicity of chemicals in males and females (Knoedler and Shah 2018; Mitsui et al., 2019). Sex differences in antioxidant defense, metabolizing enzymes, and placental responses also likely play a role (Minghetti et al., 2013; Rosenfeld 2015).

Being able to more precisely identify susceptibility windows for toxic exposures on CNS development, that may differ based on fetal sex, can provide unique insights informing future mechanistic studies. Rodent studies found increased neuroinflammation from particulate matters in several brain regions (Costa et al., 2017) and may result in changes in brain structures, including decreased thickness of the prefrontal cortex (Semmler et al., 2005) which have been linked to behavioral disorders in human studies (Hauser et al., 2014). Air pollution induced neuroinflammation can disrupt the development of CA1–3 fields of the hippocampus and the proliferation of granule neurons in the hippocampus (Bayer et al., 1993), and lesions in CA1 and CA3 fields have been linked to the development of fear responses in rodent models (Ji and Maren 2008). It has also been suggested that synaptogenesis (formation of synapses between neurons) in the fetal brain begins in the second trimester or mid-pregnancy (Tau and Peterson 2010), and disruption in synaptogenesis has been associated with behavioral deficits (Washbourne 2015). Notably, we found a significant sensitive exposure window of $PM_{2.5}$ in intervals during the second trimester for the global NA factor (14–20 weeks gestation) and Sadness subscale (15–19 weeks gestation) in the overall sample, and it was also significant for the Fear subscale in girls (20–24 weeks gestation). Neuroinflammation during mid- to late pregnancy can disrupt neuroapoptosis, myelination and 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). Development of the amygdala, an area of the brain contributing to emotional processing where its reactivity has been linked to behavioral inhibition and fear in particular (Thomas et al., 2019), begins to develop later in pregnancy with rapid changes right after birth (Gilmore et al., 2012; Humphrey 1968; Payne et al., 2010; Tottenham and Gabard-Durnam 2017). Oxidative stress disrupts circuitry linked to anxiety behaviors (McCoy et al., 2019) and other evidence shows that boys may be more vulnerable to *in utero* oxidative stress compared to girls (Minghetti et al., 2013). It is thus plausible that the mechanism underlying the finding of the sensitive window in boys for elevated Fear scale scores (35–40 weeks gestation) involves PM-induced oxidative stress in late pregnancy, leading to disruption of synaptic connectivity in the VTA and/or amygdala.

Interestingly, we also observed a relationship of maternal exposure to $PM_{2.5}$ in the first month of pregnancy with decreased Fear scale scores in the overall sample, and it was most evident among boys. Attenuated expression of fear behaviors are correlated with lower anxiety risk and reduced risk aversion (Kim et al., 2021). As higher fear behaviors in early childhood development have been linked with later internalizing problems; it is interesting in this context to note a large body of research finding a higher likelihood of developing anxiety traits and depression in females compared to males (Feingold 1994; Salk et al., 2017). Conversely, though studies in early childhood are limited, males generally

display more risk-taking behaviors, recklessness, aggression, and poorer impulse control than females (Cross et al., 2011), with animal studies suggesting a role for sex hormones in these traits (Weafer and de Wit 2014). These observed differences between boys and girls may in part be attributable to the sex-dependent role of the amygdala in the development of behavioral responses to threatening environmental or novel stimuli as observed in primate studies (Raper et al., 2013a; Raper et al., 2013b).

This study has several strengths. We utilized address-specific daily $PM_{2.5}$ exposure data estimated in high temporal and spatial resolutions for each woman over the pregnancy period using a validated hybrid spatio-temporal LUR model incorporating satellite-derived AOD measures (Just et al., 2020). These high-resolution exposure estimates were then leveraged to apply an advanced data-driven statistical method to objectively identify sensitive exposure windows of $PM_{2.5}$. Measuring prenatal exposure in a less relevant susceptibility window may miss or lead to underestimated or even biased associations (Wilson et al., 2017b). However, the exact sensitive windows are usually unknown, and it has been underscored that arbitrarily defined clinically defined trimesters may not correspond to pertinent vulnerable periods of fetal brain development (Tau and Peterson 2010). Therefore, in our primary analyses, we used an advanced data-driven statistical approach (BDLIMs) utilizing higher temporal resolution exposure data (daily) to identify potential sensitive windows of exposure rather than pre-determining the exposure timeframes. As expected, based on previous simulation studies (Wilson et al., 2017b), the results from our secondary analyses using trimester-averaged exposure (TAE) methods ($PM_{2.5}$ averaged over clinically defined trimesters) with traditional linear regressions showed that the direction and patterns of the effect estimates were generally consistent with the results from BDLIMs, but the flexibility of the BDLIMs provide increased power to detect time-varying associations and significant sensitive windows. This suggests that studies only measuring exposure at a certain time point or analyses using arbitrarily pre-defined exposure periods, such as clinical trimesters, may diminish the ability to identify the associations if the sensitive window only consists of a portion of a given trimester or crosses trimesters. In addition, our study population consists of an ethnically mixed lower-SES inner-city cohort that may be more highly exposed to ambient pollution and also more prone to poorer temperament outcomes. Further, this is to our knowledge the first study to examine sex-specific time-varying effects of prenatal particulate air pollution on infant temperament. Given well documented sexually dimorphic effects of a number of environmental toxins including air pollutants on neurodevelopment starting prenatally, effects may be obscured when not accounting for fetal sex.

