

Prenatal Exposure to PM_{2.5} and Cardiac Vagal Tone during Infancy: Findings from a Multiethnic Birth Cohort

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BACKGROUND: The autonomic nervous system plays a key role in maintaining homeostasis and responding to external stimuli. In adults, exposure to fine particulate matter (PM_{2.5}) has been associated with reduced heart rate variability (HRV), an indicator of cardiac autonomic control.

OBJECTIVES: Our goal was to investigate the associations of exposure to fine particulate matter (PM_{2.5}) with HRV as an indicator of cardiac autonomic control during early development.

METHODS: We studied 237 maternal–infant pairs in a Boston-based birth cohort. We estimated daily residential PM_{2.5} using satellite data in combination with land-use regression predictors. In infants at 6 months of age, we measured parasympathetic nervous system (PNS) activity using continuous electrocardiogram monitoring during the Repeated Still-Face Paradigm, an experimental protocol designed to elicit autonomic reactivity in response to maternal interaction and disengagement. We used multivariable linear regression to examine average PM_{2.5} exposure across pregnancy in relation to PNS withdrawal and activation, indexed by changes in respiration-corrected respiratory sinus arrhythmia (RSA_c)—an established metric of HRV that reflects cardiac vagal tone. We examined interactions with infant sex using cross-product terms.

RESULTS: In adjusted models we found that a 1-unit increase in PM_{2.5} (in micrograms per cubic meter) was associated with a 3.53% decrease in baseline RSA_c (95% CI: –6.96, 0.02). In models examining RSA_c change between episodes, higher PM_{2.5} was generally associated with reduced PNS withdrawal during stress and reduced PNS activation during recovery; however, these associations were not statistically significant. We did not observe a significant interaction between PM_{2.5} and sex.

DISCUSSION: Prenatal exposure to PM_{2.5} may disrupt cardiac vagal tone during infancy. Future research is needed to replicate these preliminary findings. <https://doi.org/10.1289/EHP4434>

Introduction

Substantial evidence documents adverse cardiovascular effects of recent (hours to days) and chronic (weeks to years) ambient air pollution exposure in older children and adults (An et al. 2018; Chuang et al. 2007; Franklin et al. 2015; Pope et al. 2004), with mechanistic research highlighting the contribution of fine particulate matter (PM < 2.5 μm in aerodynamic diameter; PM_{2.5}) to the development of adverse health outcomes (Nelin et al. 2012). For example, short- and long-term exposure to particulate pollution has been linked to reduced heart rate variability (HRV) (Chuang et al. 2007; Gold et al. 2000; Liao et al. 2004; Luttmann-Gibson et al. 2010; Park et al. 2005; Pieters et al. 2012), which in turn is associated with increased risk of myocardial infarction, arrhythmias, hypertension, metabolic syndrome, and corresponding morbidities (Buccelletti et al. 2009; Licht et al. 2010; Tentolouris et al. 2008; Thayer et al. 2010). A critical step in identifying

individuals at risk for costly chronic cardiometabolic disorders is characterizing relevant exposures and mechanisms that lead to early predisposition. Although it is increasingly recognized that complex chronic diseases have their roots in early development (Hoffman et al. 2017; Thornburg 2015), little research has examined associations between PM_{2.5} exposure and autonomic nervous system (ANS) functioning in early life.

Critical components of the ANS develop and mature during gestation. For example, differentiation of the hypothalamic lateral zone and myelination of the vagus nerve typically occur by the end of the second trimester (Cheng et al. 2004; Koutcherov et al. 2003) and baroreflex responsivity increases throughout the remainder of gestation (Porges and Furman 2011). Clinical studies also support that parasympathetic control of cardiac rhythm is functional by the first half of pregnancy (Groome et al. 1994). Likewise, animal and human data show that programming of the infant ANS response begins *in utero* (Card et al. 2005; Igosheva et al. 2004; Jansson and Lambert 1999; Mukerjee et al. 2018), suggesting environmental exposures that alter the normal course of ANS maturation may have lifelong implications for mental and physical health (Abboud 2010; Ernst 2017; Rees 2014). During rest, the parasympathetic nervous system (PNS) maintains a state of internal homeostasis optimal for physical growth and development. When faced with external challenges, parasympathetic activity withdraws, enabling the sympathetic (SNS) branch to increase arousal and mobilize resources. For example, stress-induced withdrawal of inhibitory PNS inputs to pacemaker cells in the cardiac sinoatrial node (i.e., release of the vagal brake) results in increased heart rate and contraction force, leading to greater cardiac output and ultimately enabling an optimal response to external signals (Drew and Sinoway 2012).

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Respiratory sinus arrhythmia (RSA) is a temporal pattern of HRV that reflects respiration-synchronized oscillations in PNS-SNS cycling and is widely used as a metric of cardiac vagal tone (Paton and Pickering 2012), including in young infants (Ritz et al. 2012). At rest, higher RSA indicates a greater potential to respond to stressful stimuli, whereas reduced RSA during stress reflects appropriate withdrawal of the PNS (Porges et al. 1996). Results from empirical research conducted in children suggest that higher resting RSA, as well as stress-induced reductions in RSA, are associated with positive behavioral, cognitive, and physical outcomes, including fewer externalizing problems (Calkins and Dedmon 2000; Calkins et al. 2007; El-Sheikh et al. 2007; Kahle et al. 2018), better emotion regulation (Butler et al. 2006; Oveis et al. 2009; Porges et al. 1996; Zhang et al. 2017), improved attention (Feldman 2009; Huffman et al. 1998; Suess et al. 1994), better working memory, higher cognitive efficiency (Staton et al. 2009), higher intelligence (Porges et al. 1994), better academic performance (Blair and Diamond 2008; Graziano et al. 2007; Staton et al. 2009), healthy body mass index (Graziano et al. 2011), and fewer sleep disruptions (El-Sheikh et al. 2007).

Fetal exposure to tobacco smoke is associated with lower resting RSA during infancy (Schuetze et al. 2011, 2013), suggesting prenatal programming of autonomic tone may be susceptible to disruption by environmental toxicants. No epidemiologic studies have investigated the relationship between prenatal exposure to PM_{2.5} and ANS functioning in early life. In the present study, we examined prenatal exposure to PM_{2.5} in relation to infant RSA measured during brief periods of emotional stress and recovery elicited by the Repeated Still-Face Paradigm (SFP-R). We hypothesized that higher prenatal exposure to PM_{2.5} in pregnancy would be associated with lower baseline cardiac vagal tone (i.e., lower resting RSA) and reduced PNS withdrawal during stress (i.e., attenuated decrease in RSA). We report the results of models examining prenatal PM_{2.5} exposure adjusted for postnatal PM_{2.5} among a subset of infants (86%) with available postnatal data; however, we do not investigate main effects of postnatal exposure given our focus on investigating prenatal programming effects.

Methods

Study Participants

Participants included maternal–infant pairs enrolled in the PRogramming of Intergenerational Stress Mechanisms (PRISM) study, an ethnically mixed pre-birth cohort that was designed to investigate the independent and joint effects of perinatal stress and environmental chemicals on child development (Brunst et al. 2014, 2017). Women were recruited from prenatal clinics in the Boston area at 27 ± 8 weeks gestation [mean ± standard deviation (SD)] between March 2011 and August 2012. Eligible women were English- or Spanish-speaking, ≥18 years of age, and pregnant with a singleton. Mothers who were HIV⁺ or who reported drinking ≥7 alcoholic drinks/week prior to pregnancy or any alcohol during pregnancy were excluded. All study procedures were approved by the institutional review board at the Brigham and Women's Hospital (BWH); Beth Israel Deaconess Medical Center relied on BWH for review and oversight of the protocol. Written informed consent was obtained in the mother's primary language.

