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In-utero personal exposure to $PM_{2.5}$ impacted by indoor and outdoor sources and birthweight in the MADRES cohort

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Abstract

Background: In-utero exposure to outdoor particulate matter with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) is linked with low birthweight. However, previous results are mixed, likely due to measurement error introduced by estimating personal exposure from ambient data. This study investigated the effect of total personal $PM_{2.5}$ exposure on birthweight and whether it differed when it was more heavily impacted by sources of indoor vs outdoor origin in the MADRES cohort study.

Methods: Personal $PM_{2.5}$ exposure was measured in 205 pregnant women in the 3rd trimester using 48 h integrated, filter-based sampling. Linear regression was used to test the association between personal $PM_{2.5}$ exposure and birthweight, adjusting for key covariates. Interactions of $PM_{2.5}$ with variables representing indoor sources of $PM_{2.5}$, home ventilation, or time spent indoors tested whether the effect of total $PM_{2.5}$ on birthweight varied when it was more impacted by sources of indoor vs outdoor origin.

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Results: In a sample of largely Hispanic (81%) pregnant women, total personal $PM_{2.5}$ was not significantly associated with birthweight (β = 38.6 per 1SD increase in $PM_{2.5}$; 95% CI:−21.1, 98.2). This association however, differed by home type (single family home: 156.9 (26.9, 287.0), 2–4 attached units:−16.6 (−111.9, 78.7), 5+ units:−62.6 (−184.9, 59.6), missing: 145.4 (−4.1, 294.9), interaction $p = 0.028$) and by household air conditioner use (none of the time: −27.6 (−101.5, 46.3) vs. some of the time: 139.9 (42.9, 237.0), interaction $p = 0.008$) Additionally, the effect of personal $PM_{2.5}$ on birthweight varied by time spent indoors (none or little of the time: −45.1 (−208.3, 118.1) vs. most or all of the time: 57.1 (−7.3, 121.6), interaction $p = 0.255$).

Conclusions: While no significant association between total personal $PM_{2.5}$ exposure and birthweight was found, there was evidence that multi-unit housing (vs. single-family homes), candle and/or incense smoke, and greater outdoor source contributions to personal $PM_{2.5}$ were more strongly associated with lower birthweight.

Keywords

Air pollution; PM2.5; Birthweight; Prenatal exposure; Pregnancy; Personal monitoring

1. Introduction

In the United States (U.S.), an estimated 8.3% of newborns are born with low birthweight (LBW) (Martin et al., 2019); defined as below 2500 grams (g). The impact of LBW is far reaching, with research showing it is associated with infant mortality (Vilanova et al., 2019; Watkins et al., 2016) and later life obesity (Jornayvaz et al., 2016), type-2 diabetes (Mi et al., 2017), cardiovascular disease (Risnes et al., 2011; Smith et al., 2016; Umer et al., 2020), and impaired cognitive development (Upadhyay et al., 2019; Whitaker et al., 2006). Within the U.S., such health outcomes are often disproportionate with regard to race/ethnicity, with obesity and type-2 diabetes prevalence highest in Hispanic and Black populations across the lifetime (Petersen, 2019; Rossen, 2014).

In the past decade, several epidemiological studies have established a relationship between outdoor air pollution and birthweight and/or LBW (Lamichhane et al., 2015; Li et al., 2017; Pedersen et al., 2013). Within the US, these studies primarily focused on federally-regulated criteria air pollutants. One of those is particulate matter (PM) with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) (Huang et al., 2015; Rich et al., 2015; Schembari et al., 2015). In-utero $PM_{2.5}$ exposure is hypothesized to create a hostile intrauterine environment likely resulting from oxidative stress, DNA methylation changes, mitochondrial DNA content alteration, and endocrine disruption (Clemente et al., 2016; Li et al., 2019). Such mechanistic alterations may lead to health risks in later life such as the development of visceral adiposity and altered glucose homeostasis (Barnes and Ozanne, 2011; Morrison et al., 2010; Visentin et al., 2014).

While several reviews have concluded a weak to moderate association between outdoor $PM_{2.5}$ and several birth outcomes, including a decrease in birthweight and an increased risk of LBW (Li et al., 2017; Stieb et al., 2016; Sun et al., 2016), the literature remains inconsistent. Reductions in birthweight due to outdoor $PM_{2.5}$ exposure also vary by race/ethnicity (Basu et al., 2014), possibly due to Hispanic and Black mothers experiencing

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the greatest burden of air pollution exposure (Bell and Ebisu, 2012; Mikati et al., 2018). Effect estimates also differ depending on the exposure window under study, with the 3rd trimester showing the most consistent evidence of greater risk of LBW (Dadvand et al., 2014; Schembari et al., 2015; Zhu et al., 2015). Additionally, most health studies to date estimated an individual's exposure to outdoor $PM_{2.5}$ at the residential level using models that typically incorporate ambient monitoring, remote sensing, and/or geospatial data (Ebisu et al., 2014; Gray et al., 2010; Harris et al., 2014). While these models are increasingly capable of capturing spatial variability in outdoor air pollution, they inherently suffer from exposure measurement error in terms of estimating personal exposure to air pollution of outdoor origin, which might bias effect estimates and attenuate power to detect health effects (Carroll, 2005; Kioumourtzoglou et al., 2014; Zeger et al., 2000). This is because individuals spend the majority of their time indoors, and their 'true' personal exposure to $PM_{2.5}$ of outdoor origin is a result of the infiltration efficiency of $PM_{2.5}$ indoors and time-activity patterns, most accurately captured by personal monitoring (Gray et al., 2011). Finally, there is currently very little research into the effect of total personal exposure to $PM_{2.5}$ prenatally on birthweight. Total personal $PM_{2.5}$ is impacted by multiple sources including personal activity, indoor sources, and outdoor sources (or $PM_{2.5}$ of outdoor origin, which may only represent a small fraction of an individual's total personal $PM_{2.5}$ exposure) (Habre et al., 2014). Therefore, quantifying the influence of total personal $PM_{2.5}$ on birthweight is also an important question that has not yet been thoroughly investigated.

Personal monitoring of air pollution is a sophisticated, yet often expensive and burdensome method of exposure assessment and as such, only a small number of studies have used it, the majority of which have focused on toxic polyaromatic hydrocarbons (PAHs) (Choi et al., 2012, 2008; Rundle et al., 2012). One study found an inverse association with personal $PM_{2.5}$ and birthweight (Jedrychowski et al., 2009). However, very few studies have been conducted in a health disparities population with potentially greater exposure to $PM_{2.5}$ of outdoor origin and greater vulnerability or susceptibility to its effects (Morello-Frosch et al., 2011), particularly in the 3rd trimester where most fetal weight gain occurs (Kiserud et al., 2018). Additionally, there is a pressing need to evaluate the effects of $PM_{2.5}$ impacted by sources of indoor vs outdoor origin (hereinafter referred to as indoor vs outdoor sources for simplicity) due to the differences in their chemical composition and thus potential toxicity, and the fact that only ambient $PM_{2.5}$ concentrations are regulated.

