Environment International 135 (2020) 105410

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Ambient air pollution and markers of fetal growth: A retrospective population-based cohort study of 2.57 million term singleton births in China

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ARTICLE INFO

Keywords:
Air pollution
Adverse pregnancy outcome
Low birth weight
Small for gestational age
Fetal growth

ABSTRACT

Backgrounds: Evidence is scarce on the relation between maternal exposure to ambient air pollution during pregnancy and fetal growth in developing countries. Moreover, the current evidence is inconsistent. We aimed to investigate the association of trimester-specific exposure to air pollution with risk of being born small for gestational age (SGA) and birth weight-markers of fetal growth-among Chinese term births.

Methods: This retrospective population-based cohort study consisted of 2,567,457 singleton term live-births from January 1, 2014 to December 31, 2017 across 123 Chinese districts and counties. Personal exposure to ambient air pollutants including carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), particulate matter with aerodynamic diameter < 2.5 µm ($PM_{2.5}$), and PM_{10} was assigned using the inverse distance weighting spatial interpolation algorithm. Generalized estimating equations (GEE) logistic regression models were performed to estimate the associations between trimester-specific exposure to air pollution and risk of SGA or low birth weight (LBW), and GEE linear regression to examine the associations between the exposure and term birth weight, adjusting for maternal demographics, maternal cigarette smoking status during pregnancy, mode of delivery, gravidity, gestational age, year and month of conception, neonate's sex, and meteorological factors. Stratified and sensitivity analyses were also performed.

Results: When mother exposed to ambient air pollutants over the entire pregnancy, per IQR increment (0.122 mg/m^3) in ambient CO concentrations was associated with higher risk of SGA (odds ratio (OR) = 1.04, 95% confidence interval (CI): 1.02, 1.05) and reduced birth weight among term births (−5.95 g, 95% CI: −8.01, −3.89). This association was also pronounced in the second and third trimesters. Term birth weight was negatively associated with per IQR increase of O_3 (−3.52 g, 95% CI: −6.23, −0.81), $PM_{2.5}$ (−5.93 g, 95% CI: −8.36, −3.49) and PM_{10} (−7.78 g, 95% CI: −10.41, −5.16) during the entire pregnancy, respectively. No significant association was detected between maternal exposure to air pollutants and term LBW. Effect estimates of heterogeneity suggested that maternal age and infant sex modified the impact of air pollution on birth weight.

Conclusions: The findings suggest that maternal exposure to air pollution during pregnancy is adversely affecting fetal growth. Further studies are warranted to integrate these findings and take clinical or public health interventions in pregnancy.

1. Introduction

Fetal growth, as indicated by birth weight, has important influences on human health. There is now extensive evidence that the health condition before birth and in early childhood can be linked with risks of chronic health problems later in life. For example, low birth weight (LBW) (birth weight below 2500 g) is associated with increased rates of cardiovascular and cerebrovascular diseases in adulthood (Barker,

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https://doi.org/10.1016/j.envint.2019.105410
Received 28 July 2019; Received in revised form 7 December 2019; Accepted 10 December 2019
Available online 26 December 2019

2004). Epidemiologic studies have shown that birth weight as a marker for fetal development is an important predictor of neonatal mortality and morbidity (Saigal et al., 2008; Zhang et al., 2014). At the individual level, maternal factors such as depression, smoking, nutritional deficiency, diarrhea diseases, and anti-HPA-1a antibody are known to be associated with restricted fetal growth (Maruoka et al., 1998; Grote et al., 2010; Tiller et al., 2012; Berhe et al., 2019). At the macro level, a number of factors have adverse influence on fetal growth including social factors (O'Campo et al., 1997), lower ambient temperatures, and features of man-made environment such as residential green space and urbanicity (Ebisu et al., 2016; Glazer et al., 2018; Kloog et al., 2018; Sun et al., 2019). However, these factors cannot totally explain the regional heterogeneity in birth weight worldwide. Additional risk factors may have contributed to such differences.