We also acknowledge limitations. While we utilized high-resolution outdoor $PM_{2.5}$ exposure data based on mothers' residential addresses during pregnancy and updated if they reported moving, we did not have detailed mobile profiles of mothers' locations during the day or data on indoor air pollution exposure. We did, however, adjust for tobacco smoke exposure, which is a major contributor to indoor air pollution. This adjustment did not influence our findings. Also, while we were able to control for sociodemographic factors known to be related to childhood neurodevelopment as well as perinatal smoking, we did not have data on other environmental factors that may co-vary with air pollution, such as noise exposure. Our results may be more generalizable to lower SES racial/ethnic minority populations. It

will be important to corroborate our findings in larger samples comprised of varying racial/ethnic and sociodemographic characteristics as well as to enhance power to detect complex interactions, as our sample size may not have had enough power to detect some effects. The current study considered ambient $PM_{2.5}$ in two cities in the Northeastern U.S., which may reflect a narrower range of the exposure relative to that observed across the U.S. and therefore reduce the power to detect effects. Future studies in geographic areas with greater variability of exposure are also warranted. Nonetheless, it is also notable that we found significant associations with infant negative affectivity even with the lower-level exposures observed in our study, which are below the U.S. EPA annual standard of 12 $\mu g/m^3$. Studies showing that adverse developmental effects may extend to lower exposure ranges is important for evaluating whether current air quality standards are adequate for protecting the public's health. Future studies are also needed to more specifically elucidate mechanisms underlying PM-induced neurotoxic effects on sexually dimorphic temperamental outcomes.