Therefore, the purpose of this present study was to bridge these gaps in knowledge by evaluating the role of 3rd trimester personal $PM_{2.5}$ exposure on birth weight in a health disparities population in Los Angeles, CA. In addition, this study investigated whether the effect of total personal $PM_{2.5}$ on birthweight was different when it was more impacted by indoor vs outdoor sources. To accomplish this, this study tested interactions with questionnaire-based variables that correlate directly with greater indoor (e.g., indoor burning of candles or incense) or outdoor (e.g., time spent outdoors) contributions to total personal $PM_{2.5}$.

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2. Material and methods

2.1. Study population

The Maternal and Developmental Risks from Environmental and Social Stressors (MADRES) study is an ongoing prospective cohort study of ~900 pregnant, primarily Hispanic, low-income mothers in Los Angeles County, motivated to investigate the cumulative impact of environmental pollutants and psychosocial, behavioral, and built environmental risk factors on maternal and infant health outcomes (Bastain et al., 2019). Pregnant women were enrolled via partnerships with four prenatal care providers in Los Angeles beginning November 2015, including one county hospital clinic, two non-profit community health clinics, and a private obstetrics and gynecology practice.

Participant eligibility included: (1) at least 18 years old, (2) fluency in either Spanish or English, and (3) less than 30-weeks gestation at recruitment. Exclusion criteria for the study included: (1) multiple gestation, (2) current incarceration, (3) HIV positive, and (4) having a physical, mental, or cognitive disability that would prevent the participant from providing informed consent.

The current analysis leverages data collected as part of a 214-participant personal $PM_{2.5}$ exposure monitoring study nested within the MADRES cohort. Women were asked to wear a crossbody sampling purse with a personal monitoring apparatus for a 48 h monitoring period in the 3rd trimester. This subset was comparable to the larger MADRES cohort in terms of demographics, birth outcomes, and outdoor air pollution metrics.

2.2. Personal $PM_{2.5}$ exposure monitoring

Total, 48 h integrated personal $PM_{2.5}$ exposure was measured in the 3rd trimester using a custom sampling design on a subset of 214 women recruited from the larger cohort between October 2016 and February 2020. A trained, bilingual study staff member recruited participants during one of their 3rd trimester study visit at the University of Southern California (USC) clinic. Participants were provided with a personal sampling crossbody purse containing a Gilian Plus Datalogging Pump (Sensidyne Inc., Clearwater, FL), which was programmed to start at midnight (the following day) and actively sample at a 50% cycle and flow rate of 1.8 liters per minute (LPM). The pump was connected to a Harvard $PM_{2.5}$ personal environmental monitor (PEM) with a 37mm Pall Teflo filter. Staff members provided instructions regarding proper use and demonstrated how to wear the sampling bag, with the sampling inlet located on the purse strap in the shoulder area around the breathing zone.

Participants were instructed to wear the sampling device during all waking hours while going about their normal daily activities. Exceptions to this requirement included while performing potentially dangerous activities (e.g., driving), showering, sleeping, or otherwise unable to. Participants were asked to protect the sampling device from water, high humidity (such as showering or sauna), heat, pets, and from children. When they could not wear the monitor continuously, such as when sleeping or driving, they were asked to place it on a bed side table or besides them on the passenger seat, away from surfaces as much as possible and unobstructed. Additionally, when not wearing the monitor, individuals were asked to

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keep the monitor elevated from the ground and away from the walls due to sampling artifacts that could result from resuspended dust or removal on surfaces, respectively.

The sampling pump was programmed to shut down after the 48 h sampling period was completed, and study staff coordinated device pickup and conducted a brief exit survey with participants the following day. When the sampling devices arrived at the USC Exposure Analytics lab, they were handled by trained staff. Pump data were downloaded, checked for errors, and securely stored. Filters were removed from the PEMs, allowed to equilibrate within a dedicated chamber and gravimetrically weighed in temperature and relative humidity-controlled glove box using an MT-5 calibrated microbalance to obtain $PM_{2.5}$ mass concentration.

2.3. Birthweight

Birthweight in grams was abstracted from electronic medical record (EMR) for 210 mothers. Four mothers did not have birthweight recorded, possibly due to being lost to follow-up, and were removed from the analysis. Birth weight-for-gestational age z-scores were obtained for each participant using methods described in Aris et al. (2019).

2.4. Questionnaire and other covariate data

A priori covariates assessed in this analysis included factors related to maternal demographics, pregnancy and birth outcomes, meteorology, and study design variables, including recruitment site. Covariate data was collected during follow-up within the MADRES cohort from a series of in-person and telephone staff-administered questionnaires in either English or Spanish, ascertained throughout the study period up until date of infant birth. Anthropometric measurements were conducted via regular clinic visits. Data from the 3rd trimester visit was primarily used to coincide with the exposure period being studied. Additional covariate data came from the participants' 1st visit, such as race/ethnicity, pre- pregnancy Body Mass Index (BMI, kg/m^2), etc. and from pregnancy outcome data, including infant sex.

Maternal demographic variables analyzed for potential confounding included: age at baseline (years), pre-pregnancy BMI (continuous), education level (completed <12th grade, completed high school, some college, completed college), household income (less than $15,000, $15,000–29,999, $30,000–49,999, $50,000+, Do not know), personal smoking status during pregnancy (yes/no), smoking status (ever/never), diabetes status (no diabetes, glucose intolerant, gestational diabetes, chronic diabetes), preeclampsia status (no hypertension, preeclampsia, chronic hypertension, chronic hypertension w/preeclampsia, gestational hypertension), and total weight gain (kg) during pregnancy. Diabetes and preeclampsia status were ascertained from EMR, while pre-pregnancy BMI was calculated using self-reported pre-pregnancy weight and standing height measured by MADRES staff at the first study visit via stadiometer (Perspectives Enterprises model PE-AIM-101, Portage, MI), or height from EMR if missing from first visit data. Self-reported pre- pregnancy weight was used because initial study visits ranged in terms of participants' gestation. Race was recategorized from the NIH categories to a three-level variable containing Hispanic, Black non-Hispanic, and Other non-Hispanic. This was conducted to save degrees of

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freedom in the later regression analysis and because this sample is composed of largely Hispanic women (81%), followed by a smaller subset of Black non-Hispanic women (11%), and with non-Hispanic Whites, Asians, and Others combined making up just 8%.

