Association of Seasonal Ambient Air Pollution With a Risk of Adverse Perinatal Outcomes in Full-term Pregnancies: A Retrospective Cohort Study in Wenzhou, China

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Research Article

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Abstract

Prenatal exposures to ambient air pollution have been proved to be associated with adverse perinatal outcomes in previous studies. However, few studies have examined the interaction between air pollution and season of conception on term low birth weight (TLBW) or macrosomia. Birth registry data of singleton live births in Wenzhou, China between January 2015 to December 2016 were accessed from the Wenzhou maternal and child health information management platform, and the ambient air pollutants in Wenzhou were obtained on the Chinese Air Quality Online Monitoring and Analysis Platform. Single/two-pollutant binary logistic regression models were used to assess the associations between ambient air pollutants ($PM_{2.5}$, PM_{10} , NO_2 , SO_2 , and O_3) and TLBW/macrosomia, further exploring if the season of conception interacts with air pollution to impact birth weight. Finally, 213,959 term newborns were selected, including 2452 (1.1 %) TLBW infants and 13173 (6.1 %) macrosomia. In single/two-pollutant models, we observed an increased risk of TLBW associated with maternal exposure to $PM_{2.5}$, PM_{10} , SO_2 , and NO_2 during the entire pregnancy, especially in the 2nd trimester. Maternal exposure to O_3 during the 1st trimester was associated with increased macrosomia risk, and O_3 exposure during the 3rd trimester was associated with increased TLBW risk contrarily. Pregnant women conceived in the warm season may undergo more adverse ambient air environment that is related to the risks of TLBW.

Introduction

Term low birth weight (TLBW) and macrosomia are two important adverse perinatal outcomes that indicate abnormal fetal intrauterine growth and nutrition. TLBW is interpreted as full-term (born at ≥ 37 completed weeks of gestation) newborns with birth weight less than 2500 g. Newborns with low birth weight (LBW) are not only associated with neonatal mortality and disease morbidity (Staff 2016), but also are linked with complications such as cardiovascular diseases and diabetes in later adulthoods (Osmond & Barker 2000). Commonly, macrosomia is defined as a newborn whose birth weight is equal to or more than 4000 g, which has been proved to increase the risks of maternal complications (Beta et al. 2019a), such as postpartum hemorrhage and perineal trauma. Macrosomia newborns are also more likely to develop obesity and other metabolic disorders in their childhoods and adulthoods (Beta et al. 2019b).

An increasing number of recent studies have examined the potential effects of air pollution exposures to LBW, with results across studies varying widely (Bosetti et al. 2010, Li et al. 2020, Li et al. 2019b, Liu et al. 2019, Stieb et al. 2012, Uwak et al. 2021). For instance, Stieb et al. (Stieb et al. 2012) summarized 62 studies and concluded that air exposure to NO_2 , PM_{10} , and $PM_{2.5}$ during pregnancy was in relation to newborns with LBW. But Bosetti et al. (Bosetti et al. 2010) pooled that maternal exposure to $PM_{2.5}$ and PM_{10} during pregnancy had no independent associations with the risk of LBW. These inconsistencies may be due to the risk of bias and imprecision of the articles. Uwak et al (Uwak et al. 2021) systematically evaluated the quality of individual studies regarding the associations between prenatal exposure to PM air pollution and LBW, and found that the quality of evidence for coarse PM from single-pollutant models was rated as very low/low. Models that included multi-pollutant exposures may better represent gestational ambient air pollution exposure, but most pollutants were typically reported separately and failed to consider co-exposures.

Compared with LBW, associations of air pollution exposure with risks of macrosomia were less clear. Several epidemiological studies evaluated the effects of air pollution on the risk of macrosomia, with the inconsistent findings over different trimesters. Shang et al. (Shang et al. 2021) reported that maternal exposure to $PM_{2.5}$, PM_{10} , SO_2 , and NO_2 in the 3rd trimester increased the term birth weight and increased the risk of macrosomia, but showed contrary effects during the 1st and 2nd trimesters, and the entire pregnancy. Another nationwide study in China found that maternal exposure to $PM_{2.5}$ increased the risk of macrosomia over the 1st, 2nd, 3rd trimesters and the entire pregnancy (Chen et al. 2020).