Air pollution has posed major environmental risks to human health, which has been proved by more and more epidemiological studies on the adverse effects of ambient air pollution (Samet et al., 2000; Pope et al., 2002; Epton et al., 2008; Guo et al., 2018). Several studies have revealed significant adverse effects of ambient air pollution on the fetuses and newborns. However, most studies mainly focused on the relationship between preterm birth and air pollution exposures (Bosetti et al., 2010; Chang et al., 2012; Fleischer et al., 2014). Increasing evidence suggests that environmental air pollution has a particularly impact on preterm birth, however, the extent of the impact on fetal growth retardation is not clear. For example, several recent studies have reported a negative association between birth weight and air pollutants including $PM_{2.5}$ (particulate matter with a diameter of 2.5 μm or less), PM_{10}, and SO_2 (sulfur dioxide) (Hou et al., 2014; Huang et al., 2017; Cao et al., 2019). However, findings from other studies were inconsistent or mixed (Dadvand et al., 2013; Merklinger-Gruchala et al., 2015; Erickson et al., 2016). In particular, evidence on the association between long-term exposure to ambient air pollutants and fetal growth is scarce in developing countries. In addition, as a previous study pointed out, the differences may be attributed to inadequately capturing changes in pollutant concentrations at fine spatial scales in their air monitoring data (Ritz et al., 2018). We believe that the use of more advanced technologies, such as a spatial interpolation algorithm, can improve the assessment of air pollutant exposure, and thus more effectively explore the impact of ambient air pollution on infant health.

Considering the expected rise in air pollutant levels associated with sustainable industrial development in China, we conducted a population-based retrospective cohort study including nearly 2.57 million Chinese singleton term live-births across 123 districts and counties on several prominent questions in air pollution-related epidemiology. By estimating maternal exposure to air pollutants throughout pregnancy, we investigated the markers associated with fetal growth: term small for gestational age (SGA) and birth weight. Then, we examined whether the magnitude of the associations varied by trimester, and explored the most vulnerable subgroups to the pollutants.

2. Methods

2.1. Study population

We collected data on births involving 21cities of Guangdong province in China, from January 1, 2014 to December 31, 2017, using the database of Guangdong Provincial Birth Certificate System. Guangdong province is located in the southern part of China, adjacent to the South China Sea, with a land area of around 179,800 square kilometers and annual average temperature of around 19–24 °C (Fig. 1A). Guangdong is one of the most populous provinces in China, and in recent years the development of industrialization has gradually grown, making the local air pollution situation receive special concern.

Birth data from 123 districts and counties in 21 cities continued to be available throughout the study period. The dataset included birth date, maternal age, maternal ethnicity, maternal cigarette smoking status, mode of delivery, gravidity, birth weight, fetal outcome, neonate's sex, gestational age, and mother's actual residence address. Before the birth certificate was submitted to the system, the registered information of neonates was checked by the quality control doctor or nurse in the medical institution where a newborn was born (Guo et al., 2014). As a preliminary examination, we retained the births with valid information of residential address. We restricted our analyses to the births whose mothers were permanent residents living in Guangdong province and recorded in the China's Household Registration System. Because the addresses of pregnant women were registered according to the actual home addresses, we applied the Baidu Map API interface (http://lbsyun.baidu.com/) to resolve the actual home addresses to geographical longitude and latitude information. We used the leaflet and leafletCN packages within R software to visualize and determine whether the geographic longitude and latitude were located in Guangdong province. For those records with inconsistently registered addresses, we recoded and checked the information. In the second round of geographical information conversion, a small part of records (n = 46,633, accounting for 1.5%) was further eliminated. There were 3,083,753 neonates meet the above criteria after further screening.

