Associations between maternal weekly air pollutant exposures and low birth weight: a distributed lag non-linear model

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Abstract

When discussing the association between birth weight and air pollution, previous studies mainly focus on the maternal trimester-specific exposures during pregnancy, whereas the possible associations between birth weight and weekly-specific exposures have been largely neglected. We conducted a nested 1:4 matched case-control study in Jinan, China to examine the weekly-specific associations during pregnancy between maternal fine particulate matter (aerodynamic diameter < 2.5 μm, PM$_{2.5}$), nitrogen dioxide (NO$_2$), and sulfur dioxide (SO$_2$) exposure and birth weight, which is under a representative scenario of very high pollution levels. Ambient air monitoring data from thirteen monitoring stations and daily mean temperature data for Jinan during 2013–2016 were continuously collected. Birth data were obtained from the largest maternity and child care hospital of this city during 2014–2016. Individual exposures to PM$_{2.5}$, NO$_2$, and SO$_2$ during pregnancy were estimated using an inverse distance weighting method. Birth weight for gender-, gestational age-, and parity-specific standard score (BWGAP z-score) was calculated as the outcome of interest. Distributed lag non-linear models (DLNMs) were applied to estimate weekly-specific relationship between maternal air pollutant exposures and birth weight. For an increase of per inter-quartile range in maternal PM$_{2.5}$ exposure concentration during pregnancy, the BWGAP z-score decreased significantly during the 27th–33th gestational weeks with the strongest association in the 30th gestational weeks (standard deviation units decrease in BWGAP z-score: $-0.049$, 95% CI: $-0.080$ to $-0.017$, in three-pollutant model). No significant association between maternal weekly NO$_2$ or SO$_2$ BWGAP z-score was observed. In conclusion, this study provides evidence that maternal PM$_{2.5}$ exposure during the 27th–33th gestational weeks may reduce the birth weight in the context of very high pollution level of PM$_{2.5}$.

1. Introduction

According to the World Health Organization (WHO), it was estimated that more than 20 million infants born with low birth weight (birth weight less than 2500 g, LBW) globally and over 90% of these LBW infants were born in developing countries [1, 2]. There is an overwhelming body of evidence suggesting that LBW is not only a leading cause of neonatal morbidity and mortality, but also a main risk factor for developmental problems in childhood (e.g. poor mental and psychomotor development, impaired cognitive function, and lower intelligence quotient) [1, 3]. The etiology of LBW is not yet fully understood because it presents a complex interaction of demographic (maternal age and education level) [4], genetic (race, infant sex, some of gene mutations) [1, 5], obstetric (gestational age, parity, pregnancy
complications) [6], psychological (stress, depression and anxiety) [7], social (parental social class, medical care, and area deprivation) [8], and environmental factors (passive smoking, noise, and air pollution) [9, 10]. Air pollutants, including fine particulate matter (PM_{2.5}), nitrogen dioxide (NO₂), and sulfur dioxide (SO₂), have long been speculated to have impact on infants’ birth weight and potential mechanism includes oxidative stress, inflammation, coagulation, impaired endothelial function and hemodynamic responses, which might impair placental function and subsequently result in growth retardation [11, 12].

An increasing number of studies have analyzed the associations between maternal air pollutant exposures and LBW, and trimester-specific associations were generally reported in these studies but the trimester with the greatest association differed among them, which was attributed to differences in study designs, data sources, geographic factors, and exposure assessment strategies [11, 13–26]. Trimesters of pregnancy are relatively broad range of time periods and only a few studies have been conducted to examine associations between weekly-specific air pollutant exposures during pregnancy and LBW [27–29]. For example, Warren et al reported that maternal PM_{2.5} exposure could increase the risk of delivering an infant with LBW during the 20th–23th gestational weeks, and Symanski et al identified the 21th–24th gestational weeks as critical exposure windows for small for gestational age [27, 28]. Hijuez et al reported that maternal NO₂ exposure was negatively associated with estimated fetal weight during the 20th–32th gestational weeks [29]. Therefore, more evidence is needed to detect out exact maternal susceptible exposure windows for maternal air pollutant exposures, because it has important significance in understanding the underlying mechanisms and then prenatal care departments can optimize preventive and management strategies for pregnant women basing on these findings [30].