Season of conception is an important factor affecting the association between air pollution and birth weight. Most studies only adjusted the season as a confounding factor in the model (Consortium on et al. 2019, Li et al. 2019b, Shang et al. 2021), instead of treating it as a major research factor. It has been proposed that season of conception involved in air pollutant concentration and composition could explain part of the link between intrauterine fetal growth and risk of adverse perinatal

outcomes, and the biological responsiveness of the human body to air pollution might vary with seasons (Kim et al. 2017). Furthermore, the meteorological factors, such as ambient temperature and humidity, form various specific seasonal patterns which have also been related to birth weight (Schifano et al. 2013). Wang et al. (Wang et al. 2019a) found a seasonal pattern that significant associations were observed between air pollution and small for gestational age (SGA) for women who conceived during summer or fall. Other study reported that the seasonal patterns of air pollutants increased the risk of preterm birth in autumn and winter distinguishably (Zhao et al. 2020). To our knowledge, no published studies have assessed the interaction between air pollution and season of conception on birth weight in China.

Therefore, we aimed to conduct a retrospective cohort study to assess the effects of prenatal exposure to air pollution (PM_{2.5}, PM₁₀, SO₂, NO₂, O₃) on TLBW/macrosomia at each trimester in Wenzhou using single/two-pollutant models, further examining if the season of conception interacts with air pollution to impact birth weight. We only included full-term infants in order to exclude the influence of premature infants on the results.

Methods

Study area

Wenzhou (27°03'–28°36' N, 119°37'–121°18'E) borders on the East China Sea, which is greatly influenced by subtropical monsoon. Due to the significant alternating between winter and summer monsoons of Wenzhou, the influence of the seasonal influence between air pollution and birth outcomes will be more significant.

On the other hand, Wenzhou is known as the ever shoe capital of China, the rubber footwear industries can produce volatile organic compounds (VOCs) which are classified as major contributors to air pollution, especially O₃ (Li et al. 2019a).

Study population

The data of participants were accessed from the Wenzhou maternal and child health information management platform, which covered 51 midwifery clinics and hospitals in this city. The total number of registered singleton live births from January 2015 to December 2016 was 226,721. We excluded a total of 12,762 (5.6%) of the births according to the following exclusion criteria: gestational period < 37 weeks, missing or outlier birth weight, the maternal residence address during pregnancy was not in Wenzhou, and maternal age < 13 y or > 50 y. Finally, a total of 213,959 mother-infant pairs were included for further analysis, and the selection flowchart of the birth records was shown in **Fig. 1**. The maternal information (e.g. maternal age, maternal education, ethnicity, registered residence, parity, date of delivery, and gestational age at birth) and the newborn's information (e.g. birth weight, infant sex, date of birth) were collected. The study was approved by the ethics committee of the Second Hospital Affiliated to Wenzhou Medical University.

Ambient air pollution and meteorological data

Ambient air pollutants in Wenzhou were obtained on the Chinese Air Quality Online Monitoring and Analysis Platform (<https://www.aqistudy.cn/>), which provides real-time and historical daily concentrations of pollutants from 17 monitoring site stations in Wenzhou. The data of this website originated mainly from the real-time data recorded by the Ministry of Ecology and Environment of the People's Republic of China (<http://www.mee.gov.cn/>). We collected the 24-h average of PM_{2.5}, PM₁₀, SO₂, NO₂, and the 8-h average of O₃ daily levels averaged for all of the 17 monitoring site stations from March 2014 to December 2016 for our study. The daily mean temperature data were collected from the China Meteorological Data Service Center (<http://data.cma.cn>). According to the monthly mean temperature, we classified the parturients into those conceived in the warm season (from May to October) and in the cold season (from November to April of the next year) (Jia et al. 2020, Wang et al. 2019b). In addition, the daily exposures were averaged over four exposure windows for each trimester and whole pregnancy: the 1st trimester (from pregnancy to gestational week 12), 2nd trimester (from gestational week 13–week 27), 3rd trimester (from gestational week 28 to delivery), and the entire pregnancy (from gestational week 1 to delivery). The definition of the beginning of the first trimester was calculated according to the last menstrual period.

Study outcomes

Our main outcomes were TLBW and macrosomia. We defined TLBW as birth weight less than 2500 g (born at ≥ 37 completed weeks of gestation), and defined macrosomia as birth weight equals to or more than 4000 g.

