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The effect of prenatal temperature and $PM_{2.5}$ exposure on birthweight: weekly windows of exposure throughout the pregnancy.

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Abstract

Background—Birthweight is a strong predictor of normal growth, healthy development, and survival. Several studies have found associations between temperature, fine particulate matter ($PM_{2.5}$), and birth weight. However, the relevant timing of exposures varies between studies and is yet unclear. Therefore, we assessed the difference in term birthweight (TBW) associated with weekly exposure to temperature and $PM_{2.5}$ throughout 37 weeks of gestation.

Methods—We included all singleton live term births in Massachusetts, U.S between 2004 and 2015 (n=712,438). Weekly $PM_{2.5}$ and temperature predictions were estimated on a 1 km grid from satellite-based models. We utilized a distributed lag nonlinear model (DLNM) to estimate the difference in TBW associated with weekly exposures from the last menstrual period to 37 weeks of gestation.

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Declaration of interests

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

Results—We found a nonlinear association with prenatal temperature exposure. Larger effects were observed in warmer temperatures, where higher temperatures were negatively associated with TBW. Temperature effects were larger in the first and final weeks of gestation. We observed a negative difference in TBW associated with $PM_{2.5}$ exposure. Overall, a 1 $\mu g/m^3$ increase in prenatal exposure was associated with 3.9g lower TBW (95% CI −5.0g; −2.9g). $PM_{2.5}$ effects were larger in the final weeks of gestation.

Conclusion—We found heat and $PM_{2.5}$ exposure to be related to lower TBW. Our findings suggest that women are more susceptible to both exposures towards the end of pregnancy. Susceptibility to heat was higher in the initial weeks of pregnancy as well. These critical windows of susceptibility can be communicated to pregnant women during routine prenatal visits to increase awareness and target interventions to reduce exposures.

Keywords

air pollution; temperature; Birth weight; PM2.5

1. Introduction

Birth weight is a marker for development in early life [1] with long-term health consequences in childhood and adulthood [2]. The World Health Organization has targeted the achievement of a 30% reduction in low birth weight deliveries as a sustainable developmental goal [3], emphasizing the importance of birth weight as a predictor of morbidity and mortality. Although birth weight is mostly determined by genetic factors and length of gestation [4], it is also affected by maternal health and exposures during pregnancy [5–11]. Several studies have found associations between temperature [12–16], particulate matter smaller than 2.5μm ($PM_{2.5}$) [17–21], and birthweight. However, exposure assessment methods and the definition of the time windows of susceptibility vary across studies.

In most current studies, temperature and $PM_{2.5}$ exposures are averaged over trimesters or the entire pregnancy [15, 21–25]. However, the true time windows of susceptibility are unlikely to follow the strict categorization of trimesters [12]. Another problem that can potentially arise from this approach is seasonality bias, as described by Wilson et al. Although this bias can be reduced by including all three trimester exposures in the model, it does not necessarily eliminate the bias [26].

Distributed lag models (DLMs) are a useful tool to address both limitations. DLMs can be used to identify critical windows of susceptibility in a flexible way [27]. They allow a joint assessment of multiple short intervals of exposure (i.e., the lag structure) throughout the gestation period [26]. This approach has been previously used to assess the effects of meteorological exposures or $PM_{2.5}$ exposure during pregnancy on term birth weight (TBW) [12, 26].

As we know from previous studies, there is evidence of nonlinear associations between temperature exposure and birth outcomes [5, 25, 28]. In addition, we hypothesize that the lag structure of the associations throughout the pregnancy does not necessarily follow a linear trend, and exposures during some periods of gestation may be more critical to fetal growth

than others. Distributed lag nonlinear models (DLNM) are an extension of DLMs, which allow us to flexibly model both the nonlinear exposure-effects and the lag structure of the associations [27]. Although this approach was used to assess temperature and humidity effects on the rate of preterm births [29, 30], or TBW [12] to our knowledge, it has not been used to assess the simultaneous effects of temperature and $PM_{2.5}$ exposure on TBW.

In this study, we investigate the complex lag structures and nonlinear temperature and $PM_{2.5}$ effects on TBW in a large population-based birth registry. We aim to identify critical windows of prenatal exposures using fine spatiotemporal models of temperature and $PM_{2.5}$.

2. Materials and methods

2.1. Study population

We included all eligible singleton live births in the Massachusetts birth registry data (n=712,438 births) for years with available exposures data (2004–2015). The birth registry data included 834,886 records within the study years. This data includes the newborn's information (date of birth, sex (male or female), birth weight in grams, gestational age at birth), maternal sociodemographic information (age at birth, race (White, Black, or other), parity (first delivery/ 2^{nd} or more), whether the mother received government support for prenatal care (yes/no), smoking before or during pregnancy (yes/no), the highest level of education attained (no high school diploma, high school, some college, or college), chronic conditions (e.g. diabetes (yes/no) or hypertension (yes/no)), and geocoded residential address at birth. We excluded a total of 122,448 (14.6%) of the births according to the following exclusion criteria: preterm births (<37 weeks, n=57,557), records of gestational age >42 weeks (n=8,506), records of birthweight<400 grams (n=10) or over 6 kg (n=20), and records that had missing covariates, or residence information (n=93,527). Most of the missingness was driven by missing address information, and missing information on diabetes and hypertension. Since we only included term births, we a priori assumed linear relationship between gestational age and the outcomes. We observed stronger negative associations between maternal age and TBW among the youngest and eldest mothers and therefore used a penalized spline function to allow for a nonlinear association with maternal age at delivery.