The annual mean concentrations of air pollutants in developing countries were usually much higher than those in developed countries [14, 15, 21, 24, 31–32]. However, because of the well-developed air pollution monitoring systems and registries of birth data, researchers in most developed countries (such as the United States, Canada, and some European countries) were able to conduct studies on air pollution and birth outcomes compared to their counterparts in developing countries (such as China and India), thus little is known about the relationship between air pollution and LBW in developing countries [14, 21, 24]. A global survey of 22 countries provided separate results from China and India, but the results were completely inconsistent: LBW in China was positively associated with an increment of 10 μg m⁻³ in maternal PM_{2.5} exposure during the entire pregnancy [odds ratio (OR) = 1.07; 95% confidence interval (CI), 1.01–1.14], whereas the association for India was negative (OR = 0.97, 95% CI = 0.95–0.99) [15]. In our previous study, we explored monthly-specific effects of maternal PM_{2.5} exposure on the risk of term low birth weight (TLBW) using conditional logistic regression models and we found TLBW increased in association with per 10 μg m⁻³ increment in PM_{2.5} for the 8th month (OR = 1.13, 95% CI: 1.04, 1.22) and the 9th month (OR = 1.06, 95% CI: 0.99, 1.15) [32]. However, monthly potentially relevant exposure windows are still relatively broad range of time periods. In addition, we only explored the effect of an exposure at a single gestational month and exposures during other months could not be adjusted for, which might introduce bias because exposures of adjacent gestational months are generally highly correlated [33, 34].

To address these knowledge gaps, we used air pollutants, temperature, and birth data in urban areas of Jinan, China from 2013–2016 attempting to identify a potentially relevant exposure window for maternal PM_{2.5}, NO₂, and SO₂ exposure on TLBW and we mainly focused on weekly-specific associations. To accomplish this, we used flexible statistical models based on distributed lag non-linear models (DLNM), which could be used to study the effect of an exposure at a certain time point while adjusting for all the past (lagged) values of that exposure [34, 35].

2. Materials and methods

2.1. Study sites and data

The study population was recruited from the Jinan Maternity and Child Care Hospital which provides prenatal care, delivery and postnatal care service for the whole residents in this city. The study region consists of six urban districts where 3.8 million people reside. In this city, the Shandong Provincial Environmental Information and Monitoring Center had not monitored ambient PM_{2.5}, NO₂, and SO₂ data until December 2012. Therefore, ambient air monitoring data for PM_{2.5}, NO₂, and SO₂ from thirteen government monitoring stations operating from 2013–2016 were collected. Daily mean temperature data for urban Jinan are available on the Chinese Weather Data Website (http://lishi.tianqi.com/). Medical records of obstetrical department in this hospital from 2014–2016 were retrieved from the hospital information system (HIS) and then a birth database was established.

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Review Committee of Public Health of Shandong University (grant number: 20150331). Informed consent was not required because this study involved analysis of existing secondary data and posed minimal risk to the subjects.

2.2. Study design and definitions

This is a nested 1:4 matched case-control study. Consistent with prior studies, we defined a case as an infant at term (37–42 completed weeks of gestation) with a
birth weight < 2500 g [2]. A control was an infant at term with a birth weight ≥ 2500 g but < 4000 g [2]. Gestational age at delivery was calculated according to delivery date and estimated date of conception which was based on last menstrual period and ultrasonography data. Both cases and controls must be live singleton infants without birth defect, born in the years from 2014–2016 and their mothers must have been living in the six urban districts for more than one year. Eligible cases were first identified and then four controls for each case were randomly selected and matched by maternal age in the established birth database according to case and control definitions. Only subjects from urban area (the six districts of Jinan, i.e. Shizhong, Licheng, Lixia, Huaiyin, Tianqiao, and Changqing) were considered since no ambient air monitoring networks have been well established in rural area (the four counties of Jinan, i.e. Zhangqiu, Shanghe, Jiaying, and Pingyin) during this period.

2.3. Air pollutant exposure assessment
Detailed home and work addresses including street and house number for each mother were obtained from the HIS. No missing data was found in these addresses because strict regulations on hospital registration have been executed by local hygiene departments. All of the monitoring station addresses and home as well as work addresses were converted into longitude and latitude coordinates according to an online Coordinates Identification System (http://api.map.baidu.com/lbsapi/getpoint/index.html). Inverse distance weighting (IDW) method was adopted to estimate concentrations for air pollutants at each subject’s home and work address using ArcGIS version 10.2 (ESRI, Redlands, CA, USA) [36], and personal air pollutant exposure levels were calculated by combining exposures at both home and work using a time-weighted approach [37], which has been described in detail in our previous study [32]. Daily means of temperature data were measured by one central-site monitoring station and without using any exposure assessment model, these were then assumed to be the exposure values of subjects residing in this area across the study period [38]. Then, maternal weekly average exposure concentrations corresponding to every gestational week were calculated using daily estimated air pollutant concentrations and temperature values from the above.