Statistical analyses

Differences in characteristics among TLBW, macrosomia, and normal birth weight infants ($2500 \text{ g} \leq \text{birth weight} < 4000 \text{ g}$) were examined with independent sample *F*-tests/student *t*-test or Wilcoxon-Mann-Whitney test for continuous variables and with chi-square tests for categorical variables. For descriptive analysis, the min, max, mean, standard deviation (SD), median, and interquartile range were calculated for air pollutants. The correlations between different air pollutants' concentrations were assessed by Pearson's correlation. We conducted multivariable unconditional logistic regressions to evaluate the relationships between air pollution exposures and TLBW/ macrosomia. The odds ratios (*ORs*) and 95% confidence intervals (*CI*s) were calculated for associations between per $10 \mu\text{g}/\text{m}^3$ increase of air pollution exposures ($\text{PM}_{2.5}$, PM_{10} , NO_2 , SO_2 , and O_3) during each exposure window (1st, 2nd, and 3rd trimesters, and the entire pregnancy) and the risk of TLBW/ macrosomia compared to normal birth weight. In addition, all models were constructed to adjust potential confoundings, such as gestational age (continuous), maternal age at delivery (< 20 , $20-35$, ≥ 35 years old), season of conception (warm season: from May to October, cold season: from November to April of the next year), maternal educational level (Junior high school or below, Junior high school above), parity (the numbers of delivery, once or more than once), ethnicity (Han or others), sex of infants (male or female). Single-pollutant and two-pollutant multivariate models were used to assess the effects before and after adjusting for their potential effects on each other.

To further evaluate the modification of the season of conception and meteorological conditions on the associations between air pollution and TLBW/ macrosomia in the whole pregnancy, we included a cross-product interaction term between season of conception and air pollution along with their main effect terms in multivariable unconditional logistic regressions.

In sensitivity analyses, we fitted multivariable linear models to estimate the impact of air pollutants on birth weight as a continuous measure. The models all adjusted for the covariates described above.

All *P* values were two-sided, with $P < 0.05$ considered statistically significant. All analyses were performed using R 4.0.5.

Results

The neonate and relevant maternal characteristics of the parturients were shown in **Table 1**. From 1 January 2015 to 31 December 2016, a total of 213 959 newborns' birth records were included in our final analysis. Of these, 2 452 (1.1 %) were TLBW, and 13 173 (6.1 %) were macrosomia. The mean gestational age of all included newborns was 39.01 ± 1.09 weeks, and 114 618 (54%) were male neonates. Gestational age, maternal age at delivery, maternal educational level, parity, ethnicity, and sex of infants had statistical differences between TLBW, macrosomia, and normal birth weight infants.

The distribution of air pollution

Descriptive statistics of air pollution concentrations during each exposure time window and their correlation were provided in **Table 2**. According to the new ambient air quality standards of China (GB 3095-2012, $35 \mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, $70 \mu\text{g}/\text{m}^3$ for PM_{10} , $40 \mu\text{g}/\text{m}^3$ for SO_2 , $40 \mu\text{g}/\text{m}^3$ for NO_2 , $160 \mu\text{g}/\text{m}^3$ for O_3), the average levels of $\text{PM}_{2.5}$, PM_{10} , and NO_2 were all higher than the limits, and the exposure levels of SO_2 and O_3 were lower than the limits in Wenzhou than those in national standard level. $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 were positively and strongly correlated with each other (Pearson's correlation coefficients ranged from 0.85 to 0.97). $\text{PM}_{2.5}$, PM_{10} , SO_2 and NO_2 were negatively correlated with O_3 ($r = -0.10$ to -0.67).

Considering the correlations among pollutants were strongly positively correlated except for O_3 , we evaluated the effect of air pollutants using two-pollutant models of $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 adjusting for O_3 . Then, we examined the O_3 adjusting for $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 respectively for the subsequent analysis.

Associations between air pollutants and TLBW

In the single-pollutant models (**Fig. 2A**), we observed that per $10\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 during the entire pregnancy were associated with increased risks of TLBW ($\text{PM}_{2.5}$: OR = 1.12, 95%CI : 1.02-1.24; PM_{10} : OR = 1.14, 95%CI: 1.06-1.22; SO_2 : OR = 1.31, 95%CI: 1.06-1.63; NO_2 : OR = 1.13, 95%CI :1.01-1.26). Similar to the entire pregnancy, per $10\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 during the 1st and 2nd trimesters were positively associated with the risk of TLBW, with ORs ranging from 1.06 to 1.18. Conversely, we found that maternal exposure to $\text{PM}_{2.5}$, PM_{10} , and SO_2 during the 3rd trimester decreased a risk of TLBW, with ORs ranging from 0.90 to 0.94.

In the two-pollutant models (**Fig. 2B**), after adjusting for O_3 , similar results were found during the 2nd trimester and the entire pregnancy compared to the single-pollutant models, with attenuated effects of the exposure during the 1st and 3rd trimesters on the risks of TLBW.

The effect of O_3 exposure during each trimester were opposite to the other air pollutants described above (1st: OR = 0.96, 95%CI: 0.94-0.98; 2nd: OR = 0.97, 95%CI: 0.94-1.00; 3rd: OR = 1.06, 95%CI: 1.03-1.08). The association between O_3 exposure and increased TLBW risk during the 3rd trimester was still robust in the two-pollutant model (**Table S1**). However, we did not find any association between O_3 and TLBW during the entire pregnancy in single/two-pollutant models (**Fig. 2A, Table S1**).