This study was approved by the Massachusetts Department of Public Health and the human subjects committee at the Harvard T. H. Chan School of Public Health.

2.2. Exposures

$PM_{2.5}$: Residential exposure to $PM_{2.5}$ was estimated during pregnancy using a novel model [31]. We applied extreme gradient boosting (XGBoost) modeling to predict daily $PM_{2.5}$ on a 1-km resolution for a 13-state region in the Northeastern USA. We used satellite-derived aerosol optical depth (AOD) and implemented a recursive feature selection among land use covariates to develop a robust yet parsimonious model. The model performance was excellent, with a root mean square error (RMSE) of 3.11 $\mu g/m^3$ in our spatial cross-validation withholding nearby sites and a RMSE of 2.10 $\mu g/m^3$ using a more conventional random ten-fold splitting of the dataset. For more in depth details on model methods and

performance please see Just 2020 [31]. Daily estimates were averaged to calculate weekly exposures for each week of gestation in each woman.

Temperature: Ambient temperature at the residential address was estimated during pregnancy using a second novel model [32]. We applied XGBoost to predict hourly air temperature on a 1-km resolution for the same 13-state region in the Northeastern USA. We used land surface temperature (LST) from two NASA satellites (up to four overpasses daily) as well as physiographic and land use covariates and inverse-distance weighted temperature surfaces from ~4,000 weather stations of the Integrated Mesonet. A rigorous spatial cross-validation showed excellent performance with RMSEs around 1.6 K compared with standard deviations around 11.0 K. For comparison, the mean square error (MSE) was about 1/3 of the MSE of the widely used ~11 km by 14 km NASA NLDAS-2 forcing temperature. Hourly estimates were averaged to calculate weekly exposures for each week of gestation in each woman.

2.3. Statistical analysis

We assessed the association between weekly mean temperature and $PM_{2.5}$ exposures during gestation and TBW using DLNMs [27]. We utilized a DLNM generalized additive model to estimate the difference in TBW associated with weekly exposures from the last menstrual period to 37 weeks of gestation. Both exposures were included in simultaneously in the multivariate model. The advantage of the DLNM framework is that it allows nonlinear exposure-response and time-response functions [27]. Associations between temperature exposure and birth outcomes are often nonlinear [5, 25, 28]. Therefore, we modeled the association between weekly mean temperature and TBW using a natural cubic spline with two degrees of freedom and modeled the lag function using a penalized spline. For $PM_{2.5}$ exposure, we assumed a linear association with TBW and modeled the lag function using a natural cubic spline with three degrees of freedom. Both for the association with temperature and for the lag function of $PM_{2.5}$, we selected the number of degrees of freedom that minimizes the Akaike Information Criterion (AIC). We estimated the overall cumulative exposure-response curve of temperature and $PM_{2.5}$ exposure effects on TBW. We additionally assessed the difference in TBW associated with increases in $PM_{2.5}$ and low and high temperatures.

We adjusted the model for the variables available in the birth records shown to be potential confounders of the associations between temperature, $PM_{2.5}$, and birthweight: season and year of birth, a cyclic spline of day of the year, government support for prenatal care, race, age of mother at birth, parity, maternal smoking before or during pregnancy, the maternal highest level of education attained, chronic diabetes, chronic hypertension, and gestational age at birth [6, 10, 33]. We additionally adjusted the model for census block-group socioeconomic characteristics (i.e., population density and median household income).

We present the results of the cumulative exposure-response curves, defined as the net effect of $PM_{2.5}$ or temperature across the entire lag period [27]. We additionally present the difference in birthweight, associated with 1 $\mu g/m^3$ increase in $PM_{2.5}$, and 1 °C increase in temperature in different weeks of gestation. Since the cumulative exposure-response curve suggested a nonlinear association with temperature exposure, we present the effect estimates

associated with a rise of 1 °C in the 5th (−4 °C) and the 95th (23 °C) percentiles of the temperature distribution.

2.3.1. Secondary analyses—To identify a potential modification of the associations by maternal race and income, and by newborn sex, we repeated our model separately among White versus non-White mothers, among mothers who receive governmental support for prenatal care versus mothers who do not receive governmental support, and among male versus female newborns. We treat eligibility to governmental support as a proxy for socioeconomic status.

Additionally, to capture the effects of the studied exposures on extreme abnormal fetal growth, we have assessed the effects of temperature and $PM_{2.5}$ exposures in pregnancy on newborns small for gestational age (SGA). We calculate the newborn size for gestational age (SGA, appropriate for gestational age (AGA) or large for gestational age (LGA)) using the Fenton sex-specific reference growth curves [34].

2.3.2. Sensitivity analysis—The DLNM requires identical length exposure periods across the study population. This poses a challenge in defining the exposure period when studying pregnancy outcomes where the intrauterine exposures differ in length and depend on the gestational age at birth. To overcome this limitation, we defined the exposure period in our main analysis as the first 37 weeks of gestation, starting at date of last menstrual period (LMP), and limited our data to term births. For women who gave birth after the start of 37 weeks of gestation, exposures following the 37th week were unaccounted for in our main model. We, therefore, added a sensitivity analysis aimed to examine the robustness of our findings. We created a subcohort of women who delivered at 39 weeks of gestation. Among this population, we compared the results obtained when assessing the weekly effects of temperature and $PM_{2.5}$ exposure at the first 37 weeks of gestation versus the entire pregnancy (39 weeks of gestation).