2.4. Data analysis
We calculated birth weight for gender-, gestational age-, and parity-specific standard scores (BWGAP z-scores) based on norms from the northern China as our outcomes of interest in order to make the outcome follow a normal distribution and also adjustment for gender, gestational age, and parity more precisely [18, 39].

To better characterize the relationship between maternal air pollutant exposure and infants’ BWGAP z-scores, a DLNM was used since it can simultaneously estimate the nonlinear (or linear) and delayed effects of exposures on outcomes of interest [35, 40]. The framework of DLNM is based on a ‘cross-basis’ function which can be regarded as a combination of two functions modeling the shape of exposure-response (E-R) relationship and non-linear effects across lags (i.e. lag-response [L-R] relationship) both at the same time [35, 40]. We explored the E-R relationship by fitting models using linear, threshold, piecewise constant, quadratic B-spline and natural cubic spline with various parameters and we estimated the effect of BWGAP z-score associated with an increase from 1st quartile of concentrations of PM$_{2.5}$, NO$_2$ and SO$_2$ to 3rd quartile of concentrations of them during the study period, respectively [41]. For threshold function, we varied threshold values for pollutants basing on their deciles and we varied degrees of freedom (df) from 3–10 for the latter three functions. A natural cubic spline (knots at equally-spaced values of lag range) was selected to model the L-R relationship because of its flexibility as well as the requirement for parsimony according to previous studies in this field [30, 35, 41]. The minimum gestational age was 37 weeks, and the unequal gestational lengths lead to substantial null values existing after the 37th gestational week, which might subsequently lead to inaccurate effect estimates with much wider confidence intervals. Therefore, the maximum lag was set to 36 weeks and the exposure periods were confined to gestational weeks 1–37. In addition, we also adjusted for individual-level factors: maternal highest education level (<college or ≥college), maternal height, number of prenatal visits, diabetes (pre-pregnancy and gestational combined), chronic hypertension, preeclampsia, oligohydramnios, anemia, delivery mode (cesarean or vaginal), year of conception and season of conception (Spring: March-May; Summer: June–August; Fall: September–November; Winter: December–February) [32]. Minimum Akaike Information Criterion (AIC) was used to guide selection of the optimal model [41]. Finally, a DLNM with a linear function for E-R relationship and a natural cubic spline function for L-R relationship was used for PM$_{2.5}$, NO$_2$ and SO$_2$ in the analysis, and the dfs were 7, 6, and 5, respectively. According to Gasparini, they are actually distributed lag linear models (DLM) because of the linear relationship [41]. One DLNM can include one or more ‘cross-basis’ functions simultaneously, which enables us to analyse the independent effects of one air pollutant exposure on infants’ BWGAP z-scores after adjustment for other pollutant exposures [35, 41]. Therefore, a single-pollutant model which only adjusted for other individual-level covariates was fitted and then, two-pollutant models that additionally adjusted for one of the other two pollutants, and three-pollutant model adjusted for both of the other two pollutants simultaneously were fitted, respectively. Collinearity should not be negligible in these two- or three-pollutant models, thus variance inflation factors (VIF) were assessed.
and low values of VIF (< 5) indicated that collinearity concerns were minor [21]. If there was negligible evidence of collinearity existing, results of three-pollutant models were mainly discussed because the estimated effects outputted for one pollutant were independent of the other two pollutants. Cumulative effects were computed to gain a knowledge that how serious it would be if one pregnant woman has suffered from a constant exposure to a specific air pollutant throughout the gestational weeks of interest [41].

Several sensitivity analyses were performed for three-pollutant models: (1) Dispersion pattern differs by air pollutant and using same dispersion pattern might be inaccurate [42–44]. For instance, PM$_{2.5}$ and SO$_2$ are more homogeneous in long distance, but NO$_2$ levels decay drastically in short distance [42–44]. So, for NO$_2$ exposure assessment, we weighted average of the three nearest monitoring stations by the aforementioned method, whereas for PM$_{2.5}$ and SO$_2$, the number used for weighting average of monitoring stations was still twelve. Then, three-pollutant models were re-fitted in order to test if different dispersion patterns have impact on our results. (2) To control for the underlying confounding effect of temperature, we additionally adjusted for it by introducing another ‘cross-basis’ function of maternal weekly mean temperature exposure into these aforementioned models, respectively. For E-R relationship, a piecewise constant function with 3 df was fixed since only high and low temperature may have impact on birth weight and for L-R relationships from the single-, two-, and three-pollutant models, respectively (all VIFs were < 5 in the two- and three-pollutant models). This graph shows that the E-R relationships were linear whereas for NO$_2$, SO$_2$, and temperature in Jinan during 2013–2016. The mean values of daily NO$_2$, SO$_2$, and temperature were 53.3 $\mu$g m$^{-3}$, 62.0 $\mu$g m$^{-3}$ and 15.2$^\circ$C, respectively. In addition, there were 766 (52.4%), 162 (11.1%), and 77 (5.3%) out of 1461 days exceeding China National Ambient Air Quality Standards (CNAAAQS) for daily PM$_{2.5}$, NO$_2$ and SO$_2$ concentrations, respectively [48]. The Spearman correlation coefficients between PM$_{2.5}$ and NO$_2$ as well as SO$_2$ daily concentrations during 2013 and 2016 were 0.66 and 0.59, respectively.