PM_{2.5} Exposure Assessment

We geocoded maternal residential address during pregnancy using ESRI's ArcGIS software, as previously described (Brunst et al. 2018). We estimated daily PM_{2.5} exposure for each study participant using a satellite-based hybrid model that combines

spectral aerosol optical depth (AOD) estimates with PM_{2.5} monitoring data and spatiotemporal predictors (population density, elevation, traffic density, land use type, and PM_{2.5} point and area source emissions, air temperature, wind speed, daily visibility, sea land pressure, and relative humidity) (Kloog et al. 2014). AOD products were estimated from the Moderate Resolution Imaging Spectroradiometer (MODIS) satellite sensor at a 1 × 1 km spatial resolution using the Multi-Angle Implementation of Atmospheric Correction (MAIAC) algorithm (Kloog et al. 2014). Daily PM_{2.5} concentrations were obtained from the U.S. Environmental Protection Agency (EPA) Air Quality System (AQS) database and the Interagency Monitoring of Protected Visual Environments (IMPROVE) network. Data sources for temporal and spatial predictors have been previously described in detail (Kloog et al. 2014). Briefly, a mixed model was used to regress AOD values on PM_{2.5} monitoring data while adjusting for land use variables and allowing day-specific temporal factors to vary. These PM_{2.5}-calibrated AOD values were then used to predict PM_{2.5} concentrations in grid cells without monitoring data. In grid cells with no AOD value for a given day, PM_{2.5} was predicted based on PM_{2.5} in neighboring grids as well as the relationship between PM_{2.5} and AOD across the region and within grid cells. Finally, residuals from the final model were regressed using machine learning (support vector machine) against high-resolution (200 × 200 m) spatiotemporal predictors (traffic density, population density, elevation, percent urban, distance to major roads, distance to source emission points, and visibility) specific to a given ground monitor. We used 10-fold out-of-sample cross validation to evaluate model performance. We randomly divided the data into 90% and 10% subsets 10 times. For the data sets including 10% of values, we predicted concentrations using the model fit with the remaining 90% of the data; overall model performance was excellent (mean out-of-sample $R^2 = 0.88$). The spatial and temporal components of the out-of-sample results also demonstrated good fit to the withheld data ($R^2 = 0.87$, $R^2 = 0.87$, respectively). Our results revealed minimal bias in the predicted concentrations (slope of predictions vs. withheld observations = 0.99). We averaged predicted daily PM_{2.5} across pregnancy (estimated date of conception through delivery) for each study participant. Figure 1 presents a map of predicted, average PM_{2.5} exposure levels during pregnancy for mothers enrolled in PRISM. Among a subset of 204 infants (86%) with available postnatal data, we created a summary measure of postnatal PM_{2.5} exposure by averaging predicted daily values between birth and the day of SFP-R testing.

Repeated Still-Face Paradigm

Mother–infant pairs completed the SFP-R during a follow-up visit to our laboratory when the infant was approximately 6 months of age. The SFP-R is a 10-min observational procedure designed to assess infant reactivity to and recovery from brief, moderate levels of stress induced by maternal disengagement (Tronick et al. 1978). The procedure is considered the gold-standard protocol for evaluating infant reactivity to moderate stress and is commonly coupled with measurement of RSA and other physiological indicators (Adamson and Frick 2003; Mesman et al. 2009). During the SFP-R, the infant was positioned in a car seat facing the mother, who was instructed to play with her infant as she normally would (Play). After 2 min, the mother transitioned to the first Still-Face episode (SF₁), during which she maintained a neutral facial expression and avoided touching or vocalizing with her infant. Following 2 min of disengagement, the mother resumed interacting with her infant (Reunion 1; R₁). The 4-min Still-Face-Reunion sequence was then repeated, with the mother transitioning directly to the second Still-Face episode (SF₂) following the first Reunion episode (R₁)

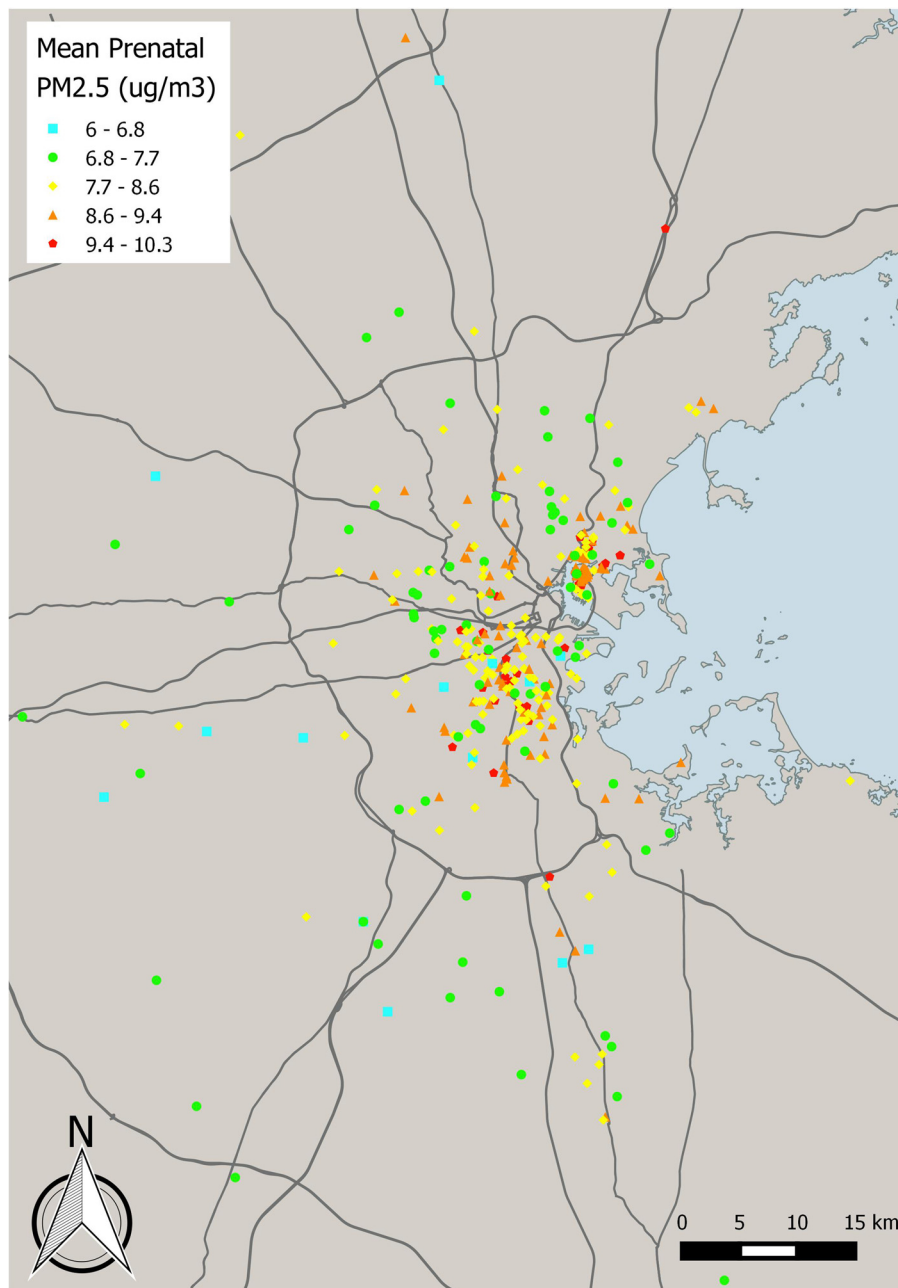


Figure 1. Map of predicted PM_{2.5} levels for PRISM study participants during pregnancy. Each point represents residential PM_{2.5} (µg/m³) averaged across pregnancy. PM_{2.5}, fine particulate matter; PRISM, PRogramming of Intergenerational Stress Mechanisms.