Associations between air pollutants and Macrosomia

In the single-pollutant models (**Fig. 3A**), we observed that per $10\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 during the entire pregnancy were associated with decreased risks of Macrosomia ($\text{PM}_{2.5}$: OR = 0.85, 95%CI : 0.81-0.89; PM_{10} : OR = 0.85, 95%CI :0.82-0.88; SO_2 : OR = 0.71, 95%CI : 0.64-0.79; NO_2 : OR = 0.85, 95%CI : 0.80-0.89). Similar to the entire pregnancy, per $10\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 during the 1st and 2nd trimesters were negatively associated with the risk of macrosomia, with ORs ranging from 0.84 to 0.94. Conversely, we found that maternal exposure to $\text{PM}_{2.5}$, PM_{10} , and SO_2 during the 3rd trimester increased the risk of macrosomia, with ORs ranging from 1.06 to 1.11.

In the two-pollutant models (**Fig. 3B**), after adjusting for O_3 , similar results were found during the 2nd trimesters and the entire pregnancy compared to the single-pollutant models, while the effects of the maternal exposure to $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 during the 3rd trimesters were attenuated, which were no longer statistically significant.

The effect of maternal exposure to O_3 on macrosomia during all the three trimesters were opposite to the other air pollutants described above (1st: OR = 1.05, 95%CI: 1.03-1.06; 2nd: OR = 1.04, 95%CI: 1.03-1.05; 3rd: OR = 0.94, 95%CI:0.93-0.95). The association between O_3 exposure and increased macrosomia risk during the 1st trimester was still robust in the two-pollutant model (**Table S1**). However, we did not find any association between O_3 and macrosomia during the entire pregnancy in single/two-pollutant models (**Figure 3A, Table S1**).

Associations between seasonal air pollution and TLBW/Macrosomia

Table 3 shows the summary statistics for air pollution and air temperature during the whole gestational period by the season of conception. Pregnant women who conceived in the cold season would experience relatively higher levels of $\text{PM}_{2.5}$, PM_{10} , SO_2 , NO_2 , and high ambient temperature, but relatively lower levels of O_3 , compared with those who conceived in the warm season during their pregnancy. The Pearson's correlation coefficients among these exposures in a different season of conception were shown in **Table S2**. The degrees of some correlations were different between warm and cold seasons. For instance, the correlations between air temperature and exposures were stronger in cold than warm seasons. Further, the correlation between O_3 and other exposures were positive in the warm season, but in the cold season, the correlations were negative.

As shown in **Table 4**, we found interactions between air pollution (except for O_3) exposure and conception season both on TLBW and macrosomia. The associations between $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 exposure and TLBW/ macrosomia were stronger

in women who conceived in the warm season compared with those who conceived in the cold season (interaction P value < 0.05). With per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 exposure during the entire pregnancy, the risk increased by 34%, 21%, 62%, and 38% for TLBW, and the risk decreased by 24%, 18%, 37% and 27% for macrosomia, respectively. We did not observe any interaction between O_3 exposure and the season of conception on TLBW / macrosomia.

Sensitivity analyses

Table S3 presents linear model results for the correlations of gestational exposure to air pollutants and birth weight in single-pollutant and two-pollutant models, which were consistent with the results in the logistic regression models. In the single/two-pollutant models, per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 during the 1st, 2nd trimester and the entire pregnancy were negatively associated with the increase in term birth weight. The effects of the $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 exposure on decreasing birth weight were stronger in women who conceived in the warm season compared with those who conceived in the cold season (**Table S4**).

Discussion

In this retrospective cohort study, increased TLBW risk was observed in maternal exposure to $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 during the entire pregnancy, especially in the 2nd trimester. Maternal exposure to O_3 during the 1st trimester was associated with increased macrosomia risk, and O_3 exposure during the 3rd trimester was associated with increased TLBW risk contrarily. The interactions between air pollution ($\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2) exposure and season of conception both on TLBW and macrosomia were observed.