### 3. Results

#### 3.1. Descriptive statistics

A total of 1845 mother-infant pairs including 369 cases and 1476 controls were included. Details of the descriptive information are shown in table 1. Mean maternal age and height were 29.3 (standard deviation [SD] = 4.7) years and 162.4 (SD = 4.7) cm respectively, and mean frequency of prenatal visits was 9.3 (SD = 3.4); 62.1% of mothers were college-educated and 60.2% were primiparous. The mean gestational age of the infants was 38.8 (SD = 1.2) weeks and 48.8% of them were males. The mean birth weight and BWGAP z-score were 3182.4 (SD = 540.8) g and -0.08 standard deviation units (SD = 0.77), respectively. Mean BWGAP z-scores were significantly lower among mothers who had lower education level, were primiparous, had cesarean delivery, and diagnosed with diabetes (pre-pregnancy and gestational combined), oligohydramnios, and anemia, but higher among mothers who were diagnosed with chronic hypertension and preeclampsia.

Table 2 presents summary statistics of PM$_{2.5}$, NO$_2$, SO$_2$, and temperature in Jinan during 2013–2016. The daily average PM$_{2.5}$ concentration over the four-year period was 91.3 $\mu$g m$^{-3}$ (ranging from 15.2 $\mu$g m$^{-3}$ to 444.5 $\mu$g m$^{-3}$), which was significantly above the WHO air quality guideline value for PM$_{2.5}$ (10 $\mu$g m$^{-3}$ annual mean) [47]. The mean values of daily NO$_2$, SO$_2$, and temperature were 53.3 $\mu$g m$^{-3}$, 62.0 $\mu$g m$^{-3}$ and 15.2$^\circ$C, respectively. For NO$_2$, SO$_2$, and temperature exposure into these aforementioned models, respectively. For E-R relationship, a piecewise constant function with 3 df was fixed since only high and low temperature may have impact on birth weight and for L-R relationships non-linear for them; there is a strong negative effect of higher PM$_{2.5}$ exposure on BWGAP z-score around the 30th gestational week, whereas for NO$_2$, and SO$_2$ exposures, strong negative effects of higher exposures on BWGAP z-score were found at around the 16th gestational week.
Table 1. Summary statistics of birth weight and birth weight for gender-, gestational age-, and parity-specific standard score (BWGAP z-score).