and to the second Reunion episode (R₂) following the second Still-Face episode (Figure 2 provides a stylized representation of a typical RSA response profile during the SFP-R procedure). The procedure was stopped if the infant remained distressed by the end of the first Reunion episode. Likewise, Still-Face episodes were terminated early (<2 min) if the infant engaged in 1 min of continuous fussing or 30 s of hard crying. Trained research assistants recorded whether a maternal behavioral violation occurred (yes/no) during the Still-Face episodes based on video recordings of the session. Violations included the following: maternal touching, verbalizing with, laughing at, turning from, making faces at, or otherwise interacting with the infant in any way, including giving the infant an object or displaying clear signs of negativity. When administering the SFP-R, study staff followed a standardized protocol, including explicit written instructions detailing

protocol set-up (e.g., where to seat the mother relative to the infant), use of video recording equipment (e.g., where to focus the camera to allow proper coding), physiology data acquisition (e.g., where and how to place electrodes), and interactions with the study participants (e.g., a verbal script that is administered to the mother at the start of the procedure). In addition, factors related to administration of the SFP-R were kept as constant as possible between laboratory visits. For example, the infant seat used during the SFP-R was strapped to a table so that it could not be moved and thus was always positioned in the same location for all SFP-R administrations. Before administering the SFP-R, study staff were trained to follow all procedures and materials by a developmental psychologist. As part of this training, staff watched video recordings of previously recorded SFP-R sessions from other studies and practiced administering the protocol under

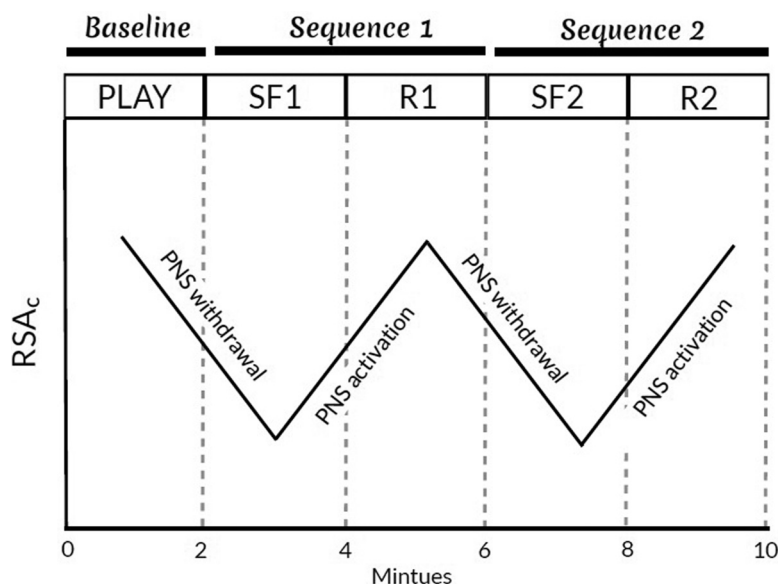


Figure 2. Stylized representation of a typical RSA_c response during the Repeated Still-Face Paradigm (SFP-R). The SFP-R is a 10 min, 5-episode procedure (episodes = Play, SF₁, R₁, SF₂, R₂) that is designed to induce moderate stress in the infant via maternal disengagement and reunion. During the Play and Reunion episodes, the mother is instructed to interact with her infant, who is seated in a car seat across from her, as she normally would. During the Still-Face episodes, the mother maintains a neutral facial expression and avoids touching or vocalizing with her infant. PNS, parasympathetic nervous system; R₁, first Reunion episode; R₂, second Reunion episode; RSA_c , respiratory sinus arrhythmia adjusted for total respiratory cycle time (T_{TOT}); SF₁, first Still-Face episode; SF₂, second Still-Face episode.

supervision. A developmental psychologist also reviewed live sessions and video recordings of sessions for quality control and met regularly with staff to discuss any concerns regarding protocol administration. Because all sessions were video recorded, including provision of instructions to the mother and all video sessions were coded for participant behaviors, any anomalies in administration were observable and noted during coding. Notably, anomalies were rare, and the SFP-R is robust to minor anomalies in administration.

We measured infant respiration and cardiac activity during the SFP-R using a noninvasive ambulatory respiratory inductance plethysmography device (BioRadio) that continuously records and stores raw signals from two inductance bands and a three-lead electrocardiogram (ECG). We calibrated inductance band output by volume using the qualitative diagnostic calibration procedure and processed respiration and heart rate data using VivoSense software (Vivonoetics), which is designed for analysis of complex waveforms, detection of artifacts, and calibration of respiratory parameters (Ritz et al. 2012; Sackner et al. 1989). We calculated tidal volume-normalized RSA within each breathing cycle as the difference between the longest (peak) and shortest (valley) cardiac inter-beat interval (IBI; in milliseconds) divided by tidal volume (V_T ; in milliliters) (Bosquet Enlow et al. 2014; Schulz et al. 2009). To correct for inter-individual variation in respiration, which has been shown to improve estimation of cardiac vagal activity (Grossman et al. 1991; Ritz et al. 2001; Saul et al. 1989), we performed a within-individual regression of natural-log transformed tidal volume-normalized RSA $\ln(RSA/V_T)$ (in milliseconds per milliliter) on total respiratory cycle time (T_{TOT} ; in seconds) during a 5-min period of natural breathing, as previously described (Enlow et al. 2009), and added the resulting residual value for each infant to the mean $\ln(RSA/V_T)$ across all infants in the sample (RSA_c ; in milliseconds per milliliter) (Ritz et al. 2012). We natural-log transformed tidal volume-normalized RSA before residualizing against T_{TOT} to meet normality assumptions of linear regression.

We quantified infant movement by coding activity in 10-s intervals from videos of the SFP-R using a four-point scale

(0 = quiet motor: no movement other than slow moving of fingers; 1 = slow/mild movements: slow bending but not lifting of limbs; 2 = moderate movements: slow lifting of limbs; 3 = pronounced movements: forceful lifting of limbs (scale modified from Bazhenova et al. 2007)). We averaged all 10-s interval scores within an episode and multiplied this value by 100 to create a possible activity score for each episode ranging from 0 to 360. Infant activity level was scored by three independent research assistants, with every fourth infant coded by two research assistants; the inter-rater reliability scores across coders indicated a high degree of consistency ($r \geq 0.83$).

Covariates

During the prenatal and early postnatal periods, trained research assistants collected extensive information on maternal sociodemographic characteristics and lifestyle factors using questionnaires. We assessed prenatal exposure to cigarette smoke based on maternal self-report of smoking during pregnancy (ever vs. never), as well as maternal report of exposure to environmental tobacco smoke (ETS) during pregnancy (<1 h/week vs. ≥ 1 h/week). Likewise, we assessed postnatal exposure to ETS based on the mother's report of infant exposure to cigarette smoke for 1 h/week or more at 2 and 6 months after birth. We evaluated material hardship based on the mother's response (not at all likely vs. somewhat likely vs. likely to extremely likely) to the question: "In the next two months, how likely is it that you and your family will experience hardships such as inadequate housing, food, or medical attention?" We evaluated maternal stress during pregnancy using the Life Stressor Checklist-Revised (LSC-R), which is an established self-report instrument for assessing traumatic and stressful life events (Wolfe and Kimerling 1997). The mother was asked whether she had ever experienced a series ($n = 30$) of stressful life events and the degree [not at all (1) to extremely (5)] to which the event affected her life in the previous year. We summed scores across the 30 items such that final scores (possible range 0–150) reflect a mother's subjective rating of how a

stressor affected her life in the previous year (i.e., through the majority of pregnancy and the entire postpartum period).