In summary, this study employed a data-driven approach to identify sensitive prenatal windows and to examine sex-specific associations between prenatal $PM_{2.5}$ and negative affectivity in early infancy. We found that increased exposure to prenatal particulate air pollution has sex-specific time-dependent effects that varied across the overarching construct of negative affectivity and related subdomains, which likely reflect complex underlying pathways. Population-based epidemiological studies utilizing highly temporally and spatially resolved exposure data combined with data-driven statistical approaches can provide unique information to guide future mechanistic studies. Elucidating the environmental factors that influence negative affectivity early in development, particularly those domains associated with internalizing disorders, may provide essential information to understand the earliest origins of adverse mental health and behavioral problems (Bosquet Enlow et al., 2017). Identifying modifiable risk factors and being able to identify those at risk as early in development as possible, will allow for interventions that place children on a more optimal developmental trajectory and prevent chronic psychopathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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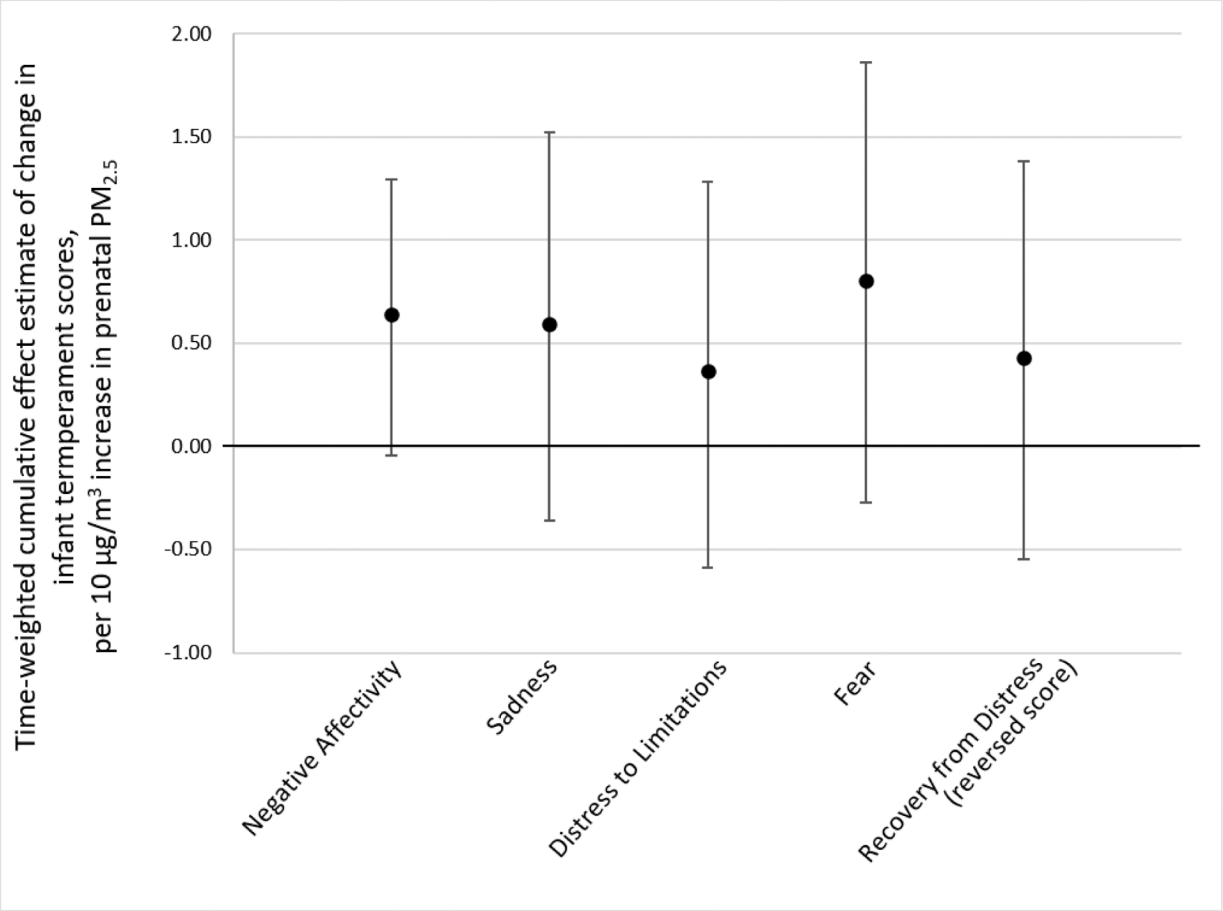

Figure 1. Time-weighted cumulative effect estimates per 10 µg/m^3 increase in prenatal $PM_{2.5}$ level across pregnancy on infant IBQ-R Negative Affectivity scores.

Time-weighted cumulative effects of $PM_{2.5}$ exposure across pregnancy on infant Negative Affectivity factor (and its subscales) scores estimated by BDLIMs, accounting for both sensitive windows and within-window effects. The models were adjusted for maternal age at delivery, race/ethnicity, maternal education status, and child sex. Cumulative effect estimates suggested that increased $PM_{2.5}$ exposure across pregnancy are generally associated with increased Negative Affectivity, although did not reach statistical significance.