The effects of $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 exposure on TLBW during the 2nd trimester, and the entire pregnancy observed in our study were consistent with some previous epidemiological studies. A recent meta-analysis including American, Asian, and European countries observed positive associations between air pollution ($\text{PM}_{2.5}$, PM_{10} , SO_2 , NO_2) and LBW in the entire pregnancy, and the pooled ORs for TLBW were 1.081, 1.053, 1.125, and 1.030, respectively, which were lower compared with our results (Li et al. 2020). These may be due to the high concentration of air pollution in Wenzhou. For instance, the average exposure concentration of $\text{PM}_{2.5}$ over the entire pregnancy in our study was around 42 $\mu\text{g}/\text{m}^3$, while the range of $\text{PM}_{2.5}$ concentrations over the observation period was 2.9–12.5 $\mu\text{g}/\text{m}^3$ in Rico, USA (Kirwa et al. 2019). Liang et al. found that exposure to $\text{PM}_{2.5}$ in the 1st and 2nd trimesters increased the LBW risk in China (Liang et al. 2019). However, Bosetti et al. (Bosetti et al. 2010) pooled that maternal exposure to $\text{PM}_{2.5}$ and PM_{10} during pregnancy did not be associated with a risk of LBW. Our findings added further evidence of the positive associations during the 2nd trimester and the entire pregnancy both in the single/two-pollutant models. The differences among these studies may be attributed to the population susceptibilities, exposure assessments, potential confounders' adjustments, and sample size.

The majority of studies reported positive or null associations between air pollution and LBW in the 3rd trimester (Bosetti et al. 2010, Li et al. 2020). We observed that maternal exposures to air pollution ($\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2) in the 3rd pregnancy were negatively related to TLBW in single pollutant models, which were only consistent with one study (Shang et al. 2021). Additionally, we found macrosomia risk increased for per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 during the 3rd trimester in single pollutant models. These results were similar to several previous studies. One study of Shaanxi Province in China reported that maternal exposure to $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 increased the term birth weight and increased the risk of macrosomia in the 3rd trimester (Shang et al. 2021). Another nationwide study in China showed that every 10 $\mu\text{g}/\text{m}^3$ increase of $\text{PM}_{2.5}$ concentration, the macrosomia risk increased by 3.3% over the 3rd trimester (Chen et al. 2020). In addition, Li et al. suggested that exposure to NO_2 in the 3rd trimester significantly increased birth weight (Li et al. 2019b). Nonetheless, these studies typically reported separately and failed to consider co-exposures. Interestingly, in our two-pollutant models, after adjusting for O_3 , the effects of the air pollution ($\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2) in the 3rd trimester both on TLBW and macrosomia were no longer statistically significant, but the correlations in the whole pregnancy were still robust. These suggested that the 2nd trimester may be the critical exposure periods for $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 . One study conducted by Zou et al. also

found that the associations between NO₂ exposures and the higher odds of LBW and TLBW were generally stronger for early months than for later months of the gestation (Zou et al. 2021). Another study demonstrated that the strongest association for SGA was found for PM_{2.5} in the 2nd trimester, but did not find critical exposure periods for PM₁₀ and SO₂ (Wang et al. 2019a). Further studies are needed to add more evidences for “critical window” during pregnancy.

The associations between O₃ and adverse perinatal outcomes have yet been to be elaborated. Several studies reported positive association between LBW and O₃ exposure in during specific trimesters and the entire pregnancy (Chen et al. 2018, Laurent et al. 2014, Michikawa et al. 2017) , and other studies found null association (Bosetti et al. 2010, Hannam et al. 2014). One study of 321,521 term newborns reported that O₃ exposure might increase birth weight and increase the risk of macrosomia during the 1st and 2nd trimester (Shang et al. 2021), the impact of exposure to O₃ on birth weight was contrary to other pollutants, and our findings added further evidence to support these results.

The detailed underlying toxicological mechanisms of air pollution exposure during pregnancy affects birth weight in different pregnancy periods are still unclear. For the entire pregnancy, some hypotheses have suggested that PM exposure entered the blood through the respiratory tract, which would cause maternal systemic oxidative stress, lung and placental inflammation, DNA damage, coagulation and endothelial dysfunction, and hemodynamic changes (Kannan et al. 2006, Parker & Woodruff 2008). Other studies have shown that air pollution might cause histopathological changes in the placenta, vascular damage and dysfunction (Bolton et al. 2012, Clemente et al. 2016, Veras et al. 2008). The above-mentioned changes may interfere with the transfer of oxygen and nutrients to the mother's placenta, thereby affecting the growth and development of the fetus, resulting in abnormal birth weight of the newborn.

O₃ is a secondary pollutant, forming from the atmosphere through a number of photochemical reactions involving VOCs. Chloe et al (Friedman et al. 2021) found positive associations between PM_{2.5} during certain exposure periods and maternal IL-6 and TNFα, and negative associations were found between O₃ and maternal CRP, IL-6, and TNFα. Thus, patterns were inconsistent for associations between PM_{2.5} and O₃ and cord blood inflammatory biomarkers. Another review reported that O₃ could interact at least theoretically with any organic molecule, activates the anti-oxidant response, promotes immune regulation towards anti-inflammatory mechanisms, and leads to the ability to extensively inhibit pro-thrombotic events (Chirumbolo et al. 2021). The molecular mechanisms between O₃ and its interaction with other pollutants on birth weight need to be further studied and clarified.