Statistical Analysis

We used multivariable linear regression to model pregnancy-averaged $PM_{2.5}$ exposure treated as a continuous variable in relation to baseline (Play) $\ln RSA_c$ (Model 1). We additionally modeled associations between continuous, pregnancy-averaged $PM_{2.5}$ and PNS withdrawal and activation, indexed by changes in back-transformed RSA_c between sequential episodes (Model 2: ΔRSA_c Play to SF_1 ; Model 3: ΔRSA_c SF_1 to R_1 ; Model 4: ΔRSA_c R_1 to SF_2 ; Model 5: ΔRSA_c : SF_2 to R_2). Associations with $PM_{2.5}$ categorized into quartiles supported the use of linear models (see Figure S1) and histograms confirmed normality of model residuals. We used *t*-tests and chi-square tests of independence to examine differences between infants included and excluded from the analysis as appropriate. To account for noise in RSA_c signals attributable to infant motor activity and jostling of ECG wires, we *a priori* adjusted models for infant activity level, which often accompanies distress on autonomic measures and was higher during Still-Face (mean \pm SD: 158.9 ± 34.7) compared with Play (80.6 ± 40.1) and Reunion (97.5 ± 44.4) episodes (see Table S1) (Bazhenova et al. 2007). For models examining RSA_c change between episodes, we adjusted for the difference in infant activity between the two episodes. We considered several sociodemographic, lifestyle, and perinatal factors as potential confounders (maternal race/ethnicity, age, education, marital status, household material hardship, life stress, depressive symptoms, smoking during pregnancy, exposure to ETS during pregnancy, parity, and infant gestational age and birthweight) and used directed acyclic graph (DAG) theory to select covariates for inclusion in adjusted models based on previous research and substantive knowledge (see Figure S2) (Textor et al. 2011, 2016). In addition to infant activity, we adjusted final models for race/ethnicity (black vs. Hispanic vs. white vs. other), material hardship (not likely vs. somewhat likely vs. likely to extremely likely), and maternal stress (continuous LSC-R score). These variables were sufficient to close biasing paths based on the conditional dependencies encoded by our proposed causal diagram, with the exception of potential confounding by postnatal exposure. As described below, in sensitivity analyses we examined models also adjusting for postnatal $PM_{2.5}$ exposure among a subset of infants with available data. Differences in physiologic stress reactivity by sex are well established (Aults et al. 2015; Tibu et al. 2014; Vidal-Ribas et al. 2017; Wilhelm et al. 2017), and previous research suggests boys and girls have differential susceptibility to prenatal air pollution exposure (Bertin et al. 2015; Brunst et al. 2018; YH Chiu et al. 2016; YM Chiu et al. 2017; Lee et al. 2018a, 2018b); therefore, we explored effect modification by infant sex using cross-product terms and stratified analyses.

We conducted several sensitivity analyses to evaluate the robustness of our findings. First, we investigated whether children who failed to complete the full SFP-R protocol differed from those who completed the protocol by analyzing final models excluding children who did not complete the second sequence. Second, we analyzed models excluding 14 infants diagnosed with a chronic medical condition (atopic disorder, acid reflux, hypothyroidism, heart murmur, dysphagia, or hydromyphosis). Third, we dropped maternal–infant pairs with one or more Still-Face violation. Fourth, we analyzed models excluding infants whose state was not “alert, rested, and feeling good” at the time of the laboratory visit as reported by the mother. Fifth, we analyzed models excluding infants exposed to cigarette exposure for ≥ 1 h per week during the postnatal period based on maternal report ($n = 14$). To examine the potential impact of short-term and long-term postnatal $PM_{2.5}$ exposure, we examined models

additionally adjusting for *a*) residential $PM_{2.5}$ levels on the day of testing treated as a continuous variable, and *b*) average $PM_{2.5}$ exposure between birth and the date of SFP-R testing treated as a continuous variable. Postnatal $PM_{2.5}$ was estimated using the same satellite-based hybrid model and methodology as was used to estimate prenatal $PM_{2.5}$ exposure; geocoding of residential addresses was updated to account for any moves between the prenatal and postnatal periods. We also evaluated the potential impact of several variables related to the day of SFP-R testing, including ambient temperature, humidity, and barometric pressure in the laboratory as well as participant travel time to the laboratory. Finally, we evaluated models adjusting for LSC-R scores treated as a dichotomous variable stratified at the fourth quartile (>11 vs. ≤ 11) to evaluate the degree to which our assumption of linearity impacted results. All analyses were conducted using SAS (version 9.4; SAS Institute Inc.) or RStudio (version 1.1.447; RStudio).

Results

Characteristics of Study Participants

At the prenatal visit, 417 mothers were eligible and enrolled into the Boston-based PRISM study. At the 6-month follow-up visit, 244 infants completed the SFP-R and had acceptable ECG data for extraction of RSA_c . We excluded 2 infants with missing $PM_{2.5}$ data and 5 infants with missing maternal stress data, resulting in a final sample size of 237 mother–infant pairs (57% of those enrolled) (see Figure S3). Table 1 presents characteristics of included participants stratified by quartile of $PM_{2.5}$ exposure. The majority of mothers were racial/ethnic minorities (26% black, 32% Hispanic, 8% mixed/other), 23% had less than a high school education, and 31% reported it was somewhat to extremely likely that her family would experience material hardship within the next 2 months. The mean \pm SD and median \pm interquartile range (IQR) LSC-R scores were 9.6 ± 11 and 6.0 ± 8.0 , respectively, and the range was 0–96. These scores are higher than those reported by a sample of 179 active-duty U.S. military service members (4.5 ± 5.7 , range: 0–35) (Bakalar et al. 2018), but lower than a clinical sample of new mothers enrolled in substance-abuse treatment program ($n = 21$, 45.1 ± 24.4 , range: 17–104) and their demographically matched controls ($n = 27$, 19.6 ± 11.2 , range: 2–58) (Goldman Fraser et al. 2010). The mean gestational age of infants was 39 weeks, with 9% of the sample born premature (<37 weeks). Estimated average prenatal $PM_{2.5}$ exposure across pregnancy was normally distributed with a mean of $8.3 \pm 0.9 \mu g/m^3$ and range of 6.0–10.3 $\mu g/m^3$.

We did not detect significant differences between enrolled participants included and excluded from the analysis except that fewer mothers included in the analysis had a high school degree (77%) compared with those excluded (86%, $p = 0.02$) (see Tables S2 and S3). Similarly, infants that completed both Still-Face sequences did not significantly differ from those completing only one sequence except that they were less likely to have been prenatally exposed to tobacco smoke (14% vs. 25%, $p = 0.04$) (see Tables S2 and S3).

Change in RSA_c across Episodes

RSA_c scores within each SFP-R episode followed a natural log-normal distribution. We found an average decrease in RSA_c during stress sequences [Play to SF_1 : $\beta = -8.30$ [95% confidence interval (CI): $-10.12, -6.47$]; R_1 to SF_2 : $\beta = -8.86$ (95% CI: $-10.78, -6.93$)] and an average increase in RSA_c during recovery sequences [SF_1 to R_1 : $\beta = 7.00$ (95% CI: 5.40, 8.60); SF_2 to R_2 : $\beta = 6.39$ (95% CI: 4.26, 8.51)], independent of $PM_{2.5}$ exposure, which is consistent with the expected pattern of PNS

Table 1. Characteristics of mother–infant pairs enrolled in the Boston-based PRISM study ($n=237$) stratified by quartile of PM_{2.5} exposure during pregnancy [mean \pm standard deviation or N (%)].