3. Theory

Multiple factors determine birthweight; some are not fully understood. It is, therefore, hard to identify a single etiology of lower birth weight. Maternal exposure to high temperatures during pregnancy can affect birthweight through different mechanisms. The first trimester of pregnancy is crucial for the correct implantation of the placenta [35]. Maternal exposure to heat in the early stages of pregnancy can reduce placental weight and umbilical cord flow [5]. The final stages of pregnancy are characterized by the fastest somatic growth of the fetus [35]. Therefore, high-temperature exposures in late gestation can also affect birth weight. Higher heat production during pregnancy, alongside weight gain and the burden of the fetus, limit the maternal ability to tolerate heat stress [13]. Heat stress and dehydration during pregnancy can cause uterine constriction and impair the uterine blood flow [36].

The $PM_{2.5}$ effect on intrauterine growth can be attributed to the limited placental ability to filter environmental chemicals [37]. Maternal exposure to air pollution during pregnancy may cause oxidative stress and endocrine disruption in the placenta, impair the transport of oxygen and nutrients to the fetus, and adversely affect the intrauterine growth [35, 38].

$PM_{2.5}$ has also been shown to impair vascular development in the placenta [39], decrease placental methylation in the leptin gene promotor [40], and decrease mitochondrial DNA content and increase mitochondrial DNA methylation in the placenta [41].

4. Results

We included 712,438 births; 71.9% were of White mothers. The mean maternal age at delivery was 30 years, 6.8% reported smoking during pregnancy, 0.9% had diabetes mellitus, and 1.3% had chronic hypertension. Half of the newborns were males, the mean gestational age at birth was 39.3 weeks, and the mean TBW was 3.4 kg (Table 1). The median household income at the maternal block group of residences was $51,700 on average.

During the study period, the mean temperature exposure was 10.2 °C, and mean $PM_{2.5}$ exposure was 8.9 $\mu g/m^3$ (Figure 1 and Table 2). Weekly temperature exposures ranged from −16.7 °C to 30.2 °C with a standard deviation of 9.2 °C. The births were distributed evenly throughout the year, with slightly more births in the summer months (Table 2). The correlation between weekly temperature and $PM_{2.5}$ exposures was low ($r=0.15$, $p<0.001$).

We observed significant associations between temperature and TBW, independent of $PM_{2.5}$ exposure. The cumulative temperature exposure-response curves over 37 weeks of gestation are presented in Figure 2. In temperatures below zero, we observed a positive difference in TBW associated with higher temperatures. The associations in colder temperatures were mostly non-significant. In warmer temperatures, we observed a negative difference in TBW associated with higher temperatures. For example, we observed a positive non-significant difference in TBW for a rise in 1 °C in temperature exposure from −4 °C to −3 °C (2.4g, 95% CI −0.1g; 4.9g). However, a rise in 1 °C in temperature exposure from 23 °C to 24 °C was associated with 7.9g lower TBW (95% CI −11.2g; −4.6g) (Figure 2.a). We observed a negative cumulative difference in TBW associated with $PM_{2.5}$ exposure, independent of temperature exposure. A 1 $\mu g/m^3$ increase was associated with 3.9g lower TBW (95% CI −5.0g; −2.9g) (Figure 2.b).

Figure 3 shows the difference in TBW associated with a unit increase in exposures across the 37 lags of exposures. In the 5^{th} percentile of temperature (−4 °C), we observed positive associations with TBW, that were similar across different weeks of gestation (Figure 3.a). In the 95^{th} percentile of temperature (23 °C), we observed larger TBW reductions associated with temperature exposure at the first and final weeks of gestation. We found smaller TBW reductions associated with weekly temperature exposure around the second trimester of pregnancy (Figure 3.b). Finally, we observed larger TBW reductions associated with $PM_{2.5}$ exposure in the final weeks of gestation (Figure 3.c). Figure 4 shows the odds ratio of SGA associated with a unit increase in exposures across the 37 lags of exposures. We did not find a statically significant association between temperature exposure and SGA. A 1 $\mu g/m^3$ increase in cumulative $PM_{2.5}$ exposure across the pregnancy was associated with a 3% (odds ratio 95%CI 1.02; 1.04) higher odds of SGA. The effects were similar across the different weeks of gestation. For example, the odds of SGA were 0.008% higher for each 1 $\mu g/m^3$

increase in $PM_{2.5}$ exposure in the 37th week of gestation, and 0.01% higher for each 1 μg/m^3 increase in $PM_{2.5}$ exposure in the first week of gestation.

Thirty-one percent of the women in our analytic dataset gave birth at 39 weeks of gestation. We repeated our model among this subcohort and compared the results for 37 weeks of exposure and complete gestational exposure (39 weeks) in this population. The cumulative effects of temperature and $PM_{2.5}$ were similar, regardless of the exposure period (Supplementary Figure 1).

Supplementary Figures 2–4 shows the cumulative differences in TBW by race, maternal governmental support for prenatal care visits, and newborn sex. The differences in TBW associated with temperature at the 5th and 95th percentiles and $PM_{2.5}$ in each sub cohort are presented in Supplementary Table 1. We observed stronger temperature effects among mothers who received governmental support, and among female newborns. Additionally, we observed stronger effects of hotter temperatures among White mothers. The effects of colder temperatures did not differ by race. The effects of $PM_{2.5}$ exposure were similar in all sub cohorts.

5. Discussion

5.1. Main findings

Our findings show that the first and final weeks of gestation are the critical windows of exposure to heat. We observed a nonlinear temperature effect, with higher temperatures associated with lower TBW in warmer temperatures. We found a significant decrease in TBW and a significant increase in the odds of SGA associated with $PM_{2.5}$ exposure. The negative association of $PM_{2.5}$ exposure with TBW was larger towards the end of pregnancy.