We initially excluded stillbirths (n = 74, < 0.1%) in the dataset. Then, we restricted our analyses to 3,079,341 births born between 22 and 42 completed weeks of gestation and in which the last menstrual period (LMP) was recorded. Maternal age outliers (< 16 or > 50 years) were then identified and excluded according to the average age of menarche and natural menopausal age in Chinese population (Shao et al., 2014; Song et al., 2011). Furthermore, we identified and excluded the missing or implausible combinations of birth weight and gestational age, according to the Tukey's rule (Arbuckle et al., 1993). Because the exact date of birth cannot be obtained directly in database, we calculated this variable using information of the LMP, completed weeks of gestation, and delivery's specific day of the week (Sun et al., 2019). To focus on the direct effects of air pollution on fetal growth not mediated through early delivery as well as avoiding bias (Strand et al., 2011), a total of 2,868,870 term singleton live-births were included in our analyses. To avoid "fixed cohort bias" which is a potential bias caused by the length of pregnancy contradicting the time when the study begins and ends in a retrospective cohort study (Shilu et al., 2011), we only included the women whose conception dates were after the start of the cohort phase (January 1, 2014) and 42 weeks before the cohort ended (December 31, 2017). We also excluded birth with missing values for the characteristics including maternal ethnicity (n = 208, < 0.1%), mode of delivery (n = 34, < 0.1%), gravidity (n = 202,979, 7.3%), neonate's sex (n = 19, < 0.1%). The final analytic sample consisted of 2,567,457 term singleton live-births (supplementary Fig. 1). The study was approved by the Medical Ethics Committee of Guangdong Women and Children Hospital. Data used in our study were anonymous, which means no individual identifiable information was present.

2.2. Air pollution exposures

We collected the station-specific daily average concentrations of ambient air pollutants, including carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), PM_{10}, $PM_{2.5}$ and SO_2 from January 1, 2014 to December 31, 2017. Data were publicly available from the PM25.in platform (http://pm25.in/). The database provided atmospheric pollution monitoring data of high quality which were extracted from the Ministry of Environmental Protection of China (Guo et al., 2019). We included 101 ground-level atmospheric pollution monitoring stations across the 123 districts and counties of Guangdong province (Fig. 1A). The layout design of the ground-level monitors is based on the diffusion law of different pollutants, and they are usually set up at the place with the largest pollutant concentration in order to accurately assess the impact of the pollutant on the local population (China MOEP, 2013). We used units of micrograms per cubic meter (μg/m^3) to record daily

