Effects of maternal exposure to fine particulate matter on birth weight in 16 counties across China: a quantile regression analysis

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Abstract
The adverse effects of air pollution during pregnancy have been studied intensively, but mainly utilizing linear and logistic models, which generally yield little information about how air pollution may change the distribution of birth weight in populations. We aimed to examine the effects of fine particulate matter (PM$_{2.5}$) on quantiles of birth weight, and if effects were heterogeneous in different populations and regions. We used a prospective cohort study of 196,283 singleton term live births from 16 counties across China during 2014–2018. PM$_{2.5}$ exposure for full gestation, each trimester and last gestational month were assessed by Inverse Distance Weighting interpolation. Linear and quantile regression were conducted to estimate associations between PM$_{2.5}$ exposure and mean birth weight, as well as birth weight distribution, with birthweight $z$-score as the main outcome. Stratified analyses and Cochran Q tests were conducted by maternal and geographical characteristics. Each 10 $\mu$g m$^{-3}$ increase in average PM$_{2.5}$ over the entire pregnancy was associated with reduced birthweight $z$-score ($-0.010$, 95% CI: $-0.015$, $-0.005$) and birth weight ($-3.21$ g, 95% CI: $-5.27$, $-1.15$). In quantile regression, more pronounced effects were observed in lower and intermediate quantiles of birthweight $z$-score, with a decrease of 0.021 (95% CI: 0.033, 0.009) and 0.009 (95% CI: 0.015, 0.002) in the 5th and 50th quantiles of birthweight $z$-score, respectively. Additionally, we observed stronger associations among well-educated, migrant and primiparous mothers as well as in coastal areas. Maternal exposure to PM$_{2.5}$ was associated with reduction in birth weight, especially for those with very low birth weight. Well-educated, migrant and primiparous mothers, as well as births in coastal areas may be more sensitive to PM$_{2.5}$ in our study population. The results may be relevant to targeted public health interventions to reduce maternal exposure to air pollution.

1. Introduction
A neonate’s weight at birth is an important indicator of intrauterine growth. Low birth weight (LBW) is linked with increased mortality in early life, growth retardation and lower cognitive performance (Sharma et al 2016, Gu et al 2017). Additionally, low birthweight is one determinant of health in adulthood, such as cardiovascular disease, obesity, and diabetes (Zhang et al 2014, Jornayvaz et al 2016).
In 2015, the estimated prevalence of LBW ranged from 3% to 28% across countries of the world, and the prevalence in China was around 5% (Blencowe et al. 2019). Several risk factors for LBW have been studied, including maternal malnutrition, maternal health problems (gestational hypertension, diabetes or infections) (Accrombessi et al. 2018), maternal characteristics (maternal age, parity and education) (Althabe et al. 2015), behavioral risk factors (tobacco, alcohol, and drugs use) (Pereira et al. 2017), and environmental factors (heavy metals and air pollution) (Claus Henn et al. 2016, Smith et al. 2017).

Air pollutants can potentially impair fetal growth by molecular mechanisms, such as oxidative stress, mitochondrial DNA content alteration and DNA methylation, and endocrine disruption (Li et al. 2019). An increasing number of epidemiological studies have examined the association between prenatal exposure to air pollution and birth weight, and a substantial number of them reported that gestational exposure to PM$_{2.5}$ was associated with reduced birth weight (Yuan et al. 2019, Bekkar et al. 2020). However, those studies have generally not focused on if and how air pollution affects the scale and shape of the distribution of health outcomes, especially specific parts of a distribution. For example, neonates at tails of the outcome distribution (e.g. lower birthweight), may suffer a disproportionate burden of prenatal morbidities (Rodosthenous et al. 2017) and may be more impacted by exposure to air pollution during pregnancy.

In previous studies on associations between PM$_{2.5}$ and birth weight, commonly used statistical approaches included logistic regression (LBW as a binary outcome) and linear regression (Sun et al. 2016, Li et al. 2017). Linear regression models focus on the changes in the mean birth weight, with an assumption that the exposure has the same effect across the entire birth weight distribution. However, the decrease in birth weight associated with PM$_{2.5}$ may be different between newborns with normal birth weight and those with LBW (Yang et al. 2020). A greater decrease in lighter births may be offset by a lesser decrease in heavier births.

Instead of using an often arbitrarily chosen threshold to dichotomize the birth weight distribution to define LBW, the application of quantile regression has been proposed as a more nuanced and flexible approach. Such an approach can estimate the associations between exposure and specific percentiles of the outcome distribution, which allows the exposure–outcome associations to differ across levels of outcomes. Therefore, the potential heterogeneity in the effects of PM$_{2.5}$ exposure across different birth weight levels, particularly the effects on one or both of the tails of the birth weight distribution, maybe be more readily detectable. In addition, the application of quantile regression is not limited by the distribution of outcomes (Bind et al. 2016), that is, quantile regression is more robust against outliers (Kiserud et al. 2018) and works well when the distribution of outcome is not normal.