We also observed a multiplicative interaction effect between the season of conception and air pollution. The associations between PM_{2.5}, PM₁₀, SO₂, and NO₂ exposure and TLBW/ macrosomia were stronger in women who conceived in the warm season compared with those who conceived in the cold season. A retrospective cohort study based on birth records in Guangdong province reported that O₃ exposure was associated with LBW for the babies conceived in cold season (Wang et al. 2021). Wang et al. found that the associations between air pollution and SGA varied by season of conception. However, these studies did not explore any multiplicative interaction. Our interaction results may be explained by the fact that women who conceived in the warm season, experiencing higher exposure level of air pollutants during their subsequent pregnancy with relatively low ambient temperatures, would increase the risk of TLBW and reduce the risk of Macrosomia. Previous studies have reported that during low ambient temperatures, fetal thermoregulatory responses to cold include increased blood viscosity and vasoconstriction, and these may limit maternal blood flow to the placenta, thereby reducing fetal growth (Bruckner et al. 2014). What's more, cold weather conditions and heating may also accumulate to the detriment of the diffusion of pollutants, resulting in a higher concentration of air pollution in the cold environment (Song et al. 2017). However, the season may also be a surrogate for other exposures with seasonal patterns, including lifestyle, outdoor activities, and the biological responses to air pollution (Kim et al. 2017). These factors have also been related to birth weight. Further researches are needed to clarify the underlying mechanism of the seasonal association between air pollution and adverse perinatal outcomes.

This study had key strengths. First, to the best of our knowledge, it was the first study to explore the multiplicative interaction between air pollution and season of conception on birth weight. Second, we considered co-exposures, which may better represent gestational ambient air pollution exposure. Third, after controlling for known confounding factors, we

comprehensively evaluated the air pollution on TLBW/ macrosomia and birth weight for continuous at three trimesters and the entire pregnancy in a large sample size, adding new evidence to the current understanding of air pollution and birth weight.

This study also had some limitations. Due to the limited information collected on the birth registration system, our study did not consider some confounding factors that may be related to birth weight, such as pregnant women's diet, BMI, socioeconomic status, smoking, and nutritional status. However, previous studies reported that the effect estimates changed little with and without adjustment for the above risk factors (Brauer et al. 2008, Kashima et al. 2011, Schramm et al. 1996). In addition, there may be misclassifications of exposure due to lack of information on pregnant women's activities and mobility of residence during pregnancy. But one study reported that the exposure misclassification is more likely to be non-differential, leading to attenuation of the associations (Wang et al. 2018).

In summary, we observed an increased risk of TLBW was associated with maternal exposure to PM_{2.5}, PM₁₀, SO₂, and NO₂ during the entire pregnancy, especially in the 2nd trimester both in single and two pollutant models. Maternal exposure to O₃ during the 1st trimester was associated with increased macrosomia risk, and O₃ exposure during the 3rd trimester was associated with increased TLBW risk contrarily. Pregnant women conceived in the warm season may undergo more harmful ambient air environment that is related to the risks of TLBW. Further studies are needed to explore the interacting mechanisms of air pollution and season change on fetal weight growth.

Declarations

Author contributions Hui-jun Huang: conceptualization, methodology, data curation, formal analysis, investigation, writing-original draft. Qiu-Yan Yu: conceptualization, methodology, writing - review & editing. Tian Zheng: conceptualization, data curation, software, validation. Shan-Shan Wang: investigation, formal analysis. Xin-Jun Yang: conceptualization, writing-review & editing, project administration, funding acquisition. All authors read and approved the final manuscript.

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Availability of data and materials All the necessary data generated or analyzed during this study are included in this published article. However, the datasets for statistical analysis are available from the corresponding author on reasonable request.

Ethics approval and consent to participate The study was approved by the Medical Ethics Committee of the Second Hospital Affiliated to Wenzhou Medical University.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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Tables

Table 1 Summary characteristics of mother-newborn pairs.