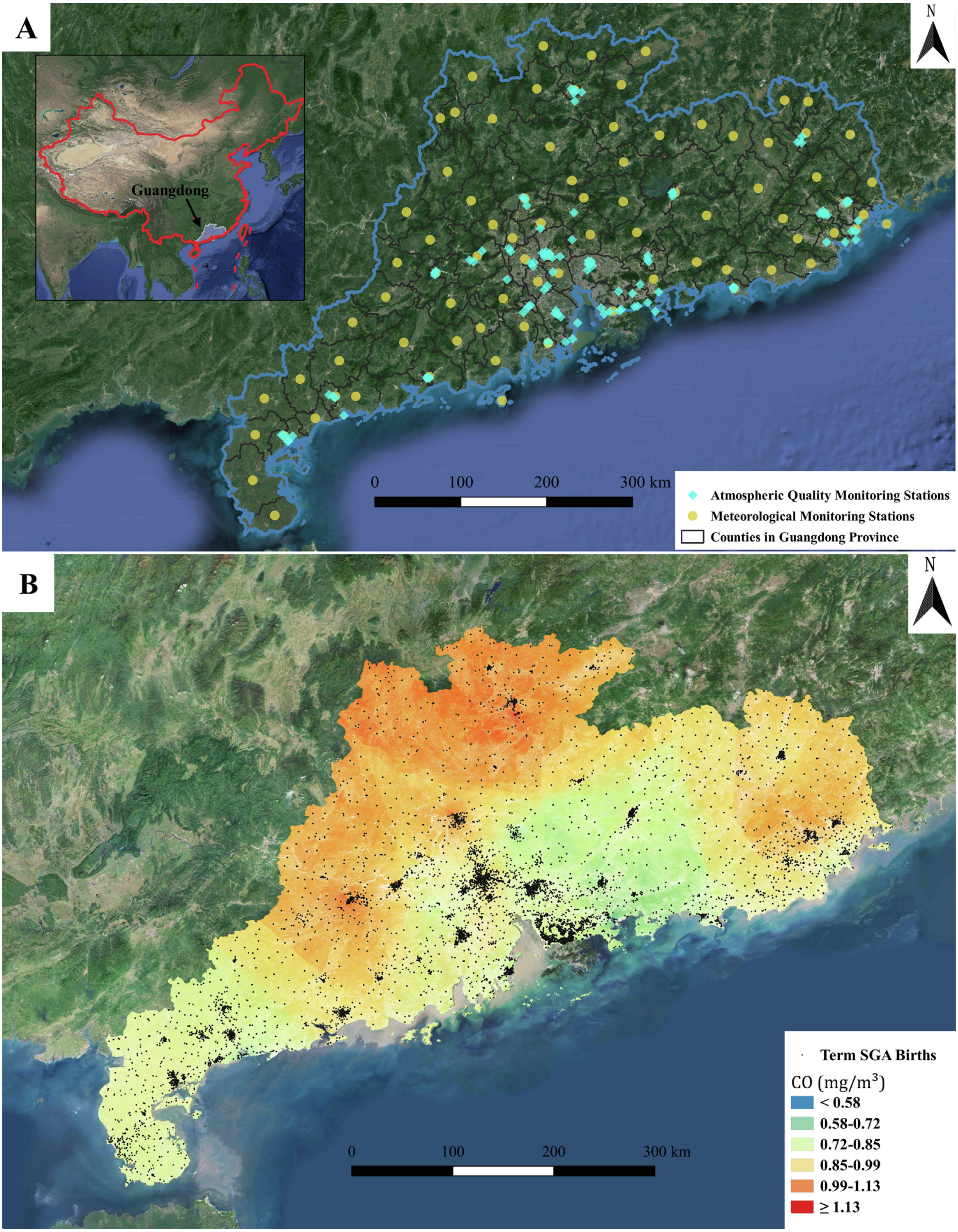

Fig. 1. Geographical distribution of atmospheric quality monitoring stations, meteorological monitoring stations and term small for gestational age (SGA), and spatial variation of CO concentration. (A) We included 101 general atmospheric quality monitoring stations (represented by blue diamonds) and 86 basic meteorological monitoring stations (represented by yellow and solid circles) in Guangdong province. (B) Geographical distribution involving term SGA births, and spatial variation of CO concentration (Unit: mg/m^3) using the inverse distance weighting (IDW) spatial interpolation algorithm from January 2014 to December 2017.

concentrations of NO_2, O_3, PM_{10}, $PM_{2.5}$ and SO_2, and units of milligrams per cubic meter (mg/m^3) to record daily concentrations of CO.

We performed the inverse distance weighting (IDW) algorithm to assess personal exposures of ambient air pollutants. There are two main parameters which are the inverse distance weighting power M and the nearest observations numbers N should be determined. We took the values of M from 0.5 to 5 at intervals of 0.5, and those of N from 5 to 20 at intervals of 1 as initial parameter settings, respectively. Then, we used the 10-fold cross validation approach to select the optimal parameter values (Liu et al., 2019). Specifically, we randomly divided all the monitoring stations into 10 subsets, and then repeatedly used the IDW algorithm to predict the exposure of each subset by setting the remaining 9 subsets as training data until all subsets were predicted. After that, we calculated the determination coefficient R^2 based on the predictions and actually measured exposure concentrations at all stations. We used the grid search method to find the optimal combination of the two parameters based on the largest R^2 (supplementary Fig. 2). We averaged daily levels of air pollutants by calculating the inverse distance ($1/d^M$) weighted average of concentrations at N nearest monitoring stations of corresponding resident address for each mother. We divide pregnancy time into four different spans. The first trimester exposure is from the date of LMP to 13 completed weeks of gestation; the second trimester exposure is from 14 to 26 completed weeks of gestation; the third trimester exposure is from 27 completed weeks of gestation to birth; and the entire pregnancy exposure is from the date of LMP to birth (Hao et al., 2016). We used the IDW algorithm to simulate the spatial distribution of air pollutant concentrations across 123 districts and counties of Guangdong province. This study used R 3.4.3 software and ArcGIS 10.2 (ESRI, Redlands, CA, USA) to visualize the geographical distributions of pregnancy outcomes and concentrations of air pollutants.