Recently, several studies have utilized quantile regression to examine how the birth outcome associated with maternal behaviors, nutrition, pregnancy complications, heavy metals and air pollution exposure (Smith et al. 2015, Karalasingam et al. 2017, Rodosthenous et al. 2017, Mitku et al. 2020). However, there is little evidence on associations between PM$_{2.5}$ exposure during pregnancy and birth weight distribution. To the best of our knowledge, only three recent studies (Fong et al. 2019, Schwarz et al. 2019, Strickland et al. 2019) have investigated how PM$_{2.5}$ exposure affects birthweight distribution, however, all of them were conducted in the US and their findings were mixed. Considering how little research on this topic has been done in China, questions remain regarding whether the relationships between PM$_{2.5}$ exposure and birth weight distribution are similar or different to those observed in the US.

In this study, we utilized quantile regression to explore whether the effects of maternal exposure to PM$_{2.5}$ on birth weight varied across birth weight distribution. We then identified potentially vulnerable gestational windows at trimester level and susceptible subgroups with different demographic and regional characteristics.

2. Methods

2.1. Study population and birth outcome

The participants in this study were collected from the National Maternal and Newborn Health Monitoring Project, launched by the Maternal and Child Health Center of the Chinese Center for Disease Control and Prevention in 2013, to understand and improve the health of mothers and infants. The project was conducted in 16 monitoring counties in eight cities (Shijiazhuang, Anshan, Xiamen, Yueyang, Zigong, Yuxi, Heyuan, and Huanggang) of China, which are distributed in the Northeast, North, South, East, Central, and Southwest China (figure S1 (available online at stacks.iop.org/ERL/16/055014/mmedia)). All pregnant women who lived in the 16 monitoring areas throughout their pregnancy were recruited in the project at their first visit for routine prenatal care when the mothers signed the informed consents. Then, all the participants were followed for up to 28 d after birth. As the project was established during 2013, in this study we only included the 222 447 births occurring from 1 January 2014 to 31 December 2018.

During the following up, maternal information, including maternal age, nationality, maternal education level, maternal residence address, maternal behavioral risk factors (an indicator of any of the factors including smoking, drinking, drugs, toxic and
harmful substances, radiation, and others) during pregnancy, maternal weight and height before pregnancy, history of diseases (including cardiac disease, kidney disease, liver disease, hypertension, diabetes, and other diseases) and maternal migrant status were collected. Neonates’ information, including date of birth, mode of delivery, infant sex, gestational weeks, birth weight and birth length, were also collected. We excluded 314 stillbirths, 6803 multiple births, 4409 births with maternal age <13 years or >50 years, 123 births with implausible gestational age (<20 weeks or >44 weeks), 156 with implausible birth weight (<500 g or >5000 g), and 3669 births with incomplete information on infant sex and pre-pregnancy body mass index (BMI).

We restricted the study population to term singleton live births (≥37 weeks of gestational age) and thus estimated a controlled direct effect (conditioning on a given gestational age and a principal stratum) of air pollution on birth weight. This approach assumes no confounder between gestational age and birthweight itself affected by air pollution. While it is difficult to envision a specific intervention to fix age of gestation for all births or prevent all preterm births, this approach directly quantifies the role of air pollution on birth weight in a principal stratum. Such an approach also helps avoiding inaccurate exposure estimates because of difference in length of exposure (Bell et al. 2007). To better account for changes in birth weight with length of gestation, birth weight for gender- and gestational age-specific standard z-score was calculated as our main outcome by using a national gestational age-specific birth weight reference of China (Dai et al. 2014). Z-score is the difference between individual and reference birth weight divided by the standard deviation. Birth weight for gender- and gestational age-specific standard z-score is defined as:

\[
Z = \frac{\text{individual birthweight} - \text{Mean for gender and gestational age}}{\text{SD for gender and gestational age}}
\]

Mean for gender and gestational age and SD for gender and gestational age are the mean birth weight and standard deviation at a specific gender and gestational age according to the reference population, respectively. One unit decrease in birth weight z-score indicates that individual birth weight is one standard deviation lower than the mean birth weight of their counterparts with same gestational age and gender.

The study was approved by the Institutional Review Board of School of Public Health, Sun Yat-sen University. All participants provided informed consent.