Pregnancy and birth outcome-related potential covariates included: sex of infant (male/female), parity (defined as 1 or more previous births), and gestational age (GA; weeks). Infant sex was obtained via EMR, or if missing, through interviewer-administered questionnaires at the 7–14 day post-pregnancy follow-up. A missing category was created for 6 participants with missing parity. Gestational age at birth was estimated using a hierarchy of methods including, the preferred ultrasound measurement of crown-rump length at <14 weeks gestation (60%), ultrasound measurement of fetal biparietal diameter at <28 weeks gestation (30%), and from physicians' clinical estimate from EMR (10%).

Meteorological parameters included ambient air temperature (Celsius) (calculated as average of minimum and maximum air temperature) and relative humidity (%), both integrated over the 48 h sampling period and estimated at the residential location based on a high-resolution (4 km x 4 km) gridded surface meteorological dataset (Abatzoglou, 2011). Season was categorized as Cool (Winter), Warm (Summer), and Transition (Spring and Autumn).

Finally, variables describing home ventilation, time-activity patterns, and presence of indoor sources of $PM_{2.5}$ came from two different questionnaires. The first was from the 3rd trimester visit that asked questions related to the past month (or since the last visit in the 2nd trimester), while the second was from the exit survey administered after completing the 48 h personal monitoring period. These variables were chosen since they correlate with the potential of outdoor $PM_{2.5}$ infiltration into the indoor home environment where participants likely spend most of their time, exposure to outdoor $PM_{2.5}$ by spending time outdoors, or exposure to $PM_{2.5}$ generated indoors from sources like cooking or candle use, respectively.

To describe these potential relationships in more detail, greater time spent indoors generally corresponds to greater exposure to indoor $PM_{2.5}$, which in turn is predominantly composed of $PM_{2.5}$ from indoor sources (or of indoor origin) and $PM_{2.5}$ from outdoor origin (infiltrated indoors). The degree to which $PM_{2.5}$ originating outdoors infiltrates into the indoor home environment depends on several factors including home ventilation (e.g., AC use, window opening, etc.) (Breen et al., 2014; Habre et al., 2014). Overall, greater time participants spend outdoors corresponds to potentially greater contribution of outdoor $PM_{2.5}$ to their personal exposures (and vice versa). Additionally, several studies reported air tightness can be lower (higher leakiness) and air exchange rates can be higher in multi-unit residences (compared to single homes), which could mean greater potential for $PM_{2.5}$ of outdoor origin or from neighboring units (e.g., secondhand smoke) to infiltrate indoors (King et al., 2010; Price et al., 2006; Rosofsky et al., 2019), but this likely varies across different contexts. AC use in the home can also remove indoor $PM_{2.5}$ or correlate with lower infiltration of outdoor $PM_{2.5}$ (due to more time with windows and doors closed and greater home sealing to the outdoors).

The final list of variables included: home type (building type/number of attached units), home ventilation (e.g., AC use, window opening time), time-activity patterns (e.g., time

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spent indoors, time spent outdoors), and indoor sources (e.g., cooking smoke, candle and incense smoke). All variables in this final list were available in both the exit survey and 3rd trimester questionnaire, apart from home type, which was only available from the 3rd trimester questionnaire, and candle smoke exposure, which was only asked in the exit survey. Several of these variables were re-categorized, when necessary, based on the distribution of the variable (Table S1).

2.5. Statistical analysis

2.5.1. Descriptive statistics—Descriptive statistics for birthweight and total personal $PM_{2.5}$ were calculated by sample population characteristics. This preliminary bivariate analysis was also used to elicit potential confounders in this analysis. The distribution of $PM_{2.5}$ exposure and birthweight were assessed to identify any deviations from normality and potential outliers. Differences in birthweight and total personal $PM_{2.5}$ by the categorical sample characteristics were evaluated using analysis of variance (ANOVA) tests. Pearson’s correlation coefficients were calculated between continuous population characteristics and birthweight and total personal $PM_{2.5}$ separately. Next, a correlation analysis was conducted to assess whether potential covariates were related to each other to examine collinearity and inform covariate inclusion in the models. Finally, a chi-square test was conducted to determine how well the two questionnaire measures correlated with one another for similar variables thereby providing a consistency check for differently worded questions, or questions that were asked at different points in time and referred to somewhat different time windows (e.g., past 48 h monitoring period versus the last month in the 3rd trimester).

2.5.2. Personal vs. outdoor residential $PM_{2.5}$ exposure—To assess the relationship between total personal and outdoor $PM_{2.5}$ exposure, daily outdoor residential $PM_{2.5}$ concentration was estimated using inverse distance-weighted spatial interpolation from regulatory monitoring data. Daily estimates were averaged to correspond to the 48 h monitoring period and to the 3rd trimester of pregnancy. Descriptive statistics were obtained for the same 48 h monitoring period and for the 3rd trimester, and Pearson’s correlation coefficients were used to evaluate the relationship between personal and outdoor residential $PM_{2.5}$.

2.5.3. Multiple linear regression models—Multiple linear regression models were used to investigate the association between in-utero exposure to $PM_{2.5}$ and the continuous outcome birthweight. All parameter estimates for continuous variables were reported per 1 SD increase in personal $PM_{2.5}$ concentrations, which is equivalent to 17.1 $\mu g/m^3$ as shown in Table 1. Maternal age and race/ethnicity were included in all models due to their importance and inclusion in prior research. Additionally, due to the design of MADRES, recruitment site was also assessed in this analysis but did not impact findings, so was not included. A list of potential covariates based on the previous literature into the effect of air pollution and birth outcomes, and from the bivariate analysis conducted within this analysis, were assessed for inclusion into the model one-by-one based on evidence of confounding. Confounding was observed by gestational age, parity, diabetes status, infant sex, and smoking status. Pre-pregnancy BMI and total weight gain during pregnancy also introduced confounding; however, they were highly correlated with each other and with diabetes status. Each of these

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variables were assessed one at a time with the other included covariates and diabetes status was finally chosen to remain as it impacted the personal $PM_{2.5}$ effect estimate the largest of the three.

The final fully adjusted model included the following covariates: GA at birth, maternal age, race/ethnicity, infant sex, parity, diabetes status, temperature, and personal smoking history. This model was used to (1) evaluate the effect of total personal $PM_{2.5}$ exposure on birthweight, (2) evaluate whether the effect of total personal $PM_{2.5}$ exposure on birthweight was modified by the degree of which indoor vs outdoor sources contributed to or impacted personal $PM_{2.5}$ exposures (broadly derived using questionnaire variables). The *a priori* significance level for the adjusted main exposure/outcome analysis was an alpha of 0.05. Model diagnostics were conducted to ensure they satisfied modeling assumptions and were not affected by multi-collinearity or influential points. Non-linear $PM_{2.5}$ effects were evaluated using graphical plots and by adding polynomials into the model and evaluating statistical significance compared to linear terms. Due to birthweight and gestational age being closely linked, birthweight-for-gestational age z-scores were evaluated with personal $PM_{2.5}$, however, results were not included as they did not reveal any additional information about the relationship between personal $PM_{2.5}$ and birthweight. The analysis was conducted using SAS v9.4 (SAS Institute, Inc., Cary, NC, USA.).