| Characteristics                      | n (%) or Mean (SD) | Birth weight (g) | BWGAP z-score |
|---------------------------------------|--------------------|------------------|---------------|
|                                       | Mean (SD)          | Mean (SD)        |               |
| All                                   | 1845 (100.0)       | 3182.4 (540.8)   | −0.08 (0.77)  |
| Gestational age (weeks)               | 38.8 (1.2)         | —                | —             |
| Maternal age (years)                  | 29.3 (4.7)         | —                | —             |
| Maternal height (cm)                  | 162.4 (4.7)        | —                | —             |
| Frequency of prenatal visits (times)  | 9.3 (3.4)          | —                | —             |
| Highest education level               |                    |                  |               |
| <college                               | 700 (37.9)         | 3145.9 (546.8)   | −0.13 (0.78)  |
| ≥college                               | 1145 (62.1)        | 3204.8 (556.0)   | −0.05 (0.76)  |
| Parity                                 |                    |                  |               |
| Primiparous                            | 1111 (60.2)        | 3158.5 (548.0)   | −0.11 (0.79)  |
| Multiparous                            | 734 (39.8)         | 3218.7 (527.9)   | −0.02 (0.72)  |
| Delivery mode                          |                    |                  |               |
| Cesarean                               | 871 (47.2)         | 3115.0 (613.5)   | −0.13 (0.86)  |
| Vaginal                                | 974 (52.8)         | 3242.6 (458.2)   | −0.03 (0.66)  |
| Infant Sex                             |                    |                  |               |
| Male                                   | 901 (48.8)         | 3256.8 (536.1)   | −0.06 (0.76)  |
| Female                                 | 944 (51.2)         | 3111.5 (536.0)   | −0.09 (0.77)  |
| Diabetes                               |                    |                  |               |
| No                                     | 1668 (90.4)        | 3171.9 (559.6)   | −0.10 (0.76)  |
| Yes                                    | 177 (9.6)          | 3281.4 (543.2)   | 0.12 (0.79)   |
| Chronic hypertension                   |                    |                  |               |
| No                                     | 1775 (96.2)        | 3190.6 (537.0)   | −0.07 (0.76)  |
| Yes                                    | 70 (3.8)           | 2975.0 (595.4)   | −0.33 (0.85)  |
| Preeclampsia                           |                    |                  |               |
| No                                     | 1765 (95.7)        | 3210.8 (521.5)   | −0.04 (0.74)  |
| Yes                                    | 80 (4.3)           | 2557.5 (582.4)   | −0.84 (0.84)  |
| Oligohydramnios                        |                    |                  |               |
| No                                     | 1603 (86.9)        | 3235.3 (514.7)   | 0.00 (0.73)   |
| Yes                                    | 242 (13.1)         | 2832.3 (578.4)   | −0.58 (0.80)  |
| Anemia                                 |                    |                  |               |
| No                                     | 1067 (57.8)        | 3134.1 (550.3)   | −0.14 (0.77)  |
| Yes                                    | 779 (42.2)         | 3248.8 (520.6)   | 0.01 (0.75)   |
| Season of conception                   |                    |                  |               |
| Spring                                 | 431 (23.4)         | 3132.4 (553.3)   | −0.14 (0.78)  |
| Summer                                 | 479 (26.0)         | 3213.3 (529.4)   | −0.05 (0.75)  |
| Fall                                   | 461 (25.0)         | 3200.1 (518.2)   | −0.07 (0.74)  |
| Winter                                 | 474 (25.7)         | 3179.6 (558.4)   | −0.07 (0.79)  |

a Percentages for categorical variables and means (standard deviation, SD) for continuous variables.
b \( p < 0.05 \) by analysis of variance or \( t \)-test.

Table 2. Summary statistics of air pollutant concentrations and temperature in Jinan (2013–2016).

| Characteristic                  | Mean (SD) | Min | 25th | Median | 75th | Max | Days exceeding CNAAQS \( a \) | Spearman correlation coefficients |
|--------------------------------|-----------|-----|------|--------|------|-----|-------------------------------|----------------------------------|
| \( PM_{2.5} \) (\( \mu g m^{-3} \)) | 91.3 (56.7) | 15.2 | 54.2 | 78.0   | 109.6| 444.5| 766                           | 1.00                             |
| \( NO_2 \) (\( \mu g m^{-3} \))     | 53.3 (22.2) | 14.0 | 36.8 | 49.4   | 65.0 | 167.0| 162                           | 0.66\( ^b \) 1.00                |
| \( SO_2 \) (\( \mu g m^{-3} \))     | 62.0 (48.1)| 9.3  | 30.6 | 47.2   | 78.6 | 418.4| 77                            | 0.59\( ^b \) 0.67\( ^b \) 1.00    |
| Temperature (\( ^\circ C \))       | 15.2 (10.3)| -12.4| 6.0  | 16.9   | 24.2 | 33.8 | -0.26\( ^b \) -0.48\( ^b \) -0.53\( ^b \) 1.00 |

\( a \) CNAAQS: China National Ambient Air Quality Standards. Daily standards were: \( PM_{2.5} \), 75 \( \mu g m^{-3} \); \( NO_2 \), 80 \( \mu g m^{-3} \); \( SO_2 \), 150 \( \mu g m^{-3} \).
\( b \) \( p < 0.05 \)

single-pollutant model and the 15th and 16th gestational weeks in two-pollutant model adjusted for \( SO_2 \). For an increase of an IQR in \( SO_2 \) concentration during pregnancy, the BWGAP z-scores decreased significantly during the 13th–19th gestational weeks in two-pollutant model adjusted for \( PM_{2.5} \) and the 14th and 16th gestational weeks in three-pollutant model.