5.2. Critical windows of exposure

This study confirms evidence from previous studies that found decreases in TBW associated with maternal exposure to heat during pregnancy. A recent review investigating the effects of prenatal exposure to air pollution and heat on birth outcomes in the U.S. has found three studies that evaluated the association between maternal exposure to heat and low birth weight [42]. In each of these studies, temperature exposure was associated with low birth weight [15, 43, 44]. Basu et al. have concluded that the observed effects of apparent temperature on low birth weight over the entire pregnancy are driven largely by exposure in the third trimester of pregnancy [43]. Similarly, Ha et al. [15] and Kloog et al. [45] have found an increased risk for low birth weight associated with heat exposure during the whole pregnancy, and the third trimester specifically. To date, there is no consensus regarding the critical windows of exposure to heat during pregnancy [46]. As pointed in the examples above, most studies identify the third trimester as the important window of susceptibility. However, our findings show that the first trimester of pregnancy is critical as well. We found that newborns are more susceptible to maternal heat exposure in the initial and final weeks of pregnancy, adjusting for the exposure across all other weeks of gestation. With the progression of pregnancy towards the 19th week of gestation, the observed effects gradually became smaller. After remaining constant in mid-pregnancy, following the 25th week of

gestation, the effects gradually became larger. The early pregnancy exposure-effect might not be captured in studies averaging the exposures over trimesters or the whole pregnancy. The added value of our study is the finer isolation of the critical windows of susceptibility.

Unlike temperature exposure, the lag-structure of the $PM_{2.5}$ effect on TBW followed a linear trend with larger effects in later weeks of gestation. The increased odds of SGA, associated with $PM_{2.5}$ exposures were very similar across the different weeks of gestation. Similar to our analysis, numerous studies have found significant associations between $PM_{2.5}$ and low birth weight, TBW [42] or SGA [20]. However, the critical windows of susceptibility for $PM_{2.5}$ are inconsistent across studies. For example, Kumar et al. [47] have identified the highest $PM_{2.5}$ effect on birth weight in the first trimester of pregnancy. Ha et al. [15] have found associations with $PM_{2.5}$ exposure in the second trimester, and Savitz et al. [48] have found significant effects of $PM_{2.5}$ exposures in all three trimesters of pregnancy. In a previous analysis done by our group, we have found significant effects of $PM_{2.5}$ exposures in all three trimesters of pregnancy. These effects were attenuated when we included exposures to greenspace, noise, and walkability in the model [49]. Studies that investigated the effects of extreme pollution events on obstetric outcomes have found exposure to $PM_{2.5}$ originating in wildfire smoke in first [50, 51], second and third trimesters [51] of pregnancy to be associated with lower birthweight.

5.3. Nonlinear association with temperature exposure

Another important finding of this study is the nonlinear relationship between temperature and TBW. The same exposure response curve was reported in animal studies which found extremely high and low temperatures to be associated with maternal stress, lower birthweight, placental weight and diameter. We observed an inverted U-shaped exposure-response curve, which suggested that both temperature extremes were associated with lower TBW. The effects were stronger in warmer temperatures, where higher exposure was associated with lower TBW. These findings are in line with current evidence, suggesting that the adverse neonatal effects of temperature exposure are stronger for heat than for cold [52].

5.4. Susceptible groups

The results of our sub cohort analyses varied by exposure. We found similar associations for $PM_{2.5}$ regardless of sex, socioeconomic and racial groups. Similarly, Bell et al also found similar air pollution effects on birthweight among male and female newborns [53]. Unlike our findings, other studies have found racial minorities and lower socioeconomic groups to be more susceptible to air pollution effects [54, 55]. This may be related to higher exposure concentrations, higher frequency of psychological stressors, or limited access to health care [56]. In accordance with the literature, we did find mothers of lower socioeconomic status to be more susceptible to both colder and hotter temperatures [57]. This may be related to limited access to air conditioning, and residence in densely populated neighborhoods. Unexpectedly, White mothers were more susceptible to hotter temperatures compared to non-White mothers. With 80% White population in Massachusetts, it is possible that our findings were not robust due to a small sample size among minority groups.

Finally, we found larger TBW reductions associated with temperature among females, especially in hotter temperatures. Boys and girls are different in terms of fetal growth patterns, placental efficiency, and susceptibility to various prenatal exposures [12]. The underlying mechanisms of susceptibility are unclear and only a few studies have investigated potential modification by sex. Jakpor et al have found higher temperature variability to be associated with lower birthweight. Unlike our findings, they have found males to be more vulnerable to temperature variability [12]. Additional studies are required to investigate the differential vulnerability to prenatal temperature exposure among males and females.

5.5. Clinical implications

The current guidelines of the American College of Obstetricians and Gynecologists for prenatal care cover a wide range of maternal risk factors during pregnancy. Health care providers advise pregnant women on topics related to immunizations, infections, nutrition, exposure to violence, food, and medication consumption during pregnancy, and more. Although the guidelines address teratogenic environmental exposures, they do not include specific recommendations regarding heat and air pollution exposure during pregnancy.

Health care providers can communicate these critical windows of susceptibility to prenatal temperature and air pollution exposure to pregnant women during routine prenatal visits. This information will increase awareness and hopefully motivate the mothers to reduce exposure as much as possible, especially during the critical gestation weeks. For example, women can be advised to limit their exposure to traffic (e.g., avoid exercising near main roads, maintain proper ventilation indoors) – especially during the final weeks of pregnancy.