Characteristics	Total (n = 213959)	Normal birth weight (n = 198334)	TLBW (n = 2452)	Macrosomia (n = 13173)	<i>p</i> ^a	<i>p</i> ^b
Birth weight (g, mean (SD))	3340.46 ± 401.77	3296.87 ± 328.88	2310.97 ± 169.24	4188.41 ± 207.48	< 0.001	< 0.001
Gestational age (weeks, mean (SD))	39.01 ± 1.09	39.0 ± 1.08	38.1 ± 1.05	39.5 ± 1.03	< 0.001	< 0.001
Maternal age (years, mean (SD))	27.00 ± 4.99	26.95 ± 4.98	26.10 ± 5.46	28.04 ± 4.97	< 0.001	< 0.001
Maternal age (years), n (%)					< 0.001	< 0.001
<20	11015 (5)	10391 (5)	262 (11)	362 (3)		
20-35	185445 (87)	172096 (87)	1995 (81)	11354 (86)		
≥ 35	17499 (8)	15847 (8)	195 (8)	1457 (11)		
Season of conception, n (%)					0.09	< 0.001
Warm (May to October)	100036 (47)	92399 (47)	1185 (48)	6452 (49)		
Cold (November to April)	113923 (53)	105935 (53)	1267 (52)	6721 (51)		
Maternal education, n (%)					< 0.001	0.016
Junior high school or below	123387 (58)	114106 (58)	1560 (64)	7721 (59)		
Junior high school above	90572 (42)	84228 (42)	892 (36)	5452 (41)		
Parity, n (%)					< 0.001	< 0.001
0	117235 (55)	109207 (55)	1607 (66)	6421 (49)		
≥1	96724 (45)	89127 (45)	845 (34)	6752 (51)		
Ethnicity, n (%)					< 0.001	< 0.001
Han	204366 (96)	189392 (95)	2304 (94)	12670 (96)		
Others	9593 (4)	8942 (5)	148 (6)	503 (4)		
Infant sex, n (%)					< 0.001	< 0.001
Male	114618 (54)	104684 (53)	1008 (41)	8926 (68)		
Female	99341 (46)	93650 (47)	1444 (59)	4247 (32)		

Note: ^a Difference in maternal and neonatal characteristics between TLBW and normal birth weight infants.

^b Differences in maternal and neonatal characteristics between macrosomia and normal birth weight infants.

^a Units are $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, PM_{10} , NO_2 , SO_2 , and O_3

^b All Pearson's correlation $P < 0.05$

Table 2 Pollutant concentration by gestational period and their correlation

Gestational period	Pollutants ^a	Mean ± SD	Min	50th	Max	Interquartile range	Pearson's correlation coefficient ^b				
							PM _{2.5}	PM ₁₀	SO ₂	NO ₂	O ₃
1st trimester	PM _{2.5}	43.92 ± 8.36	29.51	45.48	62.80	37.21-48.57	1.00				
	PM ₁₀	73.45 ± 13.83	48.64	75.26	101.28	61.67-82.84	0.97	1.00			
	SO ₂	14.97 ± 3.81	9.13	14.58	25.04	12.28-17.48	0.85	0.89	1.00		
	NO ₂	45.42 ± 8.03	29.36	46.26	65.92	39.59-51.18	0.93	0.95	0.89	1.00	
	O ₃	87.31 ± 17.91	44.26	93.7	113.83	72.44-101.46	-0.60	-0.51	-0.32	-0.52	1.00
2nd trimester	PM _{2.5}	42.41 ± 9.31	25.93	43.63	62.80	34.60-48.34	1.00				
	PM ₁₀	71.86 ± 14.20	47.30	73.69	101.28	58.73-82.19	0.96	1.00			
	SO ₂	14.71 ± 3.82	8.99	14.18	25.04	11.98-17.26	0.85	0.90	1.00		
	NO ₂	43.29 ± 9.42	24.49	44.89	61.22	34.71-50.71	0.96	0.95	0.89	1.00	
	O ₃	89.70 ± 18.44	44.26	96.81	113.83	73.98-105.36	-0.67	-0.58	-0.40	-0.62	1.00
3rd trimester	PM _{2.5}	41.02 ± 10.22	24.05	39.77	66.86	31.97-48.08	1.00				
	PM ₁₀	70.29 ± 15.23	44.45	71.45	106.76	56.37-81.78	0.97	1.00			
	SO ₂	14.36 ± 4.01	8.82	13.63	26.62	11.20-16.84	0.87	0.91	1.00		
	NO ₂	42.58 ± 10.03	23.41	44.22	64.00	33.24-50.39	0.94	0.95	0.91	1.00	
	O ₃	87.58 ± 18.12	43.41	93.23	114.03	71.20-104.03	-0.58	-0.53	-0.39	-0.61	1.00
Entire pregnancy	PM _{2.5}	42.45 ± 4.59	34.13	42.39	52.72	39.12-45.40	1.00				

PM ₁₀	71.86 ± 5.85	62.84	72.12	86.03	66.21-75.37	0.94	1.00		
SO ₂	14.68 ± 1.90	11.55	14.08	19.34	13.32-16.01	0.90	0.90	1.00	
NO ₂	43.76 ± 4.05	37.23	43.52	52.90	40.11-46.58	0.96	0.93	0.93	1.00
O ₃	88.22 ± 6.25	75.42	88.00	102.36	83.57-93.37	-0.35	-0.38	-0.10	-0.37 1.00