Characteristic	Overall ($n=237$)	Q1 ($n=59$)	Q2 ($n=58$)	Q3 ($n=60$)	Q4 ($n=60$)
Prenatal PM _{2.5} ($\mu\text{g}/\text{m}^3$)	8.3 \pm 0.9	7.2 \pm 0.4	8.0 \pm 0.2	8.6 \pm 0.2	9.5 \pm 0.3
Maternal age at enrollment (y)	30.8 \pm 5.5	32.1 \pm 5.9	30.9 \pm 4.7	30.7 \pm 5.2	29.6 \pm 5.9
Maternal race/ethnicity					
White	80 (34)	32 (54)	27 (47)	15 (25)	6 (10)
Black	61 (26)	15 (25)	17 (29)	17 (28)	12 (20)
Hispanic	77 (32)	10 (17)	9 (16)	18 (30)	40 (67)
Other/mixed	19 (8)	2 (3)	5 (9)	10 (17)	2 (3)
Maternal high school degree					
No	54 (23)	9 (16)	10 (17)	13 (22)	22 (37)
Yes	180 (77)	48 (84)	48 (83)	46 (78)	38 (63)
Material hardship					
Not likely	163 (69)	45 (76)	45 (78)	37 (62)	36 (60)
Somewhat likely	48 (20)	8 (13)	9 (16)	16 (27)	15 (25)
Likely, very likely, or extremely likely	26 (11)	6 (10)	4 (7)	7 (12)	9 (15)
Maternal Life Stressor Checklist–Revised ^a	9.6 \pm 10.8	10.9 \pm 15.3	9.4 \pm 8.7	8.9 \pm 9.6	9.0 \pm 8.6
Tobacco smoke exposure during pregnancy ^b					
No	200 (84)	52 (88)	48 (83)	48 (62)	52 (87)
Yes	37 (16)	7 (12)	10 (17)	12 (20)	8 (13)
Tobacco smoke exposure after birth ^c					
No	215 (94)	55 (98)	52 (93)	53 (93)	55 (92)
Yes	14 (6)	1 (2)	4 (7)	4 (7)	5 (8)
Infant sex					
Male	129 (54)	33 (56)	31 (53)	37 (62)	28 (47)
Female	108 (46)	26 (44)	27 (47)	23 (38)	32 (53)
Gestational age (weeks)	39.0 \pm 1.8	38.8 \pm 1.8	39.4 \pm 1.5	38.8 \pm 1.7	38.9 \pm 1.9
Birthweight (kg)	3.2 \pm 0.6	3.2 \pm 0.6	3.3 \pm 0.5	3.2 \pm 0.7	3.2 \pm 0.5
Infant alert, rested, and feeling good at SFP-R					
No	30 (19)	6 (13)	4 (10)	9 (21)	11 (35)
Yes	129 (81)	39 (87)	37 (90)	33 (79)	20 (65)

Note: There are no missing covariate data with the exception of maternal high school degree ($n=3$ missing). ETS, environmental tobacco smoke; PM_{2.5}, fine particulate matter; PRISM, Programming of Intergenerational Stress Mechanisms; Q, quartile; SFP-R, Still-Face Paradigm–Repeated.

^aAssessed with the Life Stressor Checklist–Revised, possible range: 0–150.

^bMaternal self-report of smoking or exposure to ETS for ≥ 1 h/week during pregnancy.

^cMaternal report of infant exposure to ETS for ≥ 1 h/week assessed at ages 2 and 6 months, $n=229$.

withdrawal and activation across the SFP-R (Table 2). At baseline, girls [geometric mean (GM) \pm geometric standard deviation (GSD): 16.3 \pm 0.3] had significantly lower RSA_c compared with boys (17.3 \pm 0.3) and showed less change in RSA_c between sequential episodes (Table 3).

Associations between PM_{2.5} and RSA_c

In adjusted models we found that RSA_c at baseline decreased with increasing prenatal exposure to PM_{2.5} [3.53% decrease in RSA_c for a 1-unit ($\mu\text{g}/\text{m}^3$) increase in PM_{2.5} (95% CI: –6.96, 0.02)] (Table 2). When examining change between episodes, we found that for every 1-unit increase in PM_{2.5} exposure, the average decrease in RSA_c during the first stress sequence (Play to SF₁) was attenuated by 0.74 units (95% CI: –0.12, 1.60), and the average decrease in RSA_c during the second stress sequence (R₁ to SF₂) was attenuated by 0.61 units (95% CI: –0.43, 1.66).

Although these associations were not statistically significant, they suggest a possible inhibitory effect of PM_{2.5} on PNS withdrawal during stress (Table 2; Figure 3). In models examining change in RSA_c between stress and recovery, for which we expect RSA_c to increase with PNS activation, PM_{2.5} was associated with an attenuated increase in RSA_c during the second [Δ RSA_c SF₂ to R₂: $\beta=-1.04$ (95% CI: –2.24, 0.15)], but not first [Δ RSA_c SF₁ to R₁: $\beta=0.04$ (95% CI: –0.84, 0.92)] sequence. Overall, these findings suggest that higher maternal PM_{2.5} exposure during pregnancy may be associated with less infant PNS withdrawal during stress and less infant PNS activation during recovery, resulting in an overall flattened response (Table 2; Figure 3). We did not observe a statistically significant interaction between PM_{2.5} and sex in any model (Table 3); however, with increasing PM_{2.5}, girls showed a trend toward a reduced ability to recover following stress, as indicated by negative effect estimates between Still-Face and Reunion episodes

Table 2. Adjusted change [β (95% CI)] in RSA_c at baseline (play) and between sequential SFP-R episodes (Δ RSA_c) and for a 1-unit increase in PM_{2.5} ($\mu\text{g}/\text{m}^3$).

SFP-R episode	Typical PNS response	Adjusted change in RSA _c across the SFP-R ($n=237$)	Adjusted change in RSA _c across the SFP-R per a 1-unit increase in PM _{2.5} ($n=237$)
Model 1: Play	Baseline	16.73 (15.45, 18.11) ^a	–3.53 (–6.96, 0.02) ^b
Model 2: Δ RSA _c Play to SF ₁	Withdrawal	–8.30 (–10.12, –6.47)	0.74 (–0.12, 1.60)
Model 3: Δ RSA _c SF ₁ to R ₁	Activation	7.00 (5.40, 8.60)	0.04 (–0.84, 0.92)
Model 4: Δ RSA _c R ₁ to SF ₂	Withdrawal	–8.86 (–10.78, –6.93) ^c	0.61 (–0.43, 1.66) ^c
Model 5: Δ RSA _c SF ₂ to R ₂	Activation	6.39 (4.26, 8.51) ^c	–1.04 (–2.24, 0.15) ^c

Note: The models were adjusted for infant activity, maternal race/ethnicity, maternal stress and material hardship. CI, confidence interval; PM_{2.5}, fine particulate matter; RSA_c, respiratory sinus arrhythmia [in ms/mL corrected for total respiratory cycle time (T_{TOT})]; R, Reunion; SF, Still-Face, SFP-R, Repeated Still-Face Paradigm.

^aAdjusted geometric mean.

^bRSA_c during Play is natural-log transformed; therefore, the estimate is interpreted as the percentage change in RSA_c for a 1-unit increase in PM_{2.5}.

^c $n=185$.

Table 3. Sex-stratified adjusted change [β (95% CI)] in RSA_c at baseline (play) and between sequential SFP-R episodes (Δ RSA_c) and for a 1-unit increase in PM_{2.5} ($\mu\text{g}/\text{m}^3$).

SFP-R episode	Typical PNS response	Girls (n = 108)		Boys (n = 129)		Sex \times PM _{2.5} p-Value
		Adjusted change in RSA _c across the SFP-R	Adjusted change in RSA _c across the SFP-R per a 1-unit increase in PM _{2.5}	Adjusted change in RSA _c across the SFP-R	Adjusted change in RSA _c across the SFP-R per a 1-unit increase in PM _{2.5}	
Model 1: Play	Baseline	15.04 (13.40, 16.87) ^a	-3.41 (-8.37, 1.82) ^b	18.35 (16.49, 20.42) ^a	-4.46 (-9.33, 0.47) ^b	0.66
Model 2: Δ RSA _c Play to SF ₁	Withdrawal	-7.67 (-10.01, -5.33)	0.88 (-0.35, 2.11)	-8.45 (-11.18, -5.72)	0.77 (-0.43, 1.98)	0.90
Model 3: Δ RSA _c SF ₁ to R ₁	Activation	6.36 (3.87, 8.86)	-0.77 (-2.15, 0.61)	7.33 (5.27, 9.39)	0.67 (-0.49, 1.83)	0.30
Model 4: Δ RSA _c R ₁ to SF ₂	Withdrawal	-7.82 (-10.97, -4.68) ^c	1.63 (-0.06, 3.31) ^c	-9.40 (-11.80, -7.01) ^d	0.15 (-1.22, 1.53) ^d	0.35
Model 5: Δ RSA _c SF ₂ to R ₂	Activation	7.05 (3.78, 10.33) ^c	-1.86 (-3.82, 0.11) ^c	5.11 (2.42, 7.80) ^d	0.72 (-0.83, 2.27) ^d	0.05

Note: The models were adjusted for infant activity, maternal race/ethnicity, maternal stress and material hardship. CI, confidence interval; PM_{2.5}, fine particulate matter; PNS, parasympathetic nervous system; RSA_c, respiratory sinus arrhythmia [in ms/mL corrected for total respiratory cycle time (T_{TOT})]; R, Reunion; SF, Still-Face; SFP-R, Repeated Still-Face Paradigm.