5.6. Strengths and limitations

This is a statewide analysis incorporating time-varying exposures to $PM_{2.5}$ and temperature throughout the pregnancy. The large sample size and the use of fine spatiotemporally resolved exposure models are the major strengths of this analysis. Another strength is the use of DLNM, which allowed us to flexibly investigate exposure-effects in different stages of gestation. Our study had several limitations. Since we did not collect the data for this analysis but used routinely collected data, 12% of the records had missing covariates data. This problem is common in retrospective studies. Second, since we assigned exposure based on maternal place of residence at birth, we might have had misclassified exposure for women who changed addresses during pregnancy. However, since the new residence choice is unlikely to be based on air pollution or temperature exposure and unlikely to differ greatly in terms of the socioeconomic environment, we expect the exposure measurement error to be non-differential [58, 59]. Moreover, since we assign ambient exposures, and do not have information on indoor exposures or air conditioning use, we might have misclassified the exposure. If the true exposure of women during heat events tends to be much lower than the ambient temperature exposure due to use of air conditioning, this may have attenuated our results. If the misclassification was non differential, the results may be biased either toward or away from the null. Third, since we could not control for all potential confounders (such as maternal weight), residual confounding may still be present although the specific temporal pattern of associations decreases the likelihood to non-time varying confounding factors. In addition, since our study population is restricted to live births, we do not have

information on spontaneous abortions. Therefore, our findings do not reflect the exposure effects on pregnancies which ended in an early stage. Finally, since most of our study population were White mothers, we might have not had enough representation of minority groups to allow the investigation of modification by racial group.

6. Conclusions

We found heat and $PM_{2.5}$ exposure to be related to lower birth weight among term singleton births. Our findings suggest that women are more susceptible to both exposures towards the end of pregnancy. Susceptibility to heat was higher in the initial weeks of pregnancy as well. These critical windows of susceptibility can be communicated to pregnant women during routine prenatal visits to increase awareness and motivate them to reduce exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Heat and $PM_{2.5}$ exposure were independently associated with lower TBW.
- Women are more susceptible to both exposures towards the end of pregnancy.
- Susceptibility to heat was higher in the initial weeks of pregnancy as well.

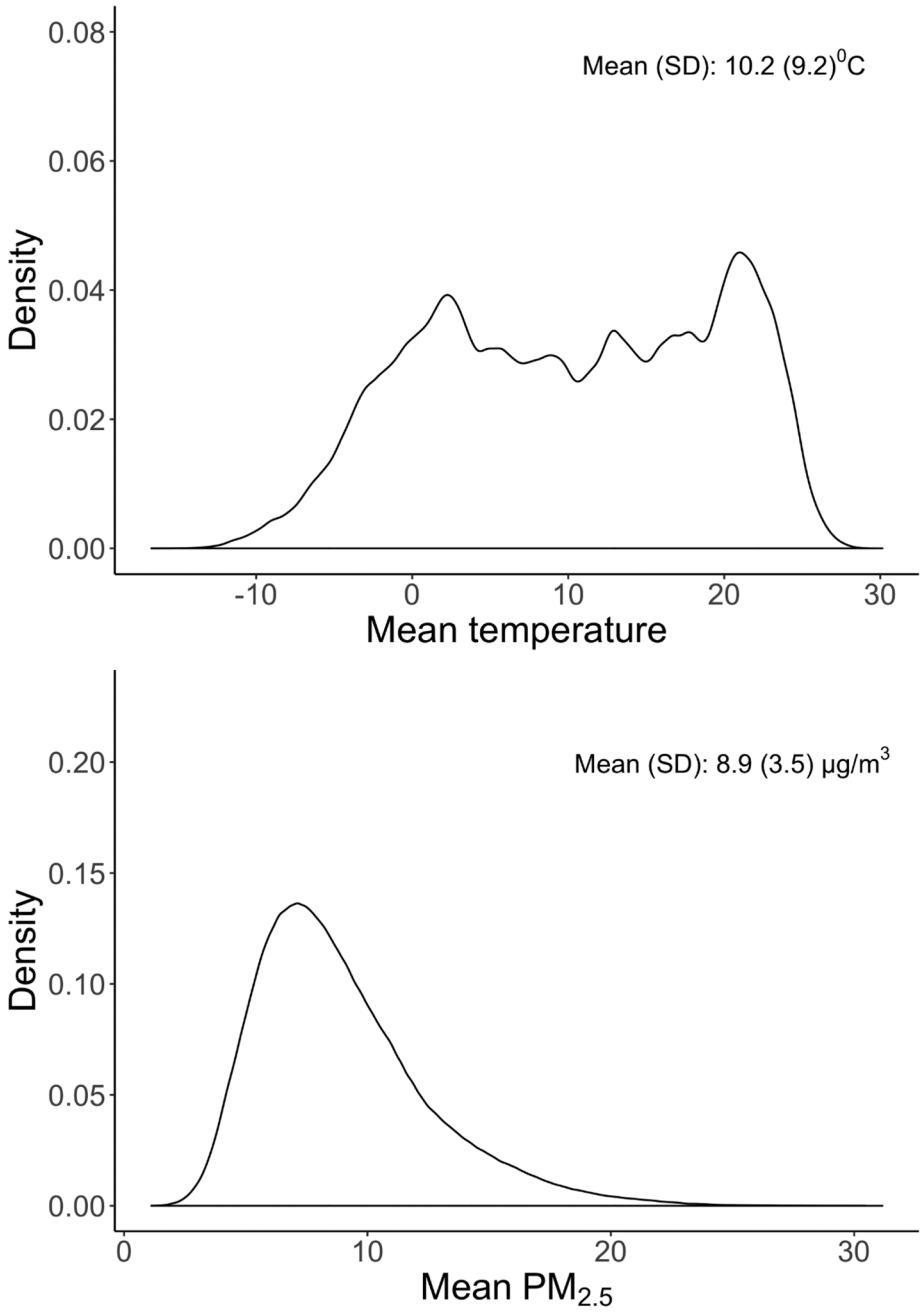

Figure 1. The distribution of mean temperature and $PM_{2.5}$ exposures over gestation.