Table 3 Average air pollution concentration and air temperature during the entire pregnancy, summarized by the season of conception

Pollutants/Air temperature		Season of conception		<i>P</i>
		Warm season	Cold season	
PM _{2.5}				
	Mean (SD)	44.91 ± 3.94	40.28 ± 3.98	< 0.001
	Median (IQR)	44.56 (42.52, 48.51)	39.83 (36.28, 42.72)	
PM ₁₀				
	Mean (SD)	74.45 ± 6.10	69.59 ± 4.53	< 0.001
	Median (IQR)	74.58 (71.57, 78.57)	67.15 (65.96, 72.53)	
NO ₂				
	Mean (SD)	45.91 ± 3.76	41.87 ± 3.28	< 0.001
	Median (IQR)	46.11 (44.39, 49.25)	41.34 (39.27, 43.69)	
SO ₂				
	Mean (SD)	15.27 ± 2.18	14.15 ± 1.41	< 0.001
	Median (IQR)	14.97 (13.48, 17.08)	13.66 (13.31, 14.32)	
O ₃				
	Mean (SD)	83.52 ± 3.98	92.35 ± 4.81	< 0.001
	Median (IQR)	84.37 (79.82, 87.02)	93.03 (90.06, 95.54)	
Air temperature				
	Mean (SD)	17.68 ± 1.57	20.73 ± 1.81	< 0.001
	Median (IQR)	17.05 (16.41, 18.91)	21.28 (19.34, 22.15)	

Table 4 Association between air pollution exposure during the entire pregnancy and TLBW/ macrosomia by the season of conception categories

Air Pollutants	Conception in warm season (May to October)	Conception in cold season (November to April of the next year)	Interaction <i>P</i>
TLBW			
PM _{2.5}	1.34 (1.16,1.54) *	0.96 (0.83,1.10)	0.001
PM ₁₀	1.21 (1.11,1.33) *	1.04 (0.92,1.16)	0.029
SO ₂	1.62 (1.25,2.10) *	0.81 (0.54,1.21)	0.004
NO ₂	1.38 (1.18,1.60) *	0.88 (0.74,1.05)	0.001
O ₃	1.00 (0.87,1.15)	0.97 (0.88,1.08)	0.753
Macrosomia			
PM _{2.5}	0.76 (0.71,0.82) *	0.95 (0.89,1.01)	0.001
PM ₁₀	0.82 (0.78,0.85) *	0.92 (0.87,0.98) *	0.001
SO ₂	0.63 (0.56,0.71) *	0.95 (0.79,1.13)	0.001
NO ₂	0.73 (0.69,0.79) *	1.01 (0.94,1.10)	0.001
O ₃	1.00 (0.94,1.07)	1.01 (0.96,1.07)	0.845

*P<0.05

Figures

Figure 1

The selection flowchart of participants.

(A) Single-pollutant models

(B) Two-pollutant models

Figure 2

Association between $PM_{2.5}$, PM_{10} , SO_2 , NO_2 , and TLBW by gestational period in single-pollutant and two-pollutant models. **A** Single-pollutant models included $PM_{2.5}$, PM_{10} , SO_2 , NO_2 respectively. **B** Two-pollutant models: included $PM_{2.5}$, PM_{10} , SO_2 , NO_2 adjusted for O_3 respectively. Multivariable unconditional logistic regression models were used to evaluate associations between air pollution (per $10\mu g/m^3$ increase) and TLBW during each exposure windows (1st, 2nd, and 3rd trimesters, and the entire pregnancy). All models were adjusted for covariates, including Gestational age, maternal age at delivery, season of conception, maternal educational level, parity, ethnicity, sex of infants.

(A) Single-pollutant models

(B) Two-pollutant models

Figure 3

Association between $PM_{2.5}$, PM_{10} , SO_2 , NO_2 , and macrosomia by gestational period in single-pollutant and two-pollutant models. (A) Single-pollutant models included $PM_{2.5}$, PM_{10} , SO_2 , NO_2 respectively. (B) Two-pollutant models included $PM_{2.5}$, PM_{10} , SO_2 , NO_2 adjusted for O_3 respectively. Multivariable unconditional logistic regression models were used to evaluate associations between air pollution (per $10\mu g/m^3$ increase) and macrosomia during each exposure windows (1st, 2nd, and 3rd trimesters, and the entire pregnancy). All models were adjusted for covariates, including Gestational age, maternal age at delivery, season of conception, maternal educational level, parity, ethnicity, sex of infants.

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