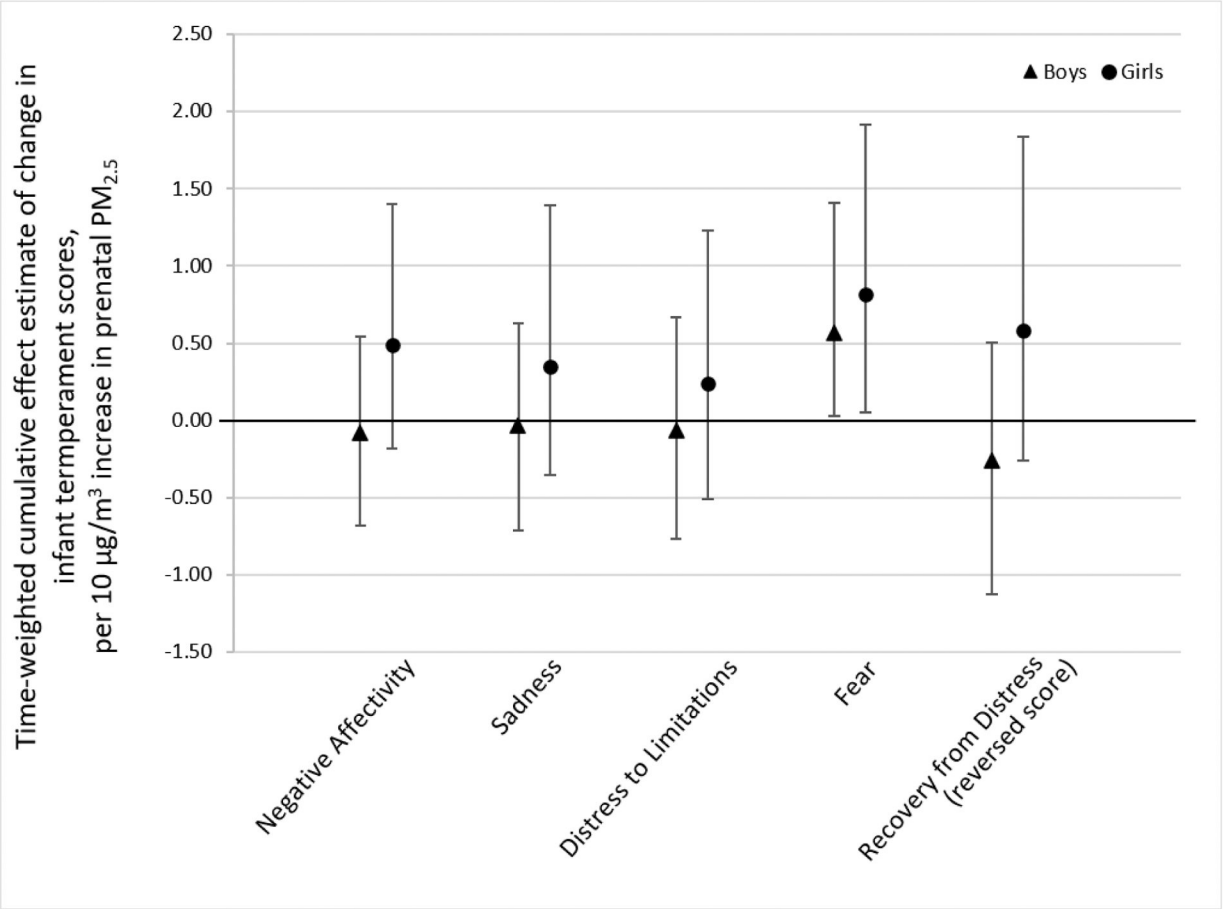

Figure 2. Sex-Specific time-weighted cumulative effect estimates per 10 µg/m^3 increase in prenatal $PM_{2.5}$ level across pregnancy on infant IBQ-R Negative Affectivity scores.

Sex-specific time-weighted cumulative effects of $PM_{2.5}$ exposure across pregnancy on infant Negative Affectivity factor (and its subscales) scores estimated by BDLIMs, accounting for both sensitive windows and within-window effects (triangles: boys, circles: girls). The models were adjusted for maternal age at enrollment, race/ethnicity, and maternal education status.

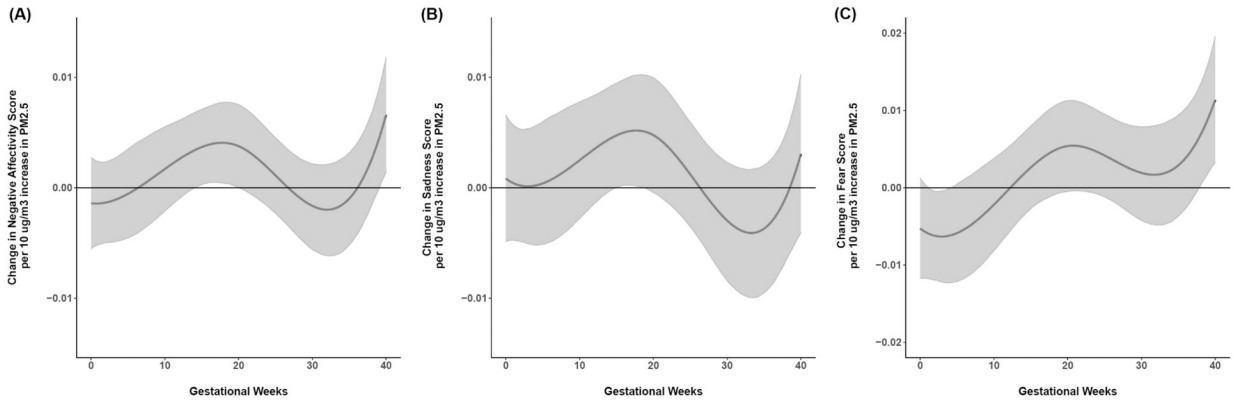

Figure 3. Time-varying effect estimates (95% CIs) of change in infant IBQ-R Negative Affectivity scores corresponding to per 10 μg/m^3 increase in prenatal daily $PM_{2.5}$ levels.