2.5.4. Effect modification analyses for $PM_{2.5}$ impacted by indoor vs outdoor sources—As described earlier, the second aim was to evaluate how the effects of total personal $PM_{2.5}$ exposure differed when the contribution of outdoor sources (or $PM_{2.5}$ of outdoor origin) was higher compared to indoor sources. Indoor vs outdoor origin of $PM_{2.5}$ was approximated using interaction terms with variables that correspond to time-activity patterns (e.g., time spent indoors vs outdoors), indoor sources (e.g., cooking, candle use), home ventilation (e.g., AC use, window use), and home type (e.g., building type/number of attached units). This study investigated effect modification by adding an interaction term to the fully adjusted model, using an *a prior* significance level of 0.10 for the interaction.

2.5.5. Sensitivity analysis—Several analyses were conducted to evaluate the sensitivity of results to various inclusions. First, in the fully adjusted model, this study examined associations only among full-term births (37 weeks or older gestation) to assess whether the pre-term births impacted the associations seen in the full sample. Additionally, due to concerns regarding bias introduced by adjusting for GA, namely, that gestational age may be a mediator (Wilcox et al., 2011), this study performed the analysis without adjustment for GA. Finally, a model was run without the inclusion of the highest 4 personal $PM_{2.5}$ concentrations, determined by concentrations being 2 SDs greater than the mean, to elicit their leverage on results.

3. Results

3.1. Descriptive statistics

Of the 214 mothers who participated in the personal exposure monitoring study, nine participants were removed due to incomplete or erroneous personal $PM_{2.5}$ exposure data or birth outcomes data, resulting in a final analytical sample of 205 mother-infant dyads (Table

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1). The women in the study were predominantly Hispanic (81%) and lower income, with over 55% of women reporting a household income less than $50,000 a year. Additionally, around 67% of participants were overweight or obese prior to pregnancy and most had at least one prior pregnancy (63%). One participant indicated that they had smoked cigarettes, cigars, or pipes during the 48 h sampling period, while all participants indicated not smoking during pregnancy on the 3rd trimester questionnaire (results not shown). Birthweight was normally distributed with a mean (SD) of 3291.2 (485.1) g Total personal $PM_{2.5}$ exposure was right skewed with a mean (SD) of 22.3 (17.1) $\mu g/m^3$ and median (IQR) of 18.2 (14.3) $\mu g/m^3$. The participants had a mean (SD) age of 28.2 (6.0) years, delivered at a mean gestational age at birth of 39.1 (1.5) weeks, and gained on average 10.9 (6.9) kilograms throughout pregnancy.

3.2. Sociodemographic and household characteristics in relation to birthweight

Mothers who spent most or all of the time indoors had infants with significantly higher birthweight (most and all of the time: 3332.0 g vs. none and a little of the time: 3065.3 g; $p = 0.005$), while those who answered yes to using AC during the sampling period had infants that were about 190 g greater in birthweight than mothers that did not use AC ($p = 0.013$). Participants who had at least one child prior to this pregnancy had infants with higher birthweight (yes: 3338.8 g vs. no: 3180.6 g; $p = 0.042$). Infants of women who have completed at least college, had gestational or chronic diabetes, or were in the non-Hispanic Other category, had higher birthweight compared to their counterparts, however, none of these differences met statistical significance (Table S1).

Birthweight displayed a positive correlation with gestational age (Pearson $r = 0.43$; $p < 0.001$) and total weight gain throughout pregnancy ($r = 0.29$; $p < 0.001$), while maternal age showed no correlation ($r = 0.02$; $p = 0.738$; Table S2).

3.3. Sociodemographic and household characteristics in relation to total personal $PM_{2.5}$ exposure

A statistically significant difference in personal $PM_{2.5}$ was observed by maternal income, however, no obvious pattern emerged, with the highest and lowest income groups having the highest personal $PM_{2.5}$ exposure ($p = 0.025$; Table S1). Participants who opened their windows none or a little of the time during the sampling period had slightly higher personal $PM_{2.5}$ exposure (24.7 $\mu g/m^3$) vs. most and all of the time (20.2$\mu g/m^3$), which was marginally significant ($p = 0.058$). Personal $PM_{2.5}$ differed by season of sampling (warm: 19.3 $\mu g/m^3$ vs. transition: 21.0 $\mu g/m^3$ vs. cool: 26.3; $p = 0.072$). Additionally, personal $PM_{2.5}$ was significantly negatively associated with average 3rd trimester temperature ($r = -0.15$; $p = 0.038$; Table S2). Next, women who spent most or all of the time inside during the sampling period had lower personal $PM_{2.5}$ exposure (21.4 vs 25.3 $\mu g/m^3$ for women who spent none or a little of the time indoors; $p = 0.249$). Using the monitoring time-aligned exit survey question on cooking smoke exposure, there was no significant difference between those reporting being near cooking smoke and those that did not (none of the time: 22.1$\mu g/m^3$ vs. a little, most, or all of the time 21.8$\mu g/m^3$; $p = 0.884$).

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3.4. Relationship Between Personal and Outdoor $PM_{2.5}$ Exposure

The mean (SD) personal $PM_{2.5}$ was 22.3 (17.1) $\mu g/m^3$, while the outdoor residential estimate had a mean of 11.9 (5.5) $\mu g/m^3$ for the same 48 h monitoring period, and 12.0 (2.3) $\mu g/m^3$ for the 3rd trimester. Fig. 1. depicts these relationships between total personal and outdoor residential $PM_{2.5}$. During the monitoring period, there was statistically significant yet weak correlation between total personal $PM_{2.5}$ and ambient $PM_{2.5}$ ($r = 0.19$; $p = 0.006$). A weak, positive and non-significant correlation between total personal $PM_{2.5}$ and 3rd trimester ambient $PM_{2.5}$ was also observed ($r = 0.11$; $p = 0.110$).

3.5. Association of total personal $PM_{2.5}$ exposure with birthweight

This study found no significant association between $PM_{2.5}$ and birthweight ($\beta = 37.4$; 95% CI: −29.6, 104.3; $p = 0.273$, per 1 SD increase in $PM_{2.5}$) in the crude (unadjusted) regression model. Results remained similar in the fully-adjusted model (with maternal age, GA, maternal race/ethnicity, infant sex, parity, diabetes status, smoking status, and 3rd trimester average temperature, ($\beta = 38.6$; 95% CI: −21.1, 98.2; $p = 0.204$), as shown in Table 2. In the fully adjusted model, a one week increase in GA was associated with a 180.3g increase in birthweight ($p < 0.001$), females were on average 124.8 g lighter than males ($p = 0.033$), and participants that had not had a pregnancy before had on average 323.4 g lighter babies compared to those that had ($p < 0.001$). Finally, diabetes status was also an important predictor of birthweight, with participants with chronic diabetes (379.4 g; $p = 0.003$) and gestational diabetes (300.9 g; $p = 0.028$) having higher birthweight infants compared to those without diabetes.