3.3. Sensitivity analysis

In sensitivity analyses, the df for these optimal models were unchanged after we recalculated the corresponding AICs. For \( PM_{2.5} \) exposure, sensitivity analyses showed that the results were similar after weighting average of the three nearest monitoring stations for \( NO_2 \) exposure assessment, controlling for the effect of temperature, removing subjects whose home or work address was located beyond 10 km of the nearest monitoring station, and controlling for fixed-cohort bias, respectively (see supplementary materials, figures S3–S6). However, results of sensitivity analyses controlling for fixed-cohort bias for \( NO_2 \) exposure and results of sensitivity analyses removing subjects whose home or work address was located beyond 10 km of the nearest monitoring station and controlling for fixed-cohort bias for \( SO_2 \) exposure showed that significant decreases in BWGAP z-score during the aforementioned gestational weeks in the main analysis were no longer observed.
Figure 1. Exposure-lag-response surfaces for the association between birth weight for gender-, gestational age-, and parity-specific standard score (BWGAP z-score) and maternal PM\textsubscript{2.5}, NO\textsubscript{2}, and SO\textsubscript{2} exposures (\(\mu g \text{ m}^{-3}\)), respectively. Changes in BWGAP z-score were relative to the reference values of 54.2, 36.8, and 30.6 \(\mu g \text{ m}^{-3}\) (1st quartile of local PM\textsubscript{2.5}, NO\textsubscript{2}, and SO\textsubscript{2} concentrations during study period). They are three-pollutant models adjusted for the other two air pollutants, maternal highest education level, maternal height, number of prenatal visits, diabetes (pre-pregnancy and gestational combined), chronic hypertension, preeclampsia, oligohydramnios, anemia, year of conception and season of conception.

Figure 2. Plots of the changes in BWGAP z-score associated with an increase from 1st quartile to 3rd quartile of PM\textsubscript{2.5}, NO\textsubscript{2}, and SO\textsubscript{2} concentrations in three-pollutant models during the study period. Models were adjusted for the other two air pollutants, maternal highest education level, maternal height, number of prenatal visits, diabetes (pre-pregnancy and gestational combined), chronic hypertension, preeclampsia, oligohydramnios, anemia, year of conception and season of conception.

Therefore, the 27th–33th gestational weeks were potentially relevant exposure windows for maternal PM\textsubscript{2.5} exposure on BWGAP z-score with the strongest effects in the 30th gestational week (SD units decrease in BWGAP z-score: \(-0.049, 95\%\) CI: \(-0.080, -0.017\), in three-pollutant model). Detailed information of the exposure-lag-response associations during the 26th–34th gestational weeks is available in supplementary materials table S1.

3.4. Cumulative effects

Because the 27th–33th gestational weeks were identified, the cumulative effects were then calculated by summing the effect estimates over these gestational
weeks in further analyses. For an IQR increase in maternal PM$_{2.5}$ cumulative exposure during the 27th–33th gestational weeks, the BWGAP z-scores decreased significantly (SD units decrease in BWGAP z-score: $-0.246$, 95% CI: $-0.415$, $-0.079$, see supplementary materials, table S1).

4. Discussion

Overall, the daily average concentration of PM$_{2.5}$ in Jinan was much higher than the WHO air quality guideline value and the days exceeding CNAQS for daily PM$_{2.5}$ were much more than those for daily NO$_2$ and SO$_2$, which may cause more severe adverse health effects. Our results support the hypothesis that higher maternal exposure concentrations of PM$_{2.5}$, other than NO$_2$ or SO$_2$, were associated with reductions in birth weight in the context of very high pollution levels. Specifically, the 27th–33th gestational weeks were identified as potentially relevant exposure windows and the strongest effects occurred in the 30th gestational weeks.

Previously, maternal PM$_{2.5}$ exposure was generally assumed to be associated with birth weight linearly and several research had confirmed this assumption [13, 20, 25]. A study exploring the association between maternal PM$_{2.5}$ exposure and birth weight for gestational age z-scores also observed a linear relationship [18]. In this study, we found the optimal function for E-R relationship in DLNM is linear from results of [18]. In this study, we found the optimal function for E-R relationship in DLNM is linear from results of [18].

In our main analysis, we initially observed possible relevant exposure windows for maternal PM$_{2.5}$, other than NO$_2$ or SO$_2$ exposure and birth weight also presented inconsistent results [29, 52–53]. In our main analysis, we initially observed possible relevant exposure windows for maternal NO$_2$ and SO$_2$ exposure on BWGAP z-score, but the results of sensitivity analysis indicated that these results might be influenced by fixed-cohort bias and the distance of subjects’ home or work address to the nearest monitoring station.