Figure 1 shows the distribution of weekly temperature and $PM_{2.5}$ exposures. Each woman contributed 37 weeks of weekly averaged exposures.

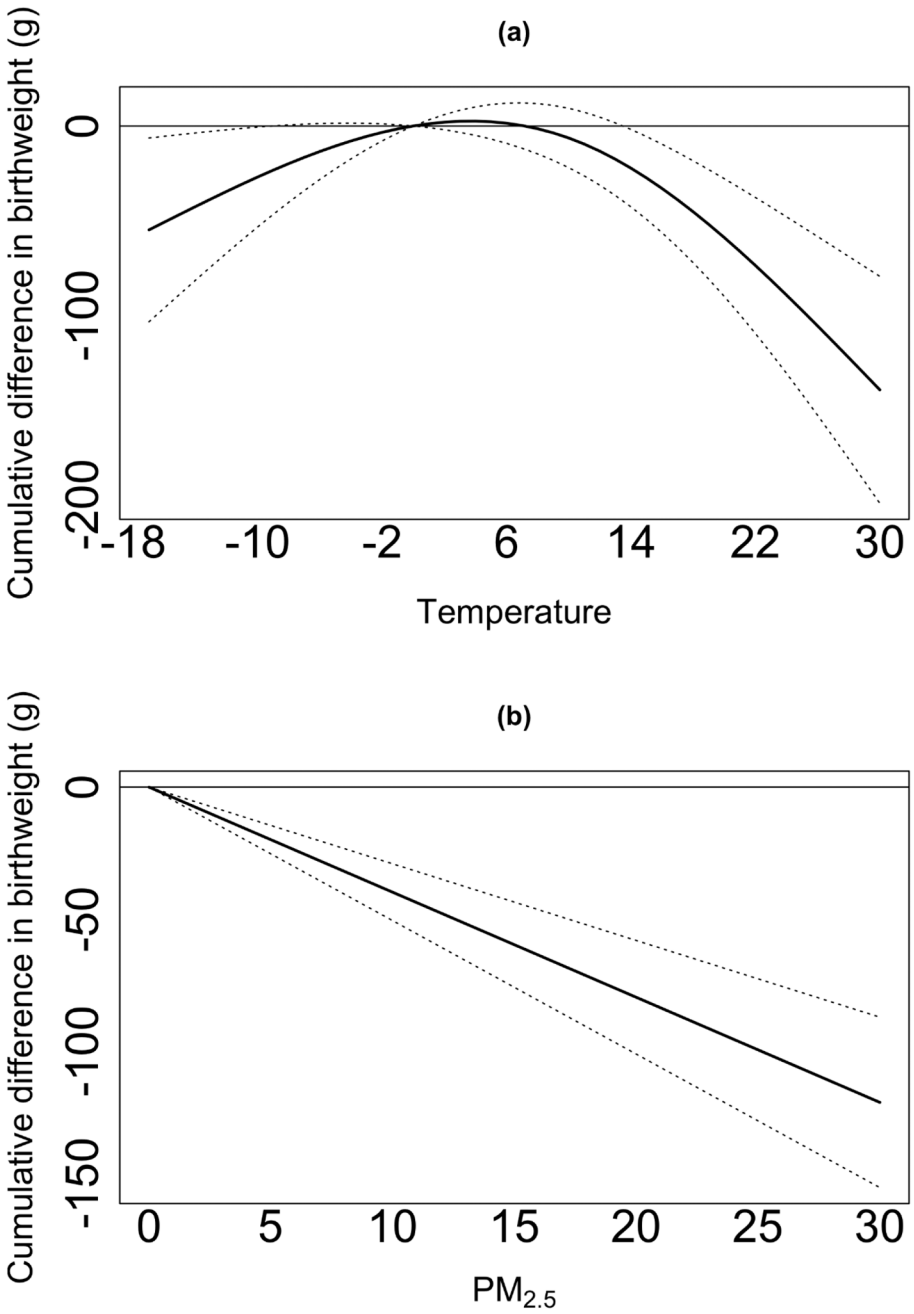

Figure 2. The cumulative exposure-response curves for differences in birth weight, associated with weekly (a) temperature and (b) $PM_{2.5}$ exposures in weeks 0–37 of pregnancy.

Figure 2 presents the cumulative exposure-response curves for the association between temperature, $PM_{2.5,}$ and term birth weight, defined as the net effects of the exposures across the entire lag period (weeks 0–37 of pregnancy). The model is adjusted for: season and year of birth, a cyclic spline of day of the year, government support for prenatal care, race, age of mother at birth, parity, maternal smoking before or during pregnancy, the maternal highest level of education attained, chronic diabetes, chronic hypertension, gestational age at birth, and census block-group socioeconomic characteristics (i.e., population density and median household income).