^aAdjusted geometric mean.

^bRSA_c during Play is natural-log transformed; therefore, the estimate is interpreted as the percentage change in RSA_c for a 1-unit increase in PM_{2.5}.

^cn = 86.

^dn = 99.

(Table 3). In contrast, among boys we observed positive, yet statistically insignificant, changes in RSA_c between stress and recovery per 1-unit increase in PM_{2.5}, suggesting a potential improved ability to recover.

Sensitivity Analyses

Results from models excluding infants who a) experienced one or more Still-Face violation (n = 46), b) were reported to be not alert or rested at the time of testing (n = 30), c) had a chronic medical condition (n = 14), or d) were postnatally exposed to ETS (n = 14) did not substantially deviate from overall findings (see Table S4). Consistent with models including all infants [n = 237, RSA_c at Play: $\beta = -3.53$ (95% CI: -6.96, 0.02)] baseline PNS levels also decreased with increasing PM_{2.5} among the subset of infants that completed both Still-Face episodes [n = 185, Δ RSA_c Play: $\beta = -3.05$ (95% CI: -6.94, 0.98)]. Likewise, results from models examining PNS withdrawal and activation among the subset of infants that completed both Still-Face episodes were not substantially different from models including all infants (see Table S4). Among the 204 participants with available postnatal data, residential PM_{2.5} concentrations between birth and the 6-month SFP-R visit were approximately normally distributed with a mean \pm SD of $7.96 \pm 0.78 \mu\text{g}/\text{m}^3$ and range of 6.12–9.95 $\mu\text{g}/\text{m}^3$. Predicted PM_{2.5} concentrations on the day of testing had a small right tail with a GM \pm GSD of $6.90 \pm 0.23 \mu\text{g}/\text{m}^3$ and range of 2.10–24.03 $\mu\text{g}/\text{m}^3$. Findings from models adjusting for these chronic and short-term postnatal exposure metrics did not substantially vary from main results (see Table S5). The mean \pm SD (range) laboratory temperature (degrees Fahrenheit), humidity (percentage), and barometric pressure [milliliters mercury (mmHg)] on the day of testing among 142 participants for which this information was collected was: 72.0 ± 2.4 (65.9–77.7), 34.4 ± 14.1 (20.0–65.0), and 30.0 ± 1.2 (19.9–39.8), respectively. Participant travel time to the laboratory was on average 33 ± 19 min (range: 5–120 min). Models adjusting for these laboratory conditions were similar to results from main models (see Table S6). Finally, models treating maternal LSC-R scores as a dichotomous (quartile 4 vs. quartiles 1, 2, and 3 collapsed) variable were similar in magnitude and direction to final results presented in the manuscript (see Table S7).

Discussion

To our knowledge this is the first study to suggest that higher maternal exposure to PM_{2.5} during pregnancy may be associated with decreased resting vagal tone among infants. We additionally detected a trend toward reduced PNS withdrawal during stress, a pattern that may indicate reduced autonomic flexibility. Although significant differences in exposure pathways and putative underlying biological mechanisms exist when considering prenatal versus postnatal PM_{2.5} exposure, we note that our findings are generally consistent with previous observational research conducted in adults that show exposure to particulate air pollution is inversely related to HRV (Devlin et al. 2003; Gold et al. 2000; Pope et al. 2004). Consistent with findings among older children and adolescents (5–19 years of age), baseline RSA_c levels were significantly lower among girls compared with boys (Koenig et al. 2017). However, we did not detect RSA_c differences between boys and girls in relation to PM_{2.5} exposure, which may in part reflect our relatively small sample size.

Although the physiological significance and precise mechanisms underlying the respiratory–cardiac coupling characteristic of RSA remain incompletely understood (Yasuma and Hayano 2004), substantial observational and clinical research has linked lower resting vagal tone with increased psychological, behavioral, and somatic disease risk across the life span. For example, low vagal