3.6. Effect modification of total personal $PM_{2.5}$ by contribution of indoor vs outdoor sources

While total personal $PM_{2.5}$ was not associated with birthweight in the first aim of this study, this association differed significantly by several factors (Table 3). Home type was a significant effect modifier of personal $PM_{2.5}$ exposure on birthweight (interaction $p = 0.028$, Fig. 2b). Participants living in a "house with no joining walls" ($\beta = 156.9$; 95% CI: 26.9, 287.0) had a positive association with birthweight; while a negative association was observed as the number of units in the housing building increased (2–4 units: $\beta = -16.6$; 95% CI:−111.9, 78.7; 5+ units: $\beta = -62.6$; 95% CI:−184.9, 59.6). Additionally, the effect of $PM_{2.5}$ on birthweight was significantly different by AC use (interaction $p = 0.008$), with more negative associations for participants that reported no AC use on the exit survey ($\beta = -27.6$; 95% CI:−101.5, 46.3), compared to any AC use during the 48 h monitoring period ($\beta = 139.9$; 95% CI: 42.9, 237.0) (Fig. 2d). A similar significant interaction and pattern was observed for AC use reported in the 3rd trimester (Table 3).

Participants who reported any exposure to smoke from candles or incense (only assessed in exit survey) had a negative association between $PM_{2.5}$ and birthweight ($\beta = -144.7$; 95% CI: −282.7, −6.8), vs those who reported no exposure ($\beta = 81.2$; 95% CI: 15.9, 146.6). This interaction was statistically significant ($p = 0.004$). There was no significant interaction with cooking smoke exposure in the 48 h monitoring period (none: $\beta = 75.5$; 95% CI: −3.5, 154.5 vs any: $\beta = -10.6$; 95% CI: −100.0, 78.8; interaction $p = 0.153$). Results were similar when using the 3rd trimester questionnaire (Table 3).

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There were also consistent, observable differences in the effect of $PM_{2.5}$ on birthweight for variables related to time-activity patterns, although these interactions were not statistically significant (Table 3). Fig. 2c depicts when participants spent most and all of their time indoors during the 48 h monitoring period (at their residence or someone else's), $PM_{2.5}$ was positively associated with birthweight ($\beta = 57.1$; 95% CI: −7.3, 121.6), as compared to participants who spent none and a little of their time indoors ($\beta = -45.1$; 95% CI: −208.3, 118.1). The 3rd trimester questionnaire revealed a similar pattern, with a positive effect of $PM_{2.5}$ on birthweight when participants spent greater than 16 h inside per day ($\beta = 50.0$; 95% CI: −13.9, 114.0) compared to a slight negative association for participants who spent less than or equal to 16 h inside ($\beta = -25.6$; 95% CI: −184.8, 133.6).

3.7. Results of sensitivity analyses with various inclusions

When the fully adjusted model was restricted to just those participants that had a full-term birth (≥ 37 weeks gestation; $n = 182$), the effect of total personal $PM_{2.5}$ on birthweight increased slightly ($\beta = 55.0$; 95% CI: −6.2, 116.1), compared to the base model used in aim 1 ($\beta = 38.6$; 95% CI: −21.1, 98.2; $p = 0.204$). In non-diabetics only (n=181), no association between total personal $PM_{2.5}$ on birthweight was observed ($\beta = 19.2$; 95% CI: −44.7, 83.2). When GA was not adjusted for, there was a 24% attenuation in the effect estimate for total personal $PM_{2.5}$ on birthweight ($\beta = 29.3$; 95% CI: −41.8, 100.5). Finally, after excluding three observations that had high leverage and particularly high $PM_{2.5}$ (>95 μg/m^3) from the model, the effect of total personal $PM_{2.5}$ on birthweight changed direction but remained non-significant ($\beta = -40.1$; 95% CI: −122.3, 42.1).

4. Discussion

Using data from the MADRES in-utero personal exposure monitoring study, this study evaluated the effect of total personal $PM_{2.5}$ in the 3rd trimester on birthweight in a largely lower income, Hispanic population in Los Angeles, CA. According to a thorough review of existing literature, this is the first time this has been attempted in a health disparities population. This study finds that total personal $PM_{2.5}$ was not statistically significantly associated with birthweight. Most studies of outdoor air pollution generally found a slight negative association with birthweight (Stieb et al., 2012); however, those studies were aimed at investigating personal exposure to $PM_{2.5}$ of outdoor origin rather than total personal $PM_{2.5}$ and generally relied on outdoor estimates of $PM_{2.5}$ as its surrogate. Albeit a different question to the effect of total personal $PM_{2.5}$ on birthweight, these outdoor estimates generally fail to account for time-activity patterns and infiltration of outdoor pollution into the home, thereby likely suffer from measurement error.

One study did look at the effect of total personal $PM_{2.5}$ on birthweight in the 2nd trimester using personal monitoring over a 48 h period in a cohort of non-smoking women in Poland. They found an increase of ~30 μg/m^3 in $PM_{2.5}$ was associated with a 97.2g (95% CI: − 201.0, 6.6) decrease in birth weight (Jedrychowski et al., 2009). Despite the Poland findings not being statistically significant, a possible hypothesis for the difference in findings could be related to the differences between the women participating in the two studies. For example, compared to this study, participants were free from chronic

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diseases including diabetes, which this current study found to be a significant predictor of higher birthweight. Additionally, sources and chemical components of $PM_{2.5}$ exposure in Poland may be different compared to this present study area in urban Los Angeles, CA. Studies have shown that $PM_{2.5}$ sources and chemical components can vary in their effect on birthweight, with differences observed across regions (Basu et al., 2014; Bell et al., 2007), and across race/ethnic groups, especially in California (Bell and Ebisu, 2012). This study participants were largely Hispanic from Los Angeles County, while the Polish study population was predominantly non-Hispanic Whites (Jedrychowski et al., 2009). This highlights the importance of treating $PM_{2.5}$ as a mixture in health analyses, with variable contributions from a wide range of indoor and outdoor sources with potentially differing physiochemical properties, components, and effects on birthweight. Comparing outdoor $PM_{2.5}$ effects across regions, or outdoor to total personal $PM_{2.5}$ effects, does not necessarily take into account this complexity or heterogeneity.