2.2. Air pollutants and meteorological exposure assessment

Daily averaged PM$_{2.5}$, carbon monoxide (CO), nitrogen dioxide (NO$_2$) and sulfur dioxide (SO$_2$), and 8 h averaged ozone (O$_3$) concentrations at 1597 stations during 2014–2018 were collected from China National Environmental Monitoring Centre (www.cnemc.cn/). Daily air pollutants concentrations were interpolated to 1 × 1 km separately for each day across all sites by using inverse distance weighting (IDW) interpolation technique in ArcGIS 10.5 (Environmental Systems Research Institute, Redlands, California, USA). IDW is a deterministic method that takes into account of spatial autocorrelation among air pollutant observations and estimates the value of a given location by weighted average of observations from monitoring stations which within a specific search window (Roberts et al. 2014).

Interpolation weights in IDW are computed as a function of the distance between observed monitoring stations and the given location to be predicted (Xu et al. 2014, Wu et al. 2017). We specified the weights as \( \lambda_i = 1/d_i^{3/2} \) for monitoring station \( i \), where \( d_i \) indicates the distance between monitoring station \( i \) and the given location to be predicted (Xu et al. 2014). Then, daily prediction surfaces of air pollutant concentrations were aggregated to a spatial resolution of 1 × 1 km for the purpose of exposure assessment at each woman’s residential address. We calculated the individual PM$_{2.5}$ exposure for exposure windows, including full gestation (conception to delivery), the first trimester (1–12 gestational weeks), second trimester (13–27 gestational weeks), third trimester (28 gestational weeks to delivery) (Wang et al. 2018, Lu et al. 2019, Zhou et al. 2019) and the last gestational month. Other pollutants were averaged over full gestation.

Considering missing PM$_{2.5}$ monitoring data, 2252 infants without eligible exposure measurements (more than 25% weeks for each trimester) were further excluded from our study population, leaving a total of 196 283 eligible neonates in our final analyses. A detailed description of the participant selection is summarized in a flowchart in figure S2.

Ambient temperature has been reported as a risk factor of reduction in birth weight (Zhang et al. 2017) and an explanation of the seasonal variability in PM$_{2.5}$ in previous studies (Bell et al. 2007). Daily mean temperatures at 680 stations during 2014–2018 were
collected from the China Meteorological Data Service Center (http://data.cma.cn) and also interpolated to $1 \times 1$ km by using IDW interpolation technique in ArcGIS 10.5. Daily average temperature was assigned to each pregnancy by the same procedure as for PM$_{2.5}$. Temperature exposures were estimated for the whole pregnancy to reflect the overall effect of temperature on birth weight.

2.3. Statistical analyses

Pearson’s correlation was used to examine the correlations among pollutants during the whole pregnancy. Linear regression model was performed to estimate the effect of exposure to PM$_{2.5}$ during each exposure period (including whole pregnancy, each trimester, and the last gestational month) on the mean change in birth weight, using birthweight (in grams) and birthweight $z$-score as outcomes, respectively. We then applied single-pollutant quantile regression models to evaluate the associations between maternal exposure to PM$_{2.5}$ during each exposure period window and the 5th, 10th, 25th, 50th, 75th, 90th, and 95th quantiles of birthweight $z$-score distribution (Schwarz et al 2019). When exploring the relationships at trimester level, we fitted models with all three trimester exposures simultaneously in a single model (Wilson et al 2017, Wang et al 2019). Effect estimates were presented as the changes in birthweight (in grams) or birthweight $z$-score with per 10 $\mu$g m$^{-3}$ increase in PM$_{2.5}$ concentration. The quantile regression model is defined as:

$$Q_\tau(Y|x) = X^T\beta(\tau), (0 < \tau < 1)$$

where $Q_\tau(Y|x)$ is the conditional quantile function of $\tau$, $X$ is vector of independent variables, and $\beta(\tau)$ is the vector of covariates’ coefficients on the $\tau$th quantile of $Y$. Unlike the traditional linear model which focuses on the changes in the averaged value of $Y$, coefficients in quantile regression reflect the fluctuation of $Y$ at any given quantile of $\tau$ ($0 < \tau < 1$) for each unit increase/decrease of the corresponding variable, when other variables in the model remain unchanged. In the models, we adjusted for maternal age (as a continuous variable), maternal education (<10 years, 10–12 years or >12 years), maternal behavioral risk factors during pregnancy (yes or no), season of conception (spring, summer, fall or winter), year of birth, parity (primiparous or multiparous), maternal pre-pregnancy BMI, mother’s residential city, and average ambient temperature during the whole pregnancy.