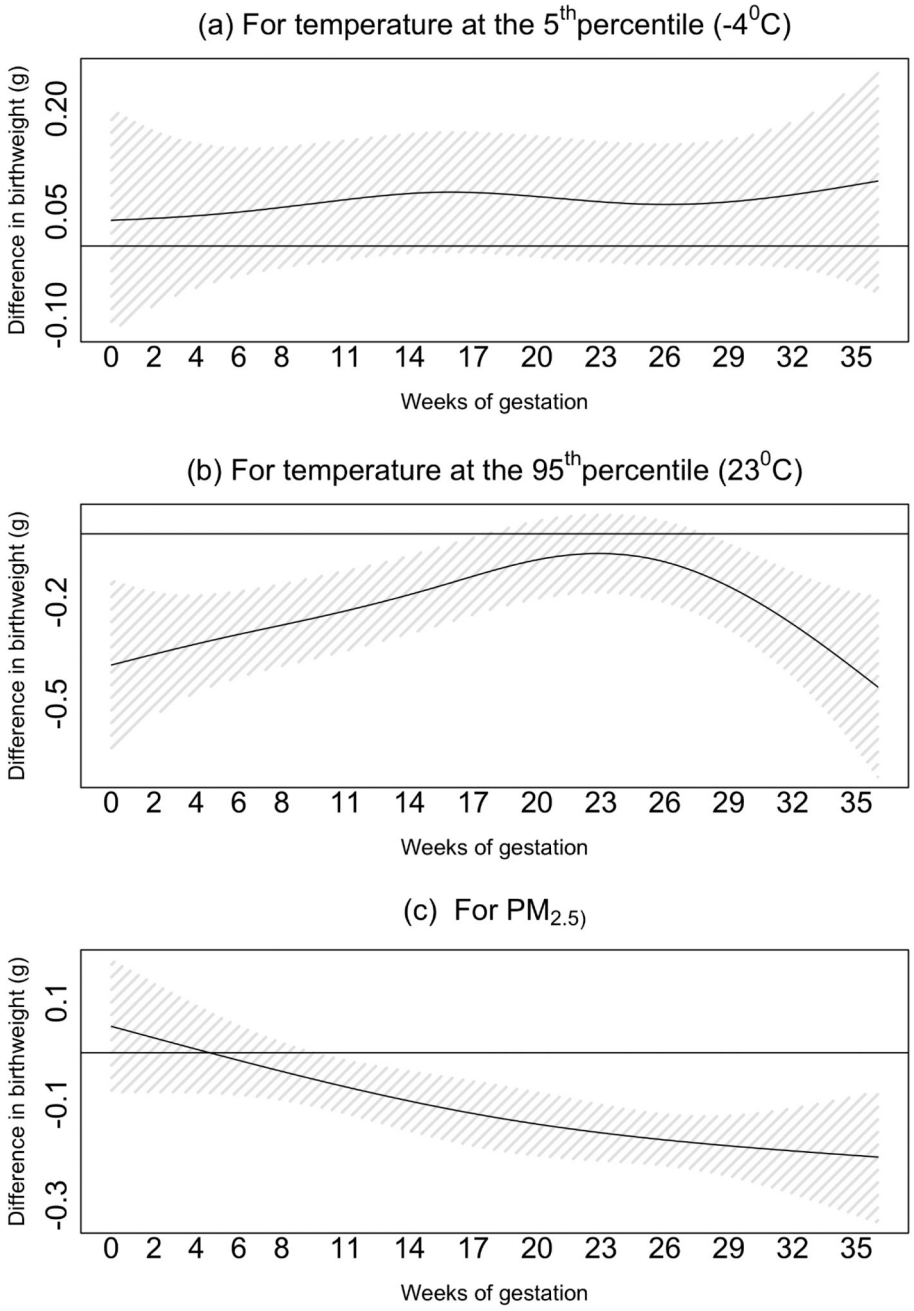

Figure 3. The difference in birth weight for temperature at the 5th percentile (−4 °C) (a), temperature at the 95th percentile (23 °C) (b), and $PM_{2.5}$ exposure (c) across the different weeks of gestation.

The model is adjusted for: season and year of birth, a cyclic spline of day of the year, government support for prenatal care, race, age of mother at birth, parity, maternal smoking before or during pregnancy, the maternal highest level of education attained, chronic diabetes, chronic hypertension, gestational age at birth, and census block-group socioeconomic characteristics (i.e., population density and median household income).