Each panel demonstrates the results for different infant temperament domain scores in separate models: (A) Negative Affectivity factor, (B) Sadness, (C) Fear. Models were estimated by BDLIMs, adjusting for maternal age at delivery, race/ethnicity, education, and child sex. The x-axis demarcates gestational age in days (labeled as weeks for presentation purposes). The y-axis represents the change of infant temperament scores per 10 μg/m^3 increase in prenatal $PM_{2.5}$ exposure. The solid line represents the predicted effect estimate, and the gray area indicates the 95% confidence interval (CI). A significant sensitive exposure window is identified for the time periods where the estimated pointwise 95% CI (shaded area) does not include zero.

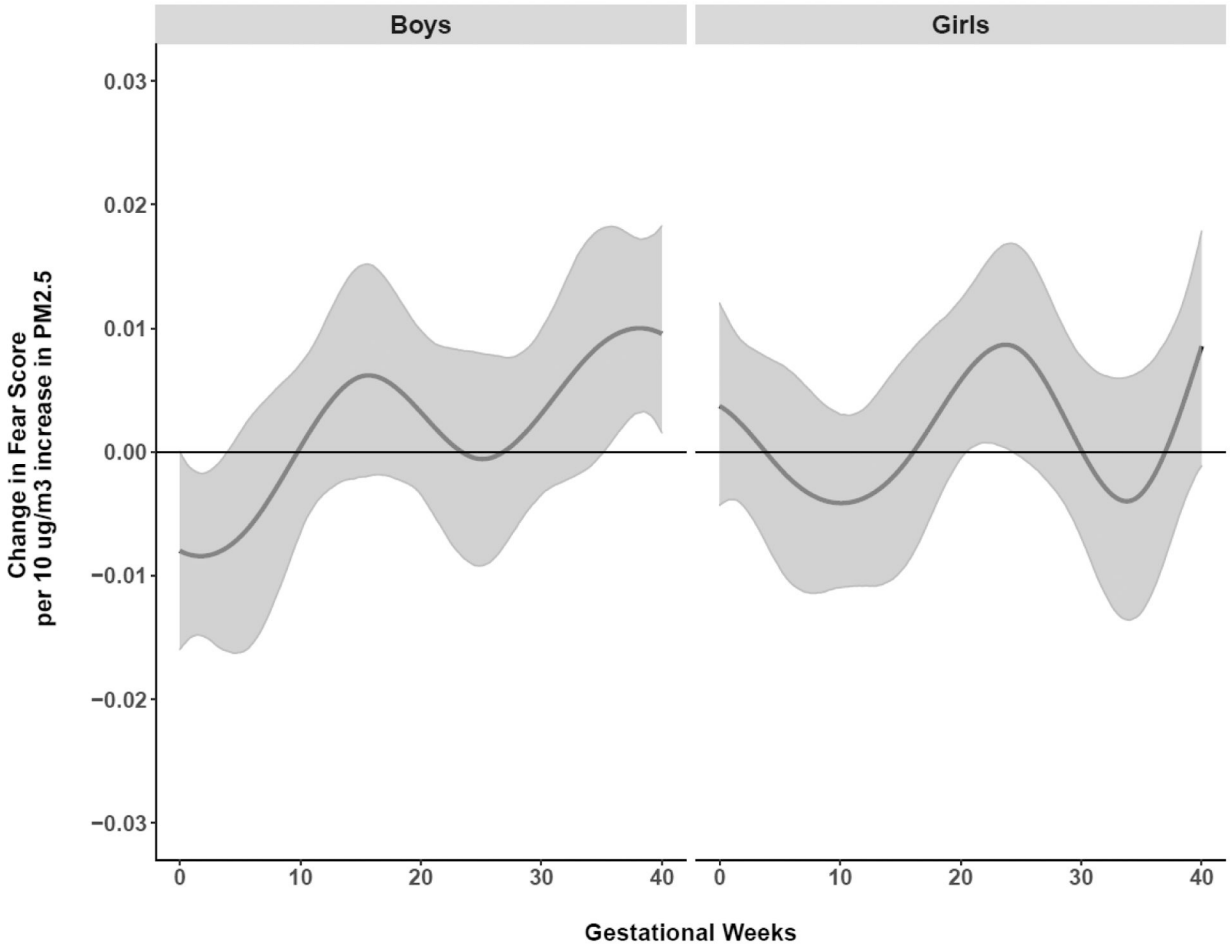

Figure 4. Sex-specific time-varying effect estimates (95% CIs) of change in infant IBQ-R Fear scores per 10 μg/m^3 increase in prenatal daily $PM_{2.5}$ levels.

Sex-specific time-varying associations between prenatal daily $PM_{2.5}$ exposure and Fear score were estimated by a BDLIM, adjusting for maternal age at delivery, race/ethnicity, and education. The x-axis demarcates gestational age in days (labeled as weeks for presentation purposes). The y-axis represents the change of infant Fear score per 10 μg/m^3 increase in prenatal $PM_{2.5}$ exposure. The solid line represents the predicted effect estimate, and the gray area indicates the 95% confidence interval (CI). A significant sensitive exposure window is identified for the time periods where the estimated pointwise 95% CI (shaded area) does not include zero.

Table 1.

Participant Characteristics: PRISM Study

	All Children (N=559)		Child sex: Boys(n=301)		Child sex: Girls (n=258)		p-value[b]