2.3. Meteorological factors

We also collected information on daily average ambient temperature (℃) and relative humidity of 86 basic meteorological monitoring stations (Fig. 1A) from the China Meteorological Data Sharing System (http://data.cma.cn/). The system is an authoritative and unified shared service platform of China Meteorological Administration. And it offers a spatially explicit representation of meteorological exposures. We adopted the similar parameter settings in the IDW spatial interpolation algorithm for meteorological factors as air pollutants. And we estimated meteorological exposures during trimester-specific pregnancy and entire pregnancy.

2.4. Outcome definition

Our study outcomes were term SGA, term LBW and continuous birth weight at term. Term LBW was defined as birth weight less than 2500 g and gestational age greater than 37 weeks (World Health Organization (WHO), 2016). SGA means that an infant is smaller or less developed than normal for the baby's gender and gestational age (Saenger et al., 2007). To better account for constitutional differences in birth weight by sex, we used the 2015 China national reference of sex-specific reference percentiles for birth weight at each gestational age (Zhu et al., 2015) to classify every infant into corresponding birth weight percentiles. Infants with birth weight in the $<$ 10th percentile are defined as SGA (Sun et al., 2019).

2.5. Statistical analysis

First, we used the Spearman's correlation to examine the correlations among the pollutants. In addition, we note that birth outcomes of neonates from the same residence may be correlated. The phenomenon may affect the independence assumption of basic regression models (Fleischer et al., 2014). Actually, in the context of environmental exposure risk assessment, the data we often encounter are clustered. Liang and Zeger (Liang et al., 1986) developed the generalized estimating equations (GEE) to extend the generalized linear models to accommodate clustered data. Unlike traditional methods that require the outcome variables being approximately multivariate normal, the GEE approach is suitable for discrete-type outcomes in a regression setting and allows for multiple levels of clustering. We also note that some previous studies proposed to use the GEE model to examine the effect of outdoor air pollution on adverse pregnancy outcomes to account for multiple nesting levels of the data and minimize the impact of spatial heterogeneity (Fleischer et al., 2014, Stied et al., 2015). We initially quantified heterogeneity in the prevalence of term SGA, term LBW and mean birth weight across the districts and counties of Guangdong using the Cochran Q test ($P < 0.10$ represents statistically significant heterogeneity) and I^2 statistic (Higgins et al., 2002; Gasparrini et al., 2015). The results of heterogeneity tests confirmed great spatial heterogeneity for the markers of fetal growth across the study area (all $P < 0.10$ and $I^2 > 91\%$). Therefore, based on this prior analysis and the previous knowledge, we adopted the GEE approach to account for clustering of observations by treating births from the same district as repeated subjects in the GEE analysis (Stied et al., 2015). In the GEE setting, we estimated the associations between different exposures time windows of the air pollutants and birth outcomes. We used the procedure of PROC GENMOD in SAS statistical software, version 9.4 (SAS Institute, Cary, NC, USA) for developing the GEE model.

The GEE model was performed to examine the associations between air pollutant exposures and either relative odds of different birth outcomes (term SGA, or term LBW) or change in term birth weight. We fitted the GEE logistic regression to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for effect estimates of term SGA or term LBW associated with interquartile range (IQR) increments in air pollutant concentrations, and the GEE linear regression to estimate the change in birth weight associated with IQR increments in the concentrations. We calculated the effect estimates associated with IQR increments to assess the effects for comparable increases across different pollutants.