Additionally, to investigate the heterogeneity in air pollution effects among different populations, stratified analyses and Cochran Q tests were performed by maternal characteristics, including maternal education (<10 years, 10–12 years, or over 12 years), parity (primiparous or multiparous), and migrant status (local or migrant). PM$_{2.5}$ source and composition may vary across regions (Hao et al 2016) and cause difference in exposure–response relationship. Thus, we also examined the heterogeneity in PM$_{2.5}$ effects among different regions by stratified analyses. Regional factors were defined as geographical characteristics (north or south; inland or coastal area), and forest coverage (<40% or ≥40%), defined as the proportion of forest cover in the total land area of a city, as a proxy for the local greenness.

We performed sensitivity analyses to examine the robustness of our results. We repeated our analyses by including all singleton live births with a gestational age from 28 to 44 weeks, as well as using birthweight (in grams) as the outcome. We also examined the effects of other pollutants in our sensitivity analyses to evaluate their possible confounding effects. Effect estimates were presented per 10 $\mu$g m$^{-3}$ increment in NO$_2$, SO$_2$, and O$_3$, and per $1$ $\mu$g m$^{-3}$ increase in CO. Considering PM$_{2.5}$ was strongly correlated with CO, NO$_2$ and SO$_2$ (table S4), we only included PM$_{2.5}$ and O$_3$ in a two-pollutant model to assess potential confounding of PM$_{2.5}$ by O$_3$ exposures.

All analyses were conducted by R version 3.4.1.

3. Results

As shown in table 1, there is a total of 196 283 full term infants included, with a mean birth weight of 3296.51 g (SD: 415.39) and a mean birth weight $z$-score of 0.04 (SD: 1.04). Birth weight and birthweight $z$-score details are shown in table S1, table S2 and table S3. On average, the gestational age for infants is 39.15 (SD: 1.12) weeks and maternal age is 33.95 (SD: 6.52) years old. The city of Shijiazhuang, Anshan, Xiamen, Yueyang, Zigong, Yuxi, Heyuan, and Huanggang, accounted for 20.25%, 6.47%, 17.78%, 14.76%, 7.54%, 9.42%, 9.67% and 14.11% of the total births included, respectively. Air pollutants and temperature exposures are presented in table 2. During the study period, the average PM$_{2.5}$ and temperature exposure over the entire pregnancy were 53.1 $\mu$g m$^{-3}$ (SD: 25.7) and 17.0 $^\circ$C (SD: 4.0), respectively. The average PM$_{2.5}$ concentration for each trimester was similar to that during the full gestational period (table 2).

In linear regression analyses, each 10 $\mu$g m$^{-3}$ increase in maternal exposure to PM$_{2.5}$ during the entire gestation was associated with a mean reduction of 0.010 (95% CI: 0.015, 0.005) in birth weight $z$-score and 3.21 g (95% CI: 5.27, 1.15) in birth weight (table 3). Stronger effects were observed during the first, third trimester and the last month before birth in table 3.

Results of quantile regressions suggested that the associations between average PM$_{2.5}$ exposure and $z$-score of birth weight varied across the birth weight distribution. Figure 1 shows that increased PM$_{2.5}$ exposure was related to reduced birth weight $z$-score.
at intermediate and low quantiles, and the associations were stronger at the 5th quantile of birthweight z-score distribution. At the 5th, 50th, and 95th percentiles of birthweight z-score, we observed a decrease of 0.021 (95% CI: 0.033, 0.009), 0.009 (95% CI: 0.015, 0.002) and 0.001 (95% CI: −0.013, 0.012), respectively, for each 10 μg m⁻² increase of PM_{2.5} (figure 1(a)). For analyses by trimesters, we identified harmful effects in all the three trimesters. Significant effects were found at lower quantiles (<50th) during the first and second trimester, and intermediate quantiles (25th–75th) during the third trimester (figure 1(b)). The relationship pattern for the last gestational month was similar with that for the third trimester, but the associations were slightly weaker.

Figures 2 and 3 show the effects of whole gestational exposure to PM_{2.5} on quantiles of birthweight z-score among different populations stratified by maternal and regional characteristics. Stronger associations were observed in infants born to primiparous mothers and migrant mothers, especially at the lowest quantile, with a 0.036 (95% CI: 0.053, 0.018) and 0.068 (95% CI: 0.125, 0.012) decrease in birth weight z-score, respectively. In addition, fetus of well-educated mothers (over 12 years of education) appeared to have more adverse effect of PM_{2.5} exposure in the lowest quantile of birthweight z-score (−0.036, 95% CI: −0.053, −0.019). Cochran Q test revealed the effects of PM_{2.5} among subgroups with different maternal characteristics were not consistent across quantiles (table S5). Greater decreases in birth weight z-score at lower quantiles were observed in both inland and coastal areas, and the greatest estimate was seen in coastal areas at the 5th percentile (−0.062, 95% CI: −0.102, −0.022). Both regions with more forest coverage and with less forest were more affected by PM_{2.5} at lower quantiles, but the Cochran Q test revealed that the heterogeneity in effects between regions with more and with less forest was not statistically significant across all quantiles (table S5). In comparison, newborns in the south seemed to be more affected by PM_{2.5}, but effects between south and north areas were not significantly different (table S5).