Several possible reasons might account for the discrepancies among those results and our results regarding maternal PM$_{2.5}$, NO$_2$, and SO$_2$ exposure on birth weight: (1) the aforementioned differences in study designs, data sources, geographic factors, and exposure assessment strategies; (2) other than previous studies using raw birth weight data and adjusting for gender, gestational age and parity in analytical models, we used BWGAP z-score as the outcome of interest, which is an essential difference; (3) the much larger proportions of potentially toxic constituents (e.g. elemental carbon and Pb) in PM$_{2.5}$ at a specific increment of PM$_{2.5}$ concentration in Jinan than those in other areas [32]; (4) A potential ‘harvest’ effect of increased possibility of miscarriage or stillbirth of the most susceptible fetuses (which would have been more probable to be delivered with LBW) might be caused by maternal NO$_2$ or SO$_2$ exposures and result in the null associations between them and BWGAP z-score [20]. Green et al reported that other than PM$_{2.5}$, maternal NO$_2$ exposure during the entire pregnancy was significantly associated with increased risk of stillbirth in both single- and two-pollutant models [56]. Faiz et al observed similar results that there were significant associations between stillbirth and maternal SO$_2$ and NO$_2$ exposure, but not PM$_{2.5}$ exposure [57]. However, it is difficult to validate this hypothesis in our study because of the lack of data on miscarriages or stillbirths.

from 1.028–1.030 in different models) [14]. Notably, our findings demonstrate quite strong concordance with a natural experiment in Beijing that an increment of 19.8 µg m$^{-3}$ in PM$_{2.5}$ exposure during the 8th month of pregnancy (corresponding to the 29th–32th gestational weeks) was associated with an 18 g (95% CI: −32 g, −3 g) decrement in birth weight [22]. A latest meta-analysis pooled ORs for the effect of PM$_{2.5}$ exposure in per IQR increment on TLBW during the third trimester and reported a non-significant but positive association (OR: 1.03, 95% CI: 0.98, 1.09) [50]. However, null or inverse associations for the third trimester have also been observed in other studies [16, 25, 51]. In our results, the associations were null after the 33th gestational week and the curves of the effect estimates showed somewhat inverse but non-significant effects of PM$_{2.5}$ on BWGAP z-scores since the 34th gestational week in single-, two-, and three-pollutant models. This could be nature of spline models because usually head and tail portion of data are unreliable with wider confidence intervals. Previous studies exploring associations between maternal NO$_2$ or SO$_2$ exposure and birth weight also presented inconsistent results [29, 52–53].
Mechanisms for maternal PM$_{2.5}$ exposure on birth weight are poorly understood at present, but several responses speculated by researchers seem to be involved: systemic oxidative stress, endothelium dysfunction, pro-inflammation and pro-thrombosis of lung or placenta after being inhaled and reaching the blood circulation of humans [58]. The development and maintenance of sufficient uteroplacental circulation in the mother is an essential circumstance for fetal growth [1, 59]. However, a healthy placenta, characterizing by transferring oxygen and nutrients required for fetal development and energy production from maternal blood to the fetus, is a major precondition of this circumstance [1]. Any or all of these speculated responses might result in inadequate trophoblast invasion into the uterine vasculature or placental hypoperfusion that subsequently retard the growth of fetus and ultimately lower the birth weight [60]. We consider the identified potentially relevant exposure windows were biologically plausible because the Chinese fetal weight rose from 876–2039 g during gestational weeks 27–33 and the growth curve sloped up sharply in weeks 30 and 31 [61]. It is in this stage that the greatest absolute demands of fetal requirements for oxygen and nutrients occur and beyond that, the metabolic rate could be accelerated by the increased body mass, which in turn, lead to an elevated inhalational dose of ambient PM$_{2.5}$ [62].

It should also be noted that the concentrations of some detrimental metal compositions of PM$_{2.5}$ in Jinan were relatively high as compared to in other regions. For instance, the arsenic (As) and manganese (Mn) concentrations (0.04 µg m$^{-3}$ and 0.06 µg m$^{-3}$, respectively) in urban area of Jinan were extremely higher than those in other areas such as Los Angeles County of California (0.0016 µg m$^{-3}$ and 0.0052 µg m$^{-3}$, respectively) where Laurent et al reported elevated risks of LBW for As and Mn in PM$_{2.5}$ exposures during the third trimester (for As in per 0.0012 µg m$^{-3}$ increment, OR = 1.002, 95% CI: 0.999, 1.006; for Mn in per 0.0024 µg m$^{-3}$ increment, OR = 1.012, 95% CI: 1.005, 1.019) [19, 63]. In gestational week 30, maternal As exposure showed a U-shaped association with pro-inflammatory cytokine (IL-1β, TNFα, and IFNγ) concentrations in cord blood [64]. That is, excessive maternal As exposure might lead to increased pro-inflammation of placenta and subsequently lower the birth weight through the aforementioned process. In addition, maternal metal exposures (e.g. Mn in blood) during the third trimester can influence the circulating levels of maternal plasma matrix metalloproteinases (MMPs) that play a critical role in placentation, embryo implantation, fetal-maternal membrane lysis, and are associated with inflammatory conditions [65]. MMP-related responses might be another pathway that maternal exposures to detrimental metal compositions of PM$_{2.5}$ mediate the adverse pregnancy outcomes such as LBW [65].