While there was no association between total personal $PM_{2.5}$ and birthweight, this study did find evidence that home characteristics, such as home type and AC use, as well as exposure to candle or incense smoke, modified this association. Mothers residing in multi-unit buildings had a negative association of personal $PM_{2.5}$ with birthweight, compared to a strong positive association for those who reside in a single-family home. One possible reason for this is that individuals in multi-unit homes may have greater secondhand smoke infiltration into their home from neighboring units (King et al., 2010; Price et al., 2006), and secondhand smoke has been shown to be negatively associated with birthweight (Ghosh et al., 2013; Wahabi et al., 2013). This study also considered whether single-family home type could be acting as a proxy for higher income. However, maternal income and educational attainment did not correlate with home type in this sample (results not shown). Additionally, despite having similar total personal $PM_{2.5}$ exposure, the effect of $PM_{2.5}$ on birthweight was significantly lower for participants that did not use AC compared to those that did. Using AC at home likely correlates with greater sealing of the home or closing of windows and doors to operate the AC unit(s), which also correlates with less infiltration outdoor $PM_{2.5}$ indoors (and thus less exposure to $PM_{2.5}$ of outdoor origin).

Although this study did not have complete information on all the possible indoor sources of $PM_{2.5}$, this study saw evidence of significantly more negative or potentially harmful effects of candle and/or incense burning indoors on birthweight. Previous literature has shown that prenatal incense burning was associated with lower birthweight (Chen and Ho, 2016). One possible explanation is candle and incense burning emit black carbon (BC) and other chemicals indoors (Habre et al., 2014; Stabile et al., 2012). Several studies have reported an association between BC concentrations in $PM_{2.5}$ and low birthweight; however, they were using outdoor BC as a surrogate or marker of outdoor, traffic-related air pollution (Lakshmanan et al., 2015; Slama et al., 2007). Bové et al. (2019) found BC accumulated on the fetal side of the human placenta, representing a potential mechanism for negative health effects. However, without further information on chemical composition and properties of the personal $PM_{2.5}$ exposure mixture in these studies, it is difficult to conclude whether the candles and incense burning mixture as a whole or any particular component of it, such as BC, is driving these adverse effects.

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This study did not find consistent effect modification results for exposure to $PM_{2.5}$ from cooking, as another potentially important indoor source in this population. Most cooking smoke exposure and birthweight studies have concentrated on solid fuel sources (e.g., coal, wood), often in low- and middle- income countries, but generally find a negative association with birthweight (Wylie et al., 2017; Zhang et al., 2016). These findings may not be a suitable comparison with this study sample considering the participants were based in Los Angeles, CA where solid fuel cooking is not common, and where the composition or mixture of cooking related exposures may be different due to most participants using gas stoves (data not shown). It is also possible that cooking emits particles in the ultrafine size range (< 0.1 μm in aerodynamic diameter) which do not contribute significantly to $PM_{2.5}$ mass concentrations, and thus, the measurements may not be sensitive enough to differentiate their contribution (as compared to particle number concentrations for example, which were not available in this study).

These analyses also revealed a consistent pattern where personal $PM_{2.5}$ exposure with greater influence or contribution of outdoor sources was generally more strongly associated with lower birthweight, despite these interactions not reaching statistical significance. This was true for greater time spent outside (and less time spent inside), and greater time with open windows. However, these associations should be explored further, as the effect modification of time with windows open reported on the exit survey was less pronounced. While the present study may be underpowered to tease apart these differences, the results are consistent with prior studies assessing the impact of specific outdoor sources of $PM_{2.5}$ or their surrogates such as on road gasoline and on road diesel, or residing closer to major roadways, respectively, which were associated with greater risk of LBW compared to $PM_{2.5}$ as a whole (Bell et al., 2010; Laurent et al., 2016).

There are several strengths of this analysis. The first is the use of personal monitoring that provides a unique opportunity to examine personal exposure to $PM_{2.5}$ and disentangle its impact on birthweight when it was more impacted by outdoor sources. This approach drastically reduces exposure measurement error as compared to using outdoor estimates of $PM_{2.5}$ despite it being limited to a small sample (Gray et al., 2010). Next, this study was able to evaluate total personal $PM_{2.5}$ exposure in the 3rd trimester, which may be particularly important for birthweight, given that most fetal growth occurs late in pregnancy. Most studies on the effect of $PM_{2.5}$ on birthweight have used ambient monitoring data to estimate personal exposure to $PM_{2.5}$ of outdoor origin, rather than the total personal $PM_{2.5}$ to which individuals are exposed. Understanding the effects of outdoor $PM_{2.5}$ on health is certainly an important question to evaluate, due to this being the fraction of $PM_{2.5}$ that is regulated, but it is not the same question as the effect of total personal $PM_{2.5}$ which takes into account all indoor, outdoor, and personal activity related sources that contribute to personal exposure as a result of realistic day-to-day behaviors and time-activity patterns. However, this study was also able to indirectly investigate whether the effects of personal $PM_{2.5}$ differed when it was more impacted by indoor vs outdoor sources using interaction analyses with detailed, time-aligned questionnaire variables. It is also important to note that the chemical composition and size distribution of outdoor $PM_{2.5}$ changes as it infiltrates indoors, which further highlights the importance of deciphering the independent effects of personal exposure to $PM_{2.5}$ of indoor versus outdoor origin (Meng et al., 2007).

Furthermore, the MADRES cohort study is a well characterized prospective study in a health disparities population, with a host of covariates available, making this an ideal study to assess the research question at hand. This study also had the advantage of using two questionnaire data sources that differed in their time coverage and alignment (a longer-term 3rd trimester questionnaire vs an exit survey immediately following the 48 h monitoring period). This also allowed us to shed light on whether the 48 h sampling period reasonably represented behaviors, time-activity patterns, and 3rd trimester exposures in general.

The sample size of this study is a potential limitation with a final working sample of 205 participants, which while small for population-based studies is actually reasonably large for personal exposure monitoring studies (Dadvand et al., 2012; Sarnat et al., 2000; Suh and Zanobetti, 2010). Despite this limitation, this study was still able to observe differences in the influence of personal $PM_{2.5}$ on birthweight by factors that drive indoor/outdoor source contributions, and most significantly for AC use and home type. Finally, participation bias may be a factor regarding who from the MADRES cohort chose to participate in the personal exposure monitoring study, however, participants who chose to participate were not noticeably different than the larger MADRES cohort study apart from being slightly more likely to have had a prior child (data not presented).