Sensitivity analyses of all singleton live births showed similar patterns of associations between PM_{2.5} exposure and birthweight z-score, however, the magnitude of effect estimates was slightly weaker across the quantiles (figure S3). When birthweight (in g) was used as the outcome, stronger estimates seemed observed at lower and higher quantiles, and the greatest decrease was still observed at the 5th quantile (−6.68 g, 95% CI: −11.57, −1.79) (figure S4). In traditional linear regression models, we did not observe adverse effects of CO (0.019, 95% CI: −0.014, 0.051), NO\textsubscript{2} (−0.008, 95% CI: −0.021, 0.006), O\textsubscript{3} (−0.005, 95% CI: −0.012, 0.003) or SO\textsubscript{2} (−0.010, 95% CI: −0.019, 0) (table S6). By examining their effects using quantile regression, we did not observe significant effects for CO, NO\textsubscript{2}, or O\textsubscript{3}. SO\textsubscript{2} tended to decrease birth weight at lower birthweight quantiles but to increase birth weight at higher quantiles (table S7). We also fitted a two-pollutant model including PM_{2.5} and O\textsubscript{3}, where similar but slightly stronger associations for PM_{2.5} and birthweight were observed (figure S5).

### Table 1. Characteristics of mothers and full-term births in eight monitoring cities.

| Variables                        | Mean/N   | SD/ (%) |
|----------------------------------|----------|---------|
| Total births                     | 196 283  | 100.00  |
| Birth weight (g)                 | 3296.51  | 415.39  |
| Birthweight z-score              | 0.04     | 1.04    |
| Maternal age (years)             | 33.95    | 6.52    |
| Gestational weeks                | 39.15    | 1.12    |
| Maternal BMI (kg m⁻²)            | 21.97    | 3.37    |
| Infant gender                    |          |         |
| Male                             | 103 563  | 52.76   |
| Female                           | 92 720   | 47.24   |
| Maternal education (years)       |          |         |
| <10                              | 67 333   | 34.41   |
| 10–12                           | 59 656   | 30.39   |
| >12                              | 63 046   | 32.12   |
| Unknown                          | 60 48    | 3.08    |
| Parity                           |          |         |
| Primiparous                      | 107 394  | 54.71   |
| Multiparous                      | 88 889   | 45.29   |
| Maternal behavior risk factors¹ |          |         |
| No                               | 189 024  | 96.30   |
| Yes                              | 72 59    | 3.70    |
| Maternal migrant status          |          |         |
| Local                            | 177 972  | 90.67   |
| Migrant                          | 14 055   | 7.16    |
| Unknown                          | 4256     | 2.17    |
| Season of conception             |          |         |
| Spring                           | 48 014   | 24.46   |
| Summer                           | 52 730   | 26.86   |
| Fall                             | 50 136   | 25.54   |
| Winter                           | 45 403   | 23.13   |
| Maternal residential cities      |          |         |
| Huanggang                        | 27 700   | 14.11   |
| Yueyang                          | 28 966   | 14.76   |
| Shijiazhuang                     | 39 753   | 20.25   |
| Anshan                           | 12 702   | 6.47    |
| Heyuan                           | 18 972   | 9.67    |
| Zigong                           | 14 795   | 7.54    |
| Yuxi                             | 18 499   | 9.42    |
| Xiamen                           | 34 896   | 17.78   |

¹ Maternal behavior risk factors is the history of exposure to smoking, drinking, drugs, toxic and harmful substances, radiation, or others.

### 4. Discussion

In a cohort of 196 283 singleton term live births, we observed that maternal exposure to PM_{2.5} was associated with reduction in birth weight, especially for the exposure in the first and third trimester. And, the adverse effects of PM_{2.5} were more pronounced for infants with relatively lower birth weight. Stronger PM_{2.5} effects were concentrated in better
Table 2. Summary of air pollutants and ambient temperature exposures by exposure periods.