It is worth noting that in results of both main analysis and sensitivity analyses, compared to results of three-pollutant models, the effect sizes attenuated distinctly in two-pollutant models adjusted for NO$_2$ in corresponding gestational weeks and in contrast, the effect sizes intensified slightly in two-pollutant models adjusted for SO$_2$. That is to say, SO$_2$ is a negative confounder but NO$_2$ a positive one, and the confounding effect of SO$_2$ is much larger than that of NO$_2$ [66]. Interestingly, in our previous study exploring monthly PM$_{2.5}$ exposure on LBW (a categorical outcome), SO$_2$ tended to be a positive confounder for the 8th and 9th gestational month [32]. The inherent mechanism of the inverse confounding effects between NO$_2$ and SO$_2$ in this study and the inverse confounding effects of SO$_2$ between the two studies is not clear and requires further exploration. Nonetheless, both NO$_2$ and SO$_2$ are potential confounders affecting the association between PM$_{2.5}$ and BWGAP z-score and should be taken into account in later research.

Our findings add to a growing literature evaluating maternal PM$_{2.5}$ exposure on birth weight. To our knowledge, this is the first study exploring the associations between weekly-specific personal exposures in a typical scenario of very high pollution level (mean PM$_{2.5}$ concentration of more than 90 µg m$^{-3}$), which may better reflect the susceptible window to PM$_{2.5}$ for outcomes of interest. In this study, all of the sensitivity analyses for PM$_{2.5}$ yielded similar results, indicating that there was negligible evidence of weighting average of different nearest monitoring stations for NO$_2$ exposure assessment, confounding effect of temperature, exposure misclassification caused by distance assignment, and potential fixed-cohort bias influencing the effect estimates. In addition, our results were statistically robust and reliable because the df for these optimal models were unchanged in sensitivity analyses.

Although results of the present study are novel, several limitations should be addressed. First, medical records could only provide limited personal information and data on some known influencing factors on birth weight (such as active or passive smoking, alcohol consumption, and nutrient supplements) was unavailable thus residual confounding in models without these covariates may be present [5, 13]. However, the estimated prevalence of smoking among Chinese women is only 2.4% and that among pregnant women is usually to be less [67, 68]. Therefore, our results were less likely to be affected by the unavailability of data on smoking either at home or at work. In addition, socioeconomic status (SES) may also have influence on the final results, but related information was limited. However, we adjusted for maternal highest education level, which was considered to be a good proxy of SES for pregnant women [69]. Besides, our target population was limited to subjects from urban area (without rural area), so the variations of SES across subjects might be minimized [70]. Second, information on maternal residential history and commuting pattern was also
unavailable, thus we cannot rule out the potential exposure misclassification caused by maternal mobility in pregnancy. Several recent research, however, found that maternal mobility had only slightly or even no impact on effect estimates [26, 71, 72]. The unavailability of information on exposure during commuting is a common limitation of similar studies regarding maternal air pollutant exposure and pregnancy outcomes [21, 73, 74]. However, recent findings suggest that in urban areas, a lack of time-activity patterns during pregnancy little influenced exposure estimates [75], although several existing studies reported that personal exposure levels varied in different commuting patterns (e.g. biking, taking a bus, and driving a car) [76, 77]. Third, birth weight also increases a lot in last few weeks before delivery, but exposures after the 37th gestational week were not included in DLNMs because of the reasons listed above. A desirable solution is to stratify the subjects by gestational weeks to ensure all mothers have the same exposure length. However, the sample size for each gestational week was insufficient after stratification. Research with large sample sizes might be qualified to adopt this approach. Fourth, the health effects of PM$_{2.5}$ can vary basing on its sources and components and a few of studies have examined effects of specific constituents of PM$_{2.5}$ on birth weight, but the limited technical condition of monitoring stations in this area impeded our further research [13, 19, 21]. Fifth, although we have adjusted for NO$_2$ and SO$_2$ when presenting results, it is also likely that PM$_{2.5}$ served as surrogates for other unmeasured pollutants. Thus, the results might be interpreted with care.

5. Conclusions

In conclusion, maternal PM$_{2.5}$ exposures during the 27th–33th gestational weeks are associated with decreases in birth weight in the context of very high pollution levels. Our findings highlight the needs to protect pregnant women from PM$_{2.5}$ exposure, especially in those potentially relevant exposure windows and in high PM$_{2.5}$ pollution areas, environmental health policies should be carried out to reduce the local PM$_{2.5}$ emissions. Further research concerning specific constituents of PM$_{2.5}$ is warranted in high PM$_{2.5}$ pollution areas.

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