5. Conclusion

Overall, the results of this study did not find a significant association between total personal $PM_{2.5}$ exposure and birthweight, however, there was evidence that multi-unit housing (vs. single family homes), candle and/or incense smoke exposure, and greater outdoor source contributions to personal $PM_{2.5}$ were more strongly associated with lower birthweight. This highlights the importance of disentangling the mixture and apportioning $PM_{2.5}$ by sources for health analyses, including potentially a more refined or chemically speciated approach to apportion indoor from outdoor source contributions to personal $PM_{2.5}$.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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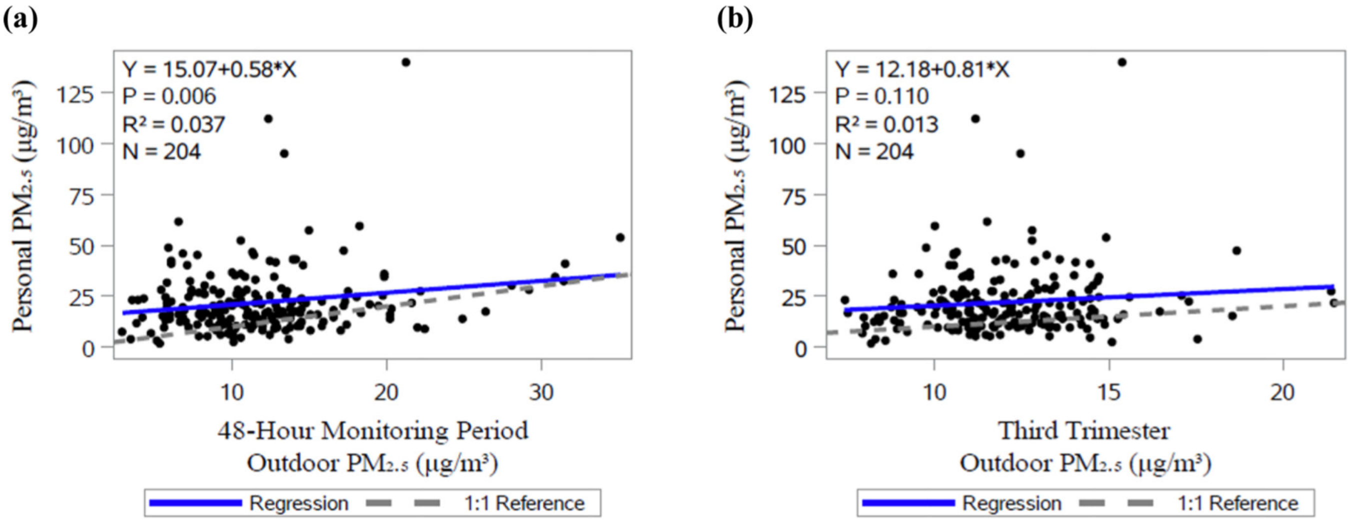

Fig. 1.

Relationship of personal $PM_{2.5}$ and outdoor $PM_{2.5}$ in (a) the 48 h monitoring period and (b) the third trimester of pregnancy.

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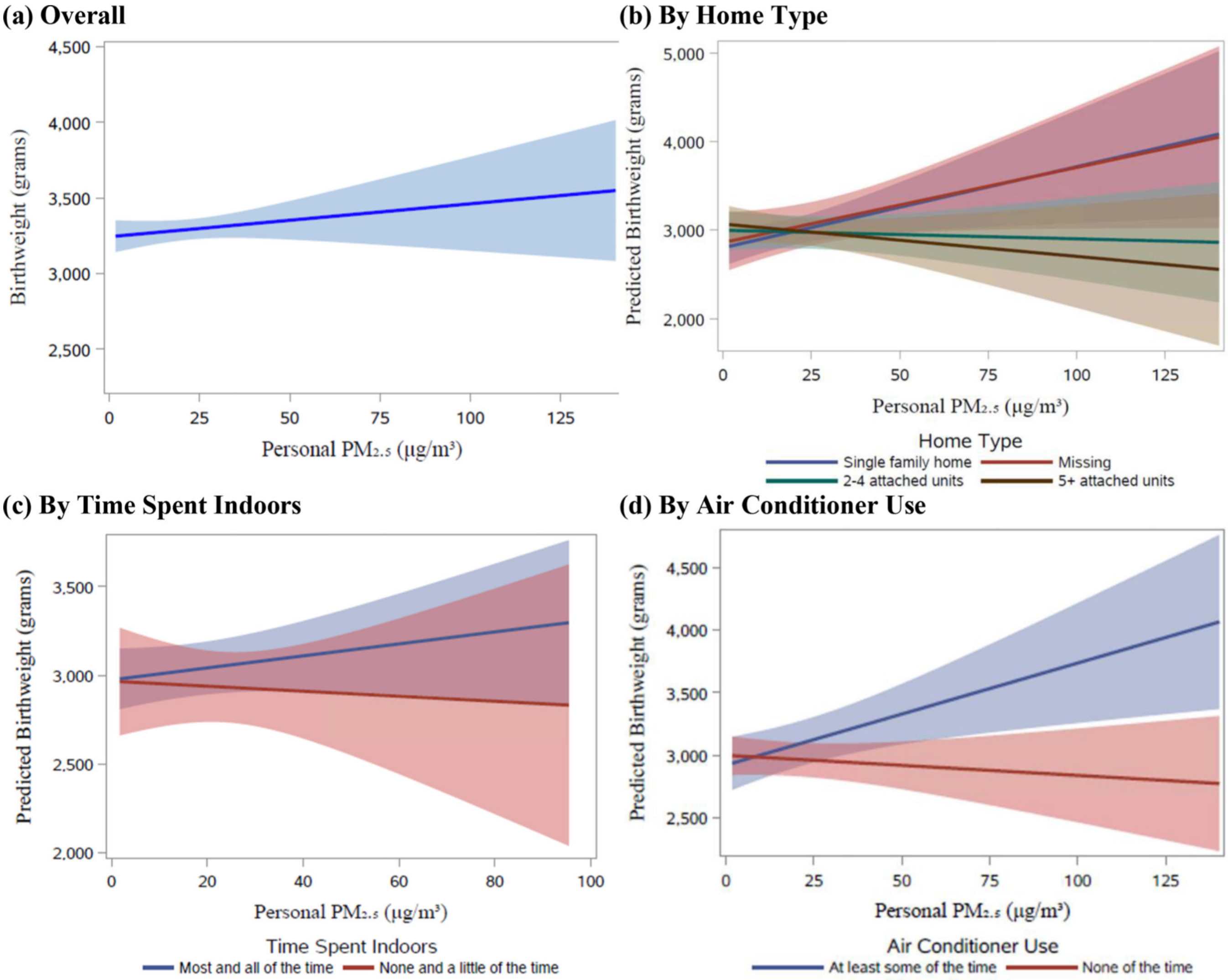
(a) Overall
(b) By Home Type
(c) By Time Spent Indoors
(d) By Air Conditioner Use

Fig. 2.

Predicted relationship of personal $PM_{2.5}$ exposure on birthweight (a) overall, (b) by type of home, (c) time spent indoors, and (d) air conditioner use at home, for each level of the interaction variable where applicable.

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Table 1

Descriptive statistics of study participants (*N* = 205).