| Exposure window | Mean | SD | Min | 25th | 50th | 75th | Max |
|-----------------|------|----|-----|------|------|------|-----|
| WP PM$_{2.5}$ b (μg m$^{-3}$) | 53.1 | 25.7 | 20.2 | 30.2 | 49.8 | 68.2 | 138.7 |
| T1 PM$_{2.5}$ c (μg m$^{-3}$) | 53.4 | 32.2 | 12.9 | 30.9 | 45.0 | 67.1 | 226.9 |
| T2 PM$_{2.5}$ c (μg m$^{-3}$) | 53.3 | 31.9 | 14.7 | 31.1 | 43.0 | 66.8 | 224.5 |
| T3 PM$_{2.5}$ c (μg m$^{-3}$) | 52.5 | 33.1 | 13.9 | 31.0 | 41.8 | 64.5 | 246.7 |
| Last month PM$_{2.5}$ c (μg m$^{-3}$) | 52.1 | 36.5 | 10.9 | 29.7 | 40.6 | 63.78 | 325.1 |
| CO (mg m$^{-3}$) | 1.1 | 0.3 | 0.5 | 0.9 | 1.0 | 1.3 | 2.2 |
| O$_3$ (μg m$^{-3}$) | 53.9 | 8.2 | 24.6 | 48.4 | 53.7 | 59.1 | 93.1 |
| NO$_2$ (μg m$^{-3}$) | 33.9 | 11.5 | 15.8 | 25.4 | 30.4 | 39.7 | 70.5 |
| SO$_2$ (μg m$^{-3}$) | 21.3 | 12.9 | 6.1 | 11.6 | 16.7 | 26.6 | 82.4 |
| Temperature d (°C) | 17.0 | 4.0 | 3.0 | 14.9 | 17.4 | 20.0 | 24.9 |

*a SD = standard deviation.
*b Mean maternal exposure to PM$_{2.5}$ over the whole pregnancy.
*c Mean maternal exposure to PM$_{2.5}$ during the first trimester (T1), the second trimester (T2), the third trimester (T3) and the last gestational month (last month).
*d Mean temperature over the whole pregnancy.

Table 3. Changes in mean birth weight z-score and birthweight (in grams) associated with per 10 μg m$^{-3}$ increase in PM$_{2.5}$ for full gestation and each trimester in linear regression.

| Exposure window | Birthweight z-score β (95% CI) | Birthweight (g) β (95% CI) |
|-----------------|--------------------------------|---------------------------|
| Whole pregnancy | −0.010, −3.21 (−0.015, −0.005) | −3.21, −1.15 (−3.27, −1.15) |
| Trimester 1     | −0.005, −2.01 (−0.007, −0.002) | −2.01, −0.93 (−2.09, −0.93) |
| Trimester 2     | −0.002, −0.18 (−0.005, 0.001) | −0.18, 1.03 (−1.40, 1.03) |
| Trimester 3     | −0.004, −1.31 (−0.007, −0.001) | −1.31, 0.25 (−2.37, 0.25) |
| Last month      | −0.002, −0.94 (−0.005, 0.000) | −0.94, 0.12 (−1.77, 0.12) |

Models were adjusted for maternal age, pre-pregnancy BMI, maternal education, mothers’ behavior risk factors during pregnancy, parity, season of conception, year of birth, average temperature, and indicators of maternal residential cities.

A relationship between birth weight and PM$_{2.5}$ consistent with the findings of the study in California (Schwarz et al 2019).

Since birth weight is influenced by gestational age, the way gestational age considered may contribute to the inconsistency of these studies. Fong et al (2019) and Schwarz et al (2019) restricted to full-term births, and Strickland et al (2019) included gestational weeks as a covariate in their model. In the study, by referring to the gestational age-specific birthweight based on a large and national database (covering 64 counties and districts from 30 provinces in China), we calculated birthweight z-score as the outcome, which may better account for the direct risk of decrease in birth weight associated with PM$_{2.5}$.

Residual confounding by co-exposures, such as CO, NO$_2$, and SO$_2$ is possible, as previous studies have reported the associations between co-exposures and adverse pregnancy outcomes (e.g. LBW, preterm birth, and small for gestational age) (Guo et al 2019). Given that these pollutants were highly positively correlated with PM$_{2.5}$, to avoid conflicting associations from multi-collinearity of PM$_{2.5}$ and other co-exposures, we only fitted two-pollutant models of PM$_{2.5}$ and O$_3$, where the effects of PM$_{2.5}$ did not change. Additionally, we have examined the effects of other co-exposures (CO, NO$_2$, SO$_2$, and O$_3$) on birth weight distribution. We did not observe significant effects for CO, NO$_2$, or O$_3$. SO$_2$ tended to decrease birth weight at lower birthweight quantiles but to increase birth weight at higher quantiles. Therefore, although we found significant associations between particulate matter and lower birthweight in a quantile regression analysis, the estimates are still likely to be confounded by other co-exposures, especially SO$_2$. However, the relationship pattern of SO$_2$ and birth weight distribution was complicated, which warrants more studies in the future.