Single-pollutant models were established to estimate the associations between maternal exposure to air pollutants during pregnancy and risk of term SGA or birth weight. In the models for birth weight, we adjusted for maternal age ($<$ 35, or $\geq$ 35 years), maternal ethnicity (Han, or ethnic minority), maternal cigarette smoking status during pregnancy (yes, or no), mode of delivery (cesarean, or vaginal), gravidity (primigravida, or multigravida), year of conception, month of conception, neonate's sex (boy, or girl), gestational age (linear and quadratic terms) (Smith et al., 2017), and meteorological factors (ambient temperature and relative humidity), which may be associated with birth outcomes (Strand et al., 2011). Because the definition of SGA already considered infant sex and gestational age, we did not further adjust for these variables in the models for term SGA (Sun et al., 2019). We selected the covariates adjusted in the model based on previous knowledge (Smith et al., 2017; Guo et al., 2019; Sun et al., 2019). For estimating the associations between each trimester average exposure (TAE) to air pollution during pregnancy and infant health, a model with a single TAE without controlling for exposures in the other 2 trimesters causes biased estimates (Wilson et al., 2017). In this case, the other TAEs act as unmeasured confounders because they are also associated with the outcome. In fact, it arises from seasonal trends in air pollutants that induce correlations between TAEs (Wilson et al., 2017). Therefore, we adopted an interaction term for pollutant exposures multiplied by month of conception in our model to reduce bias for estimating the association between the TAEs and the birth outcome when controlling for exposures in the other periods of gestation. To identify potentially susceptible population, we also performed stratified analyses to evaluate possible effect modification by maternal age ($<$ 35, or $\geq$ 35 years) or neonate's sex (boy, or girl). Based on the DerSimonian-Laird method by calculating Q-statistics, we determined the heterogeneity of ORs or regression coefficients between the subgroups (Ryti et al., 2017).

Moreover, we carried out sensitivity analyses to examine the robustness of the results. First, we further included two pollutants in the model one by one to evaluate effects of air pollution on the markers of fetal growth. By fitting two pollutant adjusted models (in all combinations except for $PM_{2.5}$ and PM_{10}), we aimed to adjust for potential residual confounding by other pollutants and identify pollutants with robust effects. We didn't synchronously include $PM_{2.5}$ and PM_{10} in the same model because of their high correlation. The other factors adjusted for in co-pollutant models were consistent with those in single pollutant models. Second, we restricted the analyses to the Han nationality only. Third, we conducted additional analyses to assess the sensitivity of the results of the IDW algorithm. We added random perturbations to the determined optimal inverse distance weighting power M (by randomly adding a value from −0.5 to 0.5 at intervals of 0.1) and nearest observations numbers N (by randomly adding −1, 0, or 1). We evaluated whether the associations were disturbed by alternative specifications in the IDW algorithm. Fourth, we adjusted ambient temperature as a nonlinear term in the model, and a natural cubic spline with 4 *df* was used to control for trimester-specific mean temperature (Wang et al., 2018). Fifth, we conducted a sensitivity analysis by classifying term SGA using 10th percentile as the threshold of our data. Sixth, we restricted the births with gestational age < 40 weeks to examine whether varied gestational age influences our results substantially. Finally, we conducted sensitivity analyses to evaluate possible random errors on the exposure level and estimation of conception date (Lin et al., 2015). To examine the impact of potential misclassification of exposure caused by estimation of pregnancy date, we applied a Monte-Carlo simulation method through adding or subtracting zero to three-day random errors on the pregnancy date to investigate whether the results were robust.