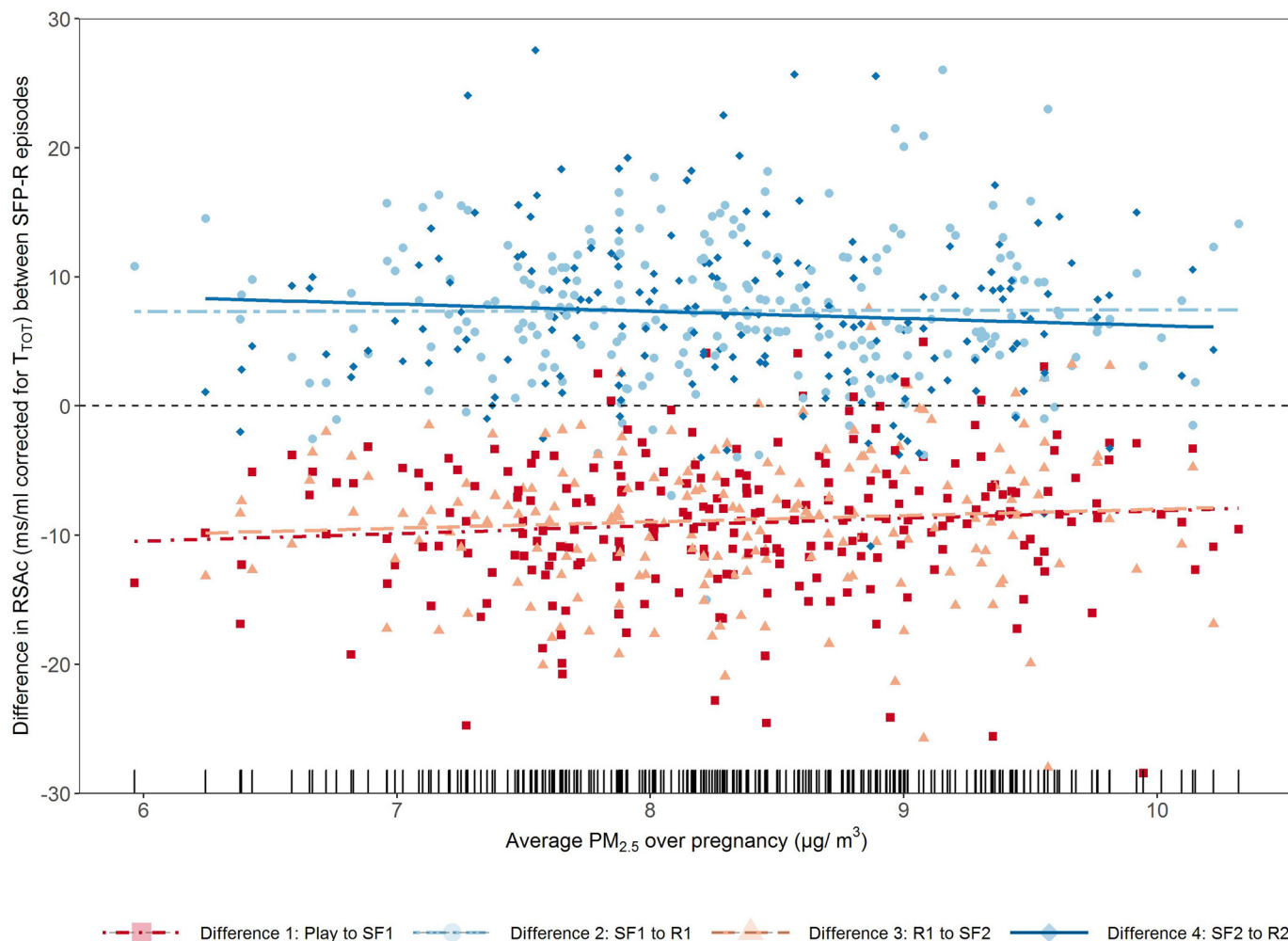


Figure 3. Scatter plot of difference in RSA_c (Δ RSA_c) between sequential SFP-R episodes by PM_{2.5} ($\mu\text{g}/\text{m}^3$) among infants enrolled in the Boston-based PRISM study ($n=237$). Plotted Δ RSA_c values are residuals from linear regression models between predictors (PM_{2.5}, infant activity, race/ethnicity, maternal stress, material hardship) and Δ RSA_c added to the grand mean Δ RSA_c for each episode. The lines correspond to the estimated coefficients in Table 2 and the rug on the x-axis represents the distribution of PM_{2.5} concentrations. PM_{2.5}, fine particulate matter; PRISM, PRogramming of Intergenerational Stress Mechanisms; R, Reunion; RSA_c, respiratory sinus arrhythmia [in ms/mL corrected for total respiratory cycle time (T_{TOT})]; SF, Still-Face; SFP-R, Repeated Still-Face Paradigm.

tone during infancy has been associated with an increased incidence of sudden infant death syndrome (Peirano et al. 1992). Among children, reduced vagal withdrawal during emotionally or cognitively challenging tests has been shown to predict obesity (Graziano et al. 2011) and high blood pressure (Gangel et al. 2017) during early to late childhood. Likewise, a recent meta-analysis of 44 studies ($n=4,996$ children) found greater RSA withdrawal in response to stress was associated with fewer externalizing, internalizing, and cognitive/academic problems (Graziano and Derefinko 2013). In adults, lower RSA is an established risk factor for cardiovascular disease (Dekker et al. 2000)—the leading cause of death worldwide (GBD 2016 Causes of Death Collaborators 2017)—as well as for other chronic diseases [diabetes, hypertension, and obesity (Masi et al. 2007)] and psychopathologies [depression, anxiety disorders, borderline personality disorder, and schizophrenia (Bylsma et al. 2014; Clamor et al. 2016; Jurysta et al. 2010; Kemp et al. 2010; Koenig et al. 2016)]. Owing to differences in study design and catchment populations, as well as variation in the approach to quantifying and reporting RSA across research labs and publications, it is not possible to directly compare the magnitude of our observed associations to previous studies examining RSA in relation to health outcomes or to determine the physiological significance of our findings. However,

the direction of observed associations is consistent with research demonstrating adverse effects of PM_{2.5} on cardiovascular and autonomic health. In addition, several observational studies in children have found inverse associations between prenatal exposure to air pollution and neurocognitive and behavioral outcomes (Chiu et al. 2016; Cowell et al. 2015; Jedrychowski et al. 2015; Yorifuji et al. 2016). It is plausible that these associations are partially mediated by PM_{2.5}-related disruption of cardiac vagal tone, which has previously been linked with poor emotional, behavioral, and cognitive outcomes in children.

Little evidence supports the passage of PM_{2.5} across the placental barrier, suggesting that the mechanisms through which maternal exposure to PM_{2.5} during pregnancy disrupt fetal development involve changes to the maternal or placental systems or to both. Putative mechanisms based on prior research include altered placental gene expression, increased oxidative stress, and changes to maternal immune system status. Experiments using a transgenic mouse model have shown insufficient levels of brain-derived neurotrophic factor (BDNF), which promotes survival of parasympathetic (i.e., cholinergic) neurons during embryonic development, results in reduced cardioinhibitory vagal activity in the brainstem and leads to decreased parasympathetic tone (Wan

et al. 2014). Prenatal exposure to PM_{2.5} has been associated with changes in expression of placental genes key to fetal neurodevelopment, including those involved in BDNF signaling pathways (Saenen et al. 2015), suggesting PM_{2.5} has the potential to disrupt central control of PNS activity. Further, although we are not aware of studies that have investigated prenatal exposure to PM_{2.5} in relation to anatomical changes in fetal brain structure, prenatal exposure to cigarette smoke has been associated with hypodevelopment of brainstem nuclei involved in autonomic control (Lavezzi et al. 2016) and reduced RSA modulation in infancy (Schuetze et al. 2013). Alternatively, it is plausible that PM_{2.5} targets overlapping pathways between the autonomic and stress response systems. A recent randomized, double-blind crossover trial in humans found higher exposure to PM_{2.5} was associated with significantly increased levels of cortisol, epinephrine, and norepinephrine (Li et al. 2017), which are end products of hypothalamic–pituitary–adrenal (HPA) axis activation. Maternal cortisol crosses the placenta leading to elevated levels in fetal circulation (Benediktsson et al. 1997; Hennessy et al. 1982) and animal models have demonstrated maternal catecholamines reduce uterine blood flow (Barton et al. 1974) and placental perfusion (Salomon et al. 2006), resulting in a sustained increase in fetal catecholamine production (Gu et al. 1985). In sheep, elevated prenatal exposure to these hormones has been associated with lower fetal blood pressure and heart rate, as well as with significantly shortened increases in fetal blood pressure during acute maternal stress, providing evidence that cardiovascular responses to stress may begin *in utero* (Dreiling et al. 2018).

Particulate air pollution is known to induce cellular oxidative stress in the peripheral circulation via several pathways (Lodovici and Bigagli 2011; Miller et al. 2012; Risom et al. 2005; Rossner et al. 2007). Recently, PM_{2.5} exposure during pregnancy has been associated with elevated oxidative stress at the maternal–fetal interface, as indicated by significantly increased levels of 3-nitrotyrosine in the placenta (Saenen et al. 2016). Likewise, cigarette smoke during pregnancy has been associated with elevated markers of oxidative stress not only in maternal blood but also in placental tissue and cord blood (Aycicek and Ipek 2008; Aycicek et al. 2011). These findings suggest environmentally induced changes in the maternal milieu may translate to the intra-uterine environment. In adults, reactive oxygen species have been shown to play a role in development of autonomic dysfunction, including disruption to central cardiovascular regulation (Hirooka et al. 2010). During fetal development, correlates of oxidative stress have been linked to programming of ANS dysfunction in rodent (Danson and Paterson 2006; YC Wu et al. 2011) and primate (Duncan et al. 2009; Slotkin et al. 2011) models. Taken together, these findings support that increased oxidative stress levels may be one putative mechanism through which particulate pollution alters early life programming of autonomic balance.

The PNS plays a key role in anti-inflammatory responses (Czura and Tracey 2005; Tracey 2002), with multiple studies demonstrating inverse correlations between C-reactive protein (CRP), a marker of acute systemic inflammation, and vagal tone in adults (Carney et al. 2007; Frasure-Smith et al. 2009; Haensel et al. 2008; Lampert et al. 2008). In murine models, exposure to PM_{2.5} or diesel exhaust particles has been shown to upregulate pro-inflammatory markers in the placenta [interleukin-6 (IL-6), tumor necrosis factor- α (TNF α), IL-1 β] (Auten et al. 2009, 2012; Fujimoto et al. 2005) and fetal brain (Bolton et al. 2012). In humans, exposure to PM has been associated with elevated IL-1 β in cord blood (Latzin et al. 2011) and increased levels of maternal (Lee et al. 2011) and fetal (van den Hooven et al. 2012) CRP. Based on these findings, it is plausible that prenatal exposure to PM_{2.5} triggers activation of anti-inflammatory neural circuits, with potential downstream consequences for programming

of other PNS-controlled pathways (i.e., parasympathetic outflow to the heart).