We observed more obvious effects of PM$_{2.5}$ exposure in the first and third trimester, for which some hypotheses from previous studies may provide clues.
Figure 1. Changes in birth weight z-score associated with per 10 µg m⁻³ increase in PM₂.₅ for full gestation and each trimester at different quantiles of birthweight z-score distribution (5th, 10th, 25th, 50th, 75th, 90th, 95th). Models were adjusted for maternal age, pre-pregnancy BMI, maternal education, mothers’ behavior risk factors during pregnancy, parity, season of conception, year of birth, average temperature, and indicators of maternal residential cities.

regarding potential biological mechanisms. In early pregnancy, PM₂.₅ may interfere with placental DNA methylation, affecting placental mitochondrial dysfunction, therefore, interrupting nutrient and oxygen supply to the fetus (Grevendonk et al 2016, Tapia et al 2020). Rapid fetal growth mainly occurs in the third trimester (Ha et al 2017), during which the fetus may be more susceptible to air pollution exposure. Additionally, PM₂.₅ related decrease of birth weight in late pregnancy may be partially explained by fluctuations in fetal thyroid hormone levels (Janssen et al 2017). We observed the adverse effects of PM₂.₅ exposure were more severe for infants with relatively lower birth weight. Fetal growth is a complex process and influenced by many other risk factors, such as maternal nutrition, health condition, genetic factors and socio-economic status (SES) factors (Accrombessi et al 2018, Campbell et al 2018). These factors could lead to lower birth weight, and may interact with air pollution, then aggravate the adverse effect of PM₂.₅ on birth weight. For example, Low-SES groups, who more likely have offspring with lower birth weight, tend to have poorer housing conditions, physical and mental health, more life stress and limited health care resources (Cho et al 2016, Campbell et al 2018), which may potentiate fetal susceptibility to air pollution, then, lead to a greater reduction of birth weight in lighter births. However, the biological mechanisms for stronger adverse impact of PM₂.₅ on lighter infants remain unclear. Future researches could be considered concerning the biomarker of lighter newborns to reveal the mechanisms.

Subgroup analyses revealed that the magnitude of effects varied based on maternal characteristics. We observed greater decreases in birth weight for infants with well-educated, migrant and primiparous mothers. Migrant mothers in our study are those who leave their hometown for jobs in other cities, and usually have low SES, which may account for their higher susceptibility to PM₂.₅. Several studies also
Figure 2. Changes in birth weight z-score associated with per 10 µg m⁻³ increase in PM₂.₅ for full gestational period at different quantiles of birthweight z-score distribution (5th, 10th, 25th, 50th, 75th, 90th, 95th), stratified by parity (primiparous or multiparous), migrant status (local or migrant), and maternal education (<10, 10–12, >12 years).

reported higher susceptibility to air pollution in well-educated mothers (Xiao et al 2018) and primiparous mothers (Guo et al 2018). Highly educated women, who are often professional women, may face the dual pressures from workplace and family, therefore may be more likely to be anxious. Due to lack of pregnancy experience and related knowledge, primiparas might be more anxious about the physiological changes during pregnancy. They may tend to exaggerate the negative impact events during pregnancy, such as illness and body damage, which also cause long-term anxiety. Maternal negative emotion (stress, depression and anxiety) during pregnancy may negatively influence fetal development, thus
Figure 3. Changes in birth weight z-score associated with per 10 µg m$^{-3}$ increase in PM$_{2.5}$ for full gestational period at different quantiles of birthweight z-score distribution (5th, 10th, 25th, 50th, 75th, 90th, 95th), stratified by geographical regions (north or south; inland or coastal), and forest coverage (<40% or ≥40%).

increase the risk of adverse birth outcomes like LBW (Gelaye et al 2020), possibly through hypothalamic–pituitary–adrenal, sympathetic–adrenal–medullary system and functioning of the placenta (Su et al 2015, Ae-Ngibise et al 2019).

In our study, stronger effects of PM$_{2.5}$ were observed in coastal areas at lower quantiles, but no significant heterogeneity was detected between areas with more and less forest as well as between northern and southern regions. These geographic heterogeneity in effects might be explained by differences in populations across study sites, particles source, meteorological and geographical conditions (Ebisu et al 2016, Hao et al 2016). A previous study on the
influence of sources of particulate matter on birth weight reported greater risk of term LBW in the coastal regions from vehicular emissions (Ng et al 2017). This study also observed different associations between northern and southern regions for several sources, like vehicular emissions, biomass burning and secondary ammonium nitrate sources, but not for total PM$_{2.5}$ (Ng et al 2017). The non-significant geographic heterogeneity between areas with more and less forest as well as between northern and southern regions in our study might be explained by complex PM$_{2.5}$ sources across regions, and potential confounding from other factors, such as different nutritional status and living habits among regions. Thus, more studies on the heterogeneity in PM$_{2.5}$ effects among regions are needed to identify high risk regions.