Variable	Mean (SD) or n (%)	Variable	Mean (SD) or n (%)
Personal $PM_{2.5}$ (μg/m^3)	22.3 (17.1)	Pre-Pregnancy BMI (kg/m^2)	28.8 (6.8)
Birthweight (g)	3291.2 (485.1)	Normal	62 (30.2%)
Total weight gain (kg)	10.9 (6.9)	Overweight	64 (31.2%)
Gestational age (weeks)	39.1 (1.5)	Obese	79 (38.5%)
Maternal age (years)	28.2 (6.0)	Parity	
Gender		Yes	130 (63.4%)
Female	105 (51.2%)	No	69 (33.7%)
Male	100 (48.8%)	Missing	6 (2.9%)
Race		Maternal Income	
Hispanic	166 (81.0%)	\$50,000–\$99,999	14 (6.8%)
Black, Non-Hispanic	23 (11.2%)	\$30,000–\$49,999	29 (14.1%)
Other, Non-Hispanic	16 (7.8%)	\$15,000–\$29,999	46 (22.4%)
Education		Less than \$15,000	41 (20.0%)
< 12th grade	49 (23.9%)	Do not know	75 (36.6%)
Completed high school	64 (31.2%)	Smoking	
Some college	62 (30.2%)	Ever	43 (21.0%)
Completed college	30 (14.6%)	Never	162 (79.0%)
Diabetes		Temperature (°C)	19.3 (4.2)
Normal	136 (66.3%)	Season	
Glucose intolerant	46 (22.4%)	Warm	40 (19.5%)
Gestational diabetes	10 (4.9%)	Cool	64 (31.2%)
Chronic diabetes	13 (6.3%)	Transition	101 (49.3%)

Notes: $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 μm; BMI = body mass index; SD = standard deviation; g = grams; kg = kilograms; transition = spring and autumn.

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Table 2

Regression results for base model of $PM_{2.5}$ and birthweight ($N = 205$).

Variable	**β**	**95% CI Lower**	**95% CI Upper**	***p*-value**
Intercept	−3452.3	−5096.7	−1807.9	**< 0.001**
Personal $PM_{2.5}$ ($\mu g/m^3$)[a]	38.6	−21.1	98.2	0.204
Gestational age (weeks)	180.3	141.1	219.5	**< 0.001**
Maternal age (years)	−8.8	−19.8	2.3	0.121
Temperature (°C) [^]	11.3	−5.8	28.4	0.194
Race/ethnicity				
Hispanic	−135.3	−356.9	86.3	0.230
Black, non-Hispanic	−248.7	−520.0	22.6	0.072
Other, non-Hispanic	Ref.			
Sex of infant				
Female	−124.8	−239.2	−10.3	**0.033**
Male	Ref.			
Parity				
Missing	176.4	−166.0	518.7	0.311
No	−323.4	−459.4	−187.4	**< 0.001**
Yes	Ref.			
Diabetes				
Chronic diabetes	379.4	129.7	629.1	**0.003**
Gestational diabetes mellitus	300.9	33.1	568.7	**0.028**
Glucose intolerant	111.3	−26.9	249.5	0.114
Normal	Ref.			
Smoking				
Ever smoker	−175.8	−319.7	−31.8	**0.017**
Never smoker	Ref.			

Notes:

[a] Per 1 SD increase in personal $PM_{2.5}$; $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5μm; CI = confidence interval

[^] - third trimester average temperature in degrees Celsius; Ref. = reference level.

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Table 3

Estimated change in birthweight (g) per 1 SD increase in personal $PM_{2.5}$ from interaction analyses (N = 204).

Time Activity Pattern	**β**	**95% CI Lower**	**95% CI Upper**	***p*-value**
Time spent indoors				
How much of the time did you spend indoors (at your residence, or someone else’s residence)?[a]				0.255
None and a little of the time	−45.1	−208.3	118.1	
Most and all of the time	57.1	−7.3	121.6	
Thinking back to a typical weekday in this past week, approximately how many hours (out of 24 h in total) did you spend indoors?[b]				0.383
≤ 16 h	−25.6	−184.8	133.6	
> 16 h	50.0	−13.9	113.9	
Time spent outdoors				
How much of the time did you spend outdoors (not commuting in a car, bus or train)?[a]				0.402
None and a little of the time	59.5	−13.6	132.6	
Most and all of the time	6.8	−94.2	107.7	
Thinking back to a typical weekday in this past week, approximately how many hours (out of 24 h in total) did you spend outdoors?[b]				0.411
< 8 h	46.0	−16.5	108.5	
≥ 8 h	−33.5	−215.2	148.3	
Home characteristics and ventilation				
Home type				
Which best describes the home in which you currently live most of the time?[b]				**0.028**
A single-family house (no joining wall)	156.9	26.9	287.0	
A building with 2–4 attached Units	−16.6	−111.9	78.7	
A building with 5+ attached Units	−62.6	−184.9	59.6	
Missing	145.4	−4.1	294.9	
Time with windows open				
How much of the time were windows (or porch/balcony doors if applicable) open in your home, when you were there with the sampler?[a]				0.936
None and a little of the time	33.8	−35.3	102.9	
Most and all of the time	28.2	−89.3	145.8	
On average, how much of the time were the windows open in your home this past week?[b]				0.230
None and a little of the time	53.9	−14.2	122.0	
Most and all of the time	−30.2	−151.8	91.5	
Air conditioner use				
How much of the time was the air conditioner used in your home, when you were there with the sampler?[a]				**0.008**
None of the time	−27.6	−101.5	46.3	
A little, most, and all of the time	139.9	42.9	237.0	
Do you use air conditioning in your home?[b]				**0.044**
No	−24.3	−107.1	58.5	

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Time Activity Pattern	β	95% CI Lower	95% CI Upper	*p*-value
Yes	99.4	13.5	185.3	
Indoor sources				
Cooking				
How much of the time were you close to smoke or fumes from cooking (yourself, or nearby cooking by someone else) e.g., burnt toast, barbeque, stir fry, etc.?[a]				0.153
None of the time	75.5	−3.5	154.5	
A little, most, and all of the time	−10.6	−100.0	78.8	
Since we last saw you/spoke to you in your first/second trimester, on average, how many times a week do you cook (using the stove/range/oven, not microwave)?[b]				0.085
Never	158.0	9.2	306.8	
1 or more times a week	15.2	−50.2	80.5	
Candle or incense				
How much of the time were you close to smoke from candles or incense burning nearby?[a]				**0.004**
None of the time	81.2	15.9	146.6	
A little, most, and all of the time	−144.7	−282.7	−6.8	

Notes: All interactions are adjusted for gestational age, gender, parity, race/ethnicity, maternal age, diabetes status, smoking, and temperature; $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 μm; CI = confidence interval

[a] From exit questionnaire administered to participants after completing the 48 h personal exposure monitoring period

[b] From 3rd trimester survey; bolded = statistically significant at *p*-value < 0.1.