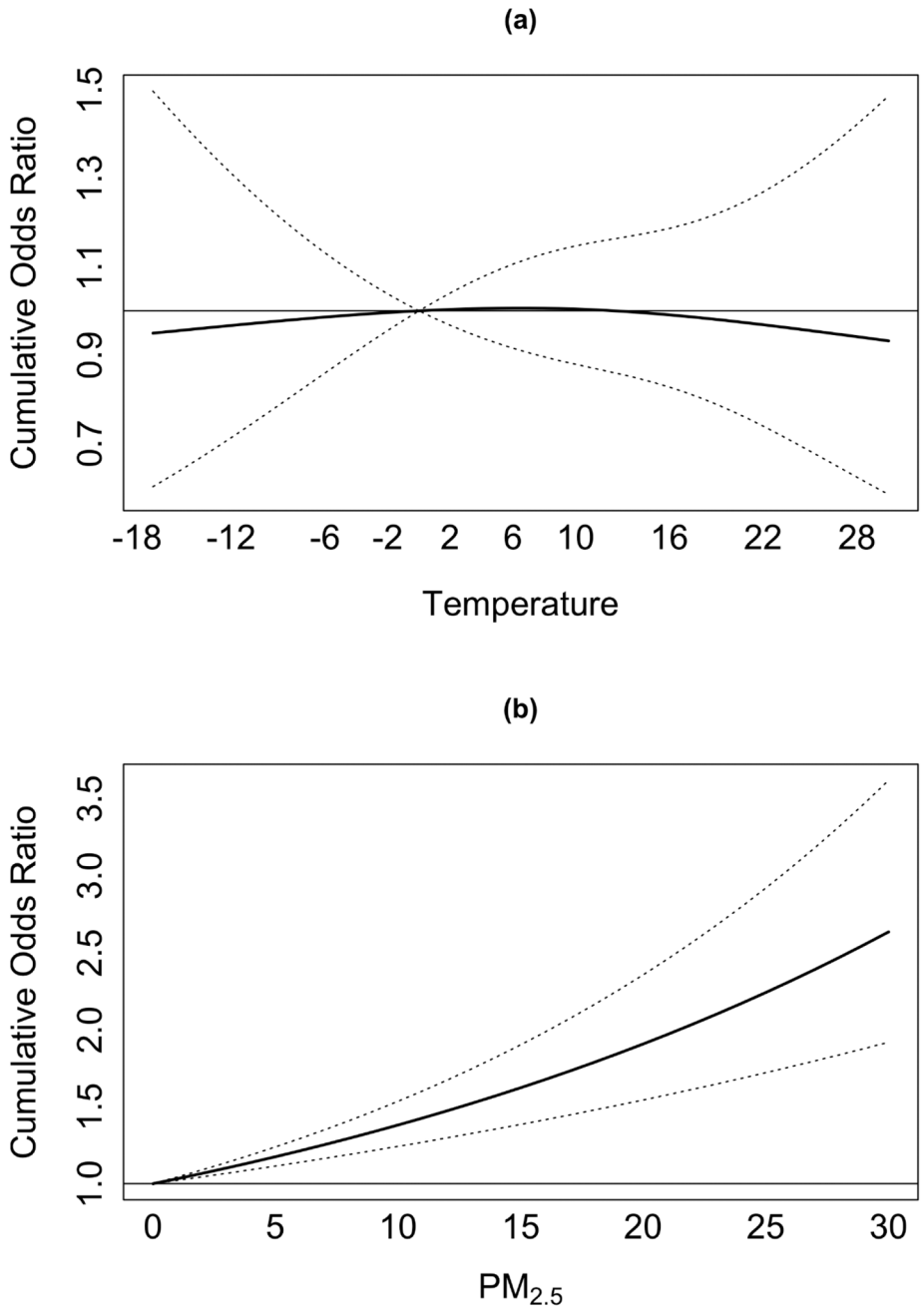

Figure 4. The cumulative exposure-response curves for the odds ratio of SGA, associated with weekly (a) temperature and (b) $PM_{2.5}$ exposures in weeks 0–37 of pregnancy.

Figure 2 presents the cumulative exposure-response curves for the association between temperature, $PM_{2.5,}$ and newborns small for gestational age (SGA), defined as the net effects of the exposures across the entire lag period (weeks 0–37 of pregnancy). The model is adjusted for: season and year of birth, a cyclic spline of day of the year, government support for prenatal care, race, age of mother at birth, parity, maternal smoking before or during pregnancy, the maternal highest level of education attained, chronic diabetes, chronic

hypertension, gestational age at birth, and census block-group socioeconomic characteristics (i.e., population density and median household income).

Table 1.

Population characteristics.

Population characteristics	N=712,438
Maternal age, Mean (SD)	30.08 (5.92)
Maternal race, n (%)	
White	512,355 (71.9)
Black	67,435 (9.5)
Other	132,648 (18.6)
Maternal education, n (%)	
Less than high school	75,511 (10.6)
High school	158,733 (22.3)
Some college	162,002 (22.7)
College or more	316,192 (44.4)
Governmental support for prenatal care, n (%)	251,633 (35.3)
Chronic hypertension, n (%)	9,073 (1.3)
Diabetes mellitus, n (%)	6,280 (0.9)
Smoking in pregnancy, n (%)	48,405 (6.8)
Gestational age in weeks, Mean (SD)	39.31 (1.18)
Parity>1, n (%)	387,393 (54.4)
Newborn sex, female, n (%)	349,086 (49.0)
Birthweight in g, Mean (SD))	3428.90 (464.14)
Birthweight for gestational age, n (%)	
AGA	590,715 (82.9)
LGA	81,300 (11.4)
SGA	40,423 (5.7)
Term low birthweight (<2500 g), n (%)	15,510 (2.1)
Median household income, Mean (SD)	51,700 (21,099)

SD=standard deviation; AGA= appropriate for gestational age; LGA=large for gestational age; SGA= small for gestational age.

Newborn size for gestational age was calculated using the Fenton sex-specific reference growth curves.

Table 2.

Summary statistics of exposures.

Exposure metrics	Summary statistics
mean temperature over gestation, °C	
Mean (SD)	10.2 (9.2)
25th percentile	2.3
50th percentile	10.4
75th percentile	18.5
mean $PM_{2.5}$ over gestation, μg/m^3	
Mean (SD)	8.9 (3.5)
25th percentile	6.4
50th percentile	8.2
75th percentile	10.8
Season of birth, n (%)	
Winter	167,435 (23.5)
Spring	180,110 (25.3)
Summer	188,097 (26.4)
Fall	176,796 (24.8)

SD=standard deviation, $PM_{2.5}$=fine particulate matter.