Some previous studies have stated the clinical significance of the extent of birthweight decreases. For example, Huang et al (2013) reported that per unit decrement of birthweight z-score (450 g) was associated with a decrease of 1.60 points in IQ. In this study, we found that each 10 µg m$^{-3}$ increase in PM$_{2.5}$ during the whole gestation was associated with a 0.021 decrease in birthweight z-score or 6.38 g decrease in birthweight. The absolute values of birthweight reduction seem much lower, however, mothers and fetus universally expose to air pollution, which could lead to huge intelligence loss in the whole population. Furthermore, compared with newborns with adequate birth weight (3000–3999 g), newborns with extremely low (<1000 g), very low (1000–1499 g) and low (1500–2499 g) birth weight have 207, 41 and 6 times risk for infant mortality, respectively (Vilanova et al 2019). In this study, we observed more pronounced adverse effects of PM$_{2.5}$ in infants with lower birth weight, which means high PM$_{2.5}$ exposure would increase the number of newborns with extremely low, very low and low birthweight, which in turn increase the risk for infant mortality.

Our findings provided a better understanding of adverse effects of PM$_{2.5}$ on the distribution of birth weight, especially on lighter infants. Lighter infants may have experienced other severe risk factors and are more susceptible to PM$_{2.5}$ exposure, thus interventions to eliminate major hazards (e.g. malnutrition and diseases) should be the priority, through nutritional supplement, prenatal care or clinical treatments. Moreover, the identification of disparities in health risk of PM$_{2.5}$ across different regions and populations is also helpful for formulating control strategies for air pollution. Thus, targeted strategies at the policy and personal levels could be considered. Policies to reduce pollution, such as promotion clean energy and afforestation could be implemented in high risk regions. Perinatal guidance to reduce maternal anxiety during pregnancy, prenatal care and nutritional support to improve maternal health condition as well as medical insurance support for migrant mothers to improve medical care can be considered.

4.1. Strengths and limitations

This study was based on a representative sample from eight cities distributed in different geographical locations across China, and then applied a more flexible method with fewer assumptions (e.g. quantile regression) to explore the association between maternal PM$_{2.5}$ exposure and birth weight distribution. The findings can provide a thorough understanding of how particulate matter affects birth weight.

Our study has several limitations. The information on potential confounding factors, such as maternal exercise, nutritional status, neighborhood and community SES were not available. While we were able to control for any time-fixed city-level confounder by including a fixed effect at the city level, within-city variability in unmeasured confounders (neighborhood segregation, education etc) may exist and may partially bias our estimates. Furthermore, air pollution exposures were estimated using IDW spatial interpolation method, without taking into account of other factors, for example, meteorological factors (e.g. temperature, wind, relative humidity), and exposures were assigned to each pregnancy only based on maternal residence because of lack of maternal activity patterns and residential mobility during pregnancy. In this case, exposure misclassification may present (Wang et al 2020). However, the exposure misclassification is more likely to be non-differential, resulting in attenuation of the associations. And, previous studies indicated that mothers usually move within short distance, and the effects of air pollution remain similar after adjusting for residential mobility during pregnancy (Pereira et al 2016). The exposure window at trimester level we focused on was relatively wide, which might cause bias if the critical period of fetal growth associated with PM$_{2.5}$ spans two trimesters. Further work applying distributed lag non-linear models to quantile regression framework may be a better approach to explore critical exposure window (Neophytou 2019). We explored the potential modification of maternal and regional characteristics by stratified analyses, however, the pattern (additive or multiplicative) and direction (positive or negative) of interaction between them and PM$_{2.5}$ are still unclear. It would be worthwhile to assess the interactive effects under the quantile regression framework in future analyses.

5. Conclusion

Maternal PM$_{2.5}$ exposure was associated with decreased birth weight and the exposure–response relationship was more apparent in the lower quantiles of the birthweight distribution. In addition, there was some evidence to suggest that well-educated, migrant and primiparous mothers in our cohort, and their
infants, were more susceptible to PM_{2.5}. Our findings add to limited existing evidence about the effects of air pollution on adverse birth outcomes, and may be relevant to strategies aiming to protect vulnerable pregnant women and their babies against air pollution.

Data availability statements

The data generated and/or analysed during the current study are not publicly available for legal/ethical reasons but are available from the corresponding author on reasonable request.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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