Maternal age at delivery							
Age in years (median, IQR[a])	29.9	(24.9–34.3)	29.8	(24.5–33.6)	30.0	(25.1–34.8)	0.28
Maternal education (n, %)							0.04
>12 years	333	59.6	191	63.5	142	55.0	
≤12 years	226	40.4	110	36.5	116	45.0	
Maternal race/ethnicity (n, %)							0.38
Black/Hispanic-Black	210	37.6	109	36.2	101	39.2	
Non-Black Hispanic	205	36.7	107	35.6	98	38.0	
Non-Hispanic White	111	19.9	63	20.9	48	18.6	
Other/unknown	33	5.9	22	7.3	11	4.3	
Maternal perinatal smoking (n, %)							0.58
Did not smoke	485	86.8	256	85.1	229	88.8	
Smoked prenatally, but not postnatally	25	4.5	16	5.3	9	3.5	
Smoked postnatally, but not prenatally	4	0.7	2	0.7	2	0.8	
Smoked both prenatally & postnatally	45	8.1	27	9.0	18	7.0	
Secondhand smoke exposure during pregnancy (n, %)							
No	346	61.9	183	60.8	163	63.2	0.56
Yes	213	38.1	118	39.2	95	36.8	
Prenatal $PM_{2.5}$ exposure level ($\mu g/m^3$; median, IQR)							
1st Trimester	9.07	(7.99–10.39)	9.14	(7.96–10.43)	9.00	(8.04–10.36)	0.99
2nd Trimester	8.76	(7.76–9.84)	8.74	(7.69–9.63)	8.77	(7.85–9.98)	0.26
3rd Trimester	8.55	(7.39–9.73)	8.46	(7.37–9.78)	8.57	(7.45–9.71)	0.96
Prenatal average	8.93	(8.27–9.74)	8.89	(8.25–9.60)	8.95	(8.32–9.78)	0.30
Child IBQ-R scores (median, IQR)							
Negative Affect	3.0	(2.6–3.5)	3.0	(2.7–3.5)	3.1	(2.6–3.5)	0.90
Sadness	3.2	(2.6–3.8)	3.3	(2.6–3.8)	3.1	(2.6–3.9)	0.79
Distress to Limitations	3.6	(3.0–4.2)	3.6	(3.0–4.2)	3.6	(3.0–4.2)	0.78
Fear	2.4	(1.8–3.3)	2.3	(1.7–3.1)	2.5	(1.8–3.6)	0.01
Recovery from Distress (reversed score)	2.8	(2.2–3.5)	2.8	(2.3–3.5)	2.8	(2.0–3.5)	0.21

[a] IQR = interquartile range (25th percentile – 75th percentile).

[b] p-values of the tests comparing between boys and girls. Wilcoxon ranked sum test for continuous variables, and χ^2 test for categorical variables.