We are not aware of experimental animal research that has directly investigated the effects of PM_{2.5} exposure during pregnancy on offspring autonomic parameters. However, several studies using rodent models have suggested that maternal exposure to PM_{2.5} during pregnancy can program other key physiological systems, including cardiovascular, renal, and metabolic systems, independent of offspring exposure during postnatal life. For example, adult offspring of dams exposed to PM_{2.5} throughout pregnancy show evidence of altered cardiac volume, cardiac inflammation, electrical remodeling, and significant cardiac dysfunction (Gorr et al. 2014; Stapleton et al. 2018; Tanwar et al. 2017). Likewise, murine research has linked later life metabolic dysfunction with gestational PM_{2.5} exposure. Specifically, research has shown that adult offspring prenatally exposed to PM_{2.5} present with significantly altered β cell function and morphology and impaired glucose tolerance (Chen et al. 2018). These offspring also show significantly decreased birthweight, but increased adiposity and body weight among males (Chen et al. 2017). Evidence of prenatal reprogramming by PM_{2.5} also extends to the renal system; research in rats suggests that adult offspring of dams exposed to PM_{2.5} via oropharyngeal drip during pregnancy have impaired renal dopamine D1 receptor-mediated sodium excretion and increased blood pressure (Ye et al. 2018). Although these studies do not provide direct experimental evidence to support our findings or hypothesis of a prenatal programming mechanism, they suggest that maternal exposure to PM_{2.5} during pregnancy has the potential to disrupt offspring physiological systems independent of direct postnatal exposure. Given putative differences in PM_{2.5} exposure pathways and biological mechanisms between the prenatal and postnatal periods, including little evidence of a correlation between direct infant exposure and biologically relevant effects of maternal exposure, we do not conceptualize infant PM_{2.5} exposure as a confounder of prenatal PM_{2.5}–infant RSA associations. The results of sensitivity analyses examining models additionally controlling for postnatal PM_{2.5} exposure *a*) on the day of RSA testing and *b*) averaged between birth and RSA testing further support that postnatal exposure does not confound the prenatal PM_{2.5}–RSA_c association that we observed in the PRISM sample.

This study is one of the first to examine prenatal exposure to ambient PM_{2.5} in relation to early life autonomic function, which we assessed in a controlled laboratory environment. We measured RSA during the SFP-R, which is considered the gold-standard protocol for eliciting vagal withdrawal in infants and is commonly coupled with assessment of physiological measures (Adamson and Frick 2003; Mesman et al. 2009). Assessing HRV using an electrophysiological approach parallel to adult studies is challenging in young infants given their rapid underlying heart and respiration rates. We were able to improve precision of RSA values by correcting for respiration using our previously validated approach (Ritz et al. 2012), as well as adjusting for infant activity, which we coded at a high temporal resolution (10-s intervals). As is typical given challenges with obtaining valid cardiac data from young children, we were unable to use data from 53 infants due to excessive respiratory artifacts ($n = 49$) or technical problems with the equipment ($n = 4$), which reduced our power to detect associations with PM_{2.5}.

The high predictive accuracy of our 1 \times 1 km–resolution spatiotemporal land-use regression model for estimating PM_{2.5} exposure is expected to minimize measurement error and consequent downward biases in effect estimates. However, our use of maternal residential location to predict individual PM_{2.5} exposure may have introduced misclassification among mothers who spent substantial time away from the home. It is possible that maternal

time spent away from home could be positively (i.e., maternal employment outside the home leading to better socioeconomic circumstances and more household resources) or negatively (less bonding and direct interaction with baby during early life) related to infant autonomic reactivity to stress. Given these uncertainties, we are unable to speculate how potential misclassification would affect observed associations.

In the PRISM cohort, pregnancy-averaged PM_{2.5} concentrations (maximum: 10.3 µg/m³) are lower than the U.S. EPA National Ambient Air Quality Standards annual limit (i.e., 12.0 µg/m³), suggesting exposure reflects that of the general U.S. population; however, our findings may not be generalizable to regions with higher ambient PM_{2.5} levels. In addition, although we view the sociodemographic diversity of the sample, including a large representation of minority and lower income families, as a strength of this research, our findings may not be generalizable to more racially homogenous, rural communities. Likewise, given that we examined autonomic tone only once, at approximately 6 months of age, it remains unknown whether our findings will extend to later childhood.

Previous research in adults has documented associations between recent (hours) exposure to PM_{2.5} and changes in resting HRV (Breitner et al. 2019; He et al. 2011; S Wu et al. 2011; Zanobetti et al. 2010). Unfortunately, we were not able to monitor PM_{2.5} levels in the testing room during the SFP-R. However, all laboratory procedures took place in the same climate-controlled, indoor testing room with no windows open to the ambient environment, reducing the likelihood of fluctuations in indoor PM_{2.5} levels. In addition, in sensitivity analyses, adjusting for short-term postnatal PM_{2.5} exposure did not attenuate associations between prenatal PM_{2.5} and measures of RSA_c. Likewise, including average postnatal PM_{2.5} exposure during the first 6 months of life as a covariate did not substantially alter associations between prenatal PM_{2.5} and RSA_c. Importantly, if there is misclassification in our measure of postnatal PM_{2.5} (e.g., due to variability in the amount of time infants spend outdoors), it is possible that uncontrolled, residual confounding by postnatal exposure remains. In addition, because the precise biological mechanisms linking maternal exposure to PM_{2.5} during pregnancy with changes in infant RSA are unknown, it is possible fetal exposure to the biologically relevant consequences of maternal PM_{2.5} exposure is misclassified due to inter-individual variability in maternal biology. As with all observational studies, there is also a possibility for residual confounding by unmeasured factors related to both PM_{2.5} and RSA. For example, it is plausible that cultural differences not captured by race/ethnicity could influence where a mother resides and may also relate to parenting styles, which in turn could be linked to infant autonomic reactivity during the SFP-R. We were not able to investigate associations between RSA and other air pollutants (e.g., ozone, carbon monoxide, nitrogen oxides, sulfur dioxide, elemental carbon) that may co-vary or interact with PM_{2.5} (Buteau and Goldberg 2016). Future research that is able to investigate combined exposures to these pollutants is needed to better understand how mixtures of ambient air pollutants impact the developing autonomic and cardiovascular systems. In addition, although we had information on postnatal exposure for a subset of infants, we focused analyses on gestational exposure given our interests in understanding prenatal programming effects. Future research investigating PM_{2.5} exposure during infancy and studies evaluating whether the mechanisms underlying associations differ depending on the timing of exposure (e.g., prenatal vs. postnatal) will contribute to our understanding of how early life PM_{2.5} exposure impacts autonomic system development and function.

In summary, our findings support previous research conducted in older children and adults that has found PM_{2.5} is inversely associated with HRV and suggest that environmentally

induced disruption of autonomic tone may extend to the prenatal period. Putative mechanisms include altered immune function, endocrine signaling, enhanced oxidative stress, or disruption of central control of PNS activity at the level of the brainstem or a combination of these mechanisms potentially via altered placenta gene signaling pathways. Although it is difficult to interpret the physiological relevance associated with the degree of change we observed, previous research has linked lower RSA and reduced PNS withdrawal with a number of chronic diseases and psychopathologies (Bylsma et al. 2014; Clamor et al. 2016; Dekker et al. 2000; Gangel et al. 2017; Graziano et al. 2011; Jurysta et al. 2010; Kemp et al. 2010; Koenig et al. 2016; Masi et al. 2007). These findings, in combination with increasing worldwide exposure to PM_{2.5}, emphasize the importance of examining early life exposure to PM_{2.5} in relation to autonomic outcomes. However, until these preliminary findings are replicated by future studies, it is critical they be interpreted with caution.

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