3. Results

3.1. Baseline characteristics

Table 1 shows that the percentage of LBW and SGA infants was 2.3% and 13.7% among all term births, respectively. The average birth weight of term births was 3174 g. The average birth weight, percentages of term LBW or SGA births, and average exposure levels of pollutants during pregnancy by neonate's sex, birth season, birth year, maternal age, maternal ethnicity, maternal cigarette smoking status, mode of delivery, and gravidity are also depicted. Characteristics of the infants and distribution of pregnancy outcomes by city are shown in supplementary Table 1. The performance of the IDW algorithm in assessing air pollutant exposures were relatively high for PM_{10}, $PM_{2.5}$, O_3 and NO_2, and moderate for SO_2 and CO, with 10-fold cross validation R^2 ranging from 0.46 to 0.89 (supplementary Fig. 2). Table 2 shows that average exposure levels of pollutants during the entire pregnancy were positively correlated (0.16 to 0.93), except with O_3 (−0.09 to −0.64). For different gestational periods, there was a slight change in the direction of the correlation between O_3 and SO_2. Ambient CO concentrations were estimated from 2014 to 2017 in Guangdong province at 0.18° spatial resolution using the IDW algorithm (Fig. 1B). The spatial distribution of CO concentration presented the characteristics of higher in the western and northern parts of Guangdong province. The regional distribution of term SGA infants was observed to be correlated with that of the simulated ambient CO concentrations. The variations of other pollutants ($PM_{2.5}$, NO_2, O_3, PM_{10}, and SO_2) concentrations, meteorological factors, number of term LBW neonates and mean birth weight of term infants also revealed the heterogeneity in the spatial distribution (supplementary Fig. 3 to 5).

3.2. Air pollution and term SGA

Fig. 2 shows that in single-pollutant models, IQR increases in concentrations of air pollutants (CO, NO_2, O_3, PM_{10}, $PM_{2.5}$, or SO_2) during the entire pregnancy were associated with 3% to 4% increased odds of term SGA (e.g., OR = 1.04 (95% CI: 1.02, 1.05) for CO, and OR = 1.03 (95% CI: 1.01, 1.04) for $PM_{2.5}$). Fig. 2 also shows that in two air pollutant models, only CO pollutant consistently had ORs above one associated with term SGA when adjusted, in turn, for other air pollutants. Results in the second and third trimester were similar to those observed across the entire pregnancy (supplementary Figs. 6 to 8). For example, IQR increases in the exposure levels of CO in the second and third trimester were associated with 5% to 6% increased odds of term SGA in two air pollutant models, respectively. The O_3 pollutant also showed a marginally statistically significant effect on the increased risk of term SGA. In addition, increased odds of SGA were observed with first trimester-average PM_{10} exposures (supplementary Fig. 6).

Supplementary Fig. 15 shows the odds of term SGA associated with IQR increases in air pollutant concentrations during the entire pregnancy, stratified by potential modifiers (maternal age or neonate's sex). We only observed that maternal age had a border modification effect on the relationship between NO_2 exposure and SGA (P-value = 0.066). Results were similar across different scenarios of sensitivity analyses regarding to the variation of parameter value in the IDW algorithm, potential misclassification of exposure, Han ethnicity, ambient temperature adjusted as a nonlinear term in the model, the use of 10th percentile as the cutting point to determine term SGA or the varied gestational age (supplementary Fig. 17).

3.3. Air pollution and term LBW

Average exposure concentrations of air pollutants during entire pregnancy were not associated with higher odds of term LBW (Fig. 3). The slightly increased odds of 1.03 (95% CI: 0.99, 1.07) of term LBW tended to be associated with average exposure levels of CO, although the association was not statistically significant. For other air pollutants, average exposure concentrations during entire pregnancy were also not associated with the relative odds of term LBW. The results of LBW in single-pollutant models were consistent with those in two pollutants adjusted models. In addition, the assessment results of trimester-specific exposure were similar to those of entire pregnancy exposure (supplementary Figs. 9 to 11). A marginally statistically significant effect (OR = 1.04, 95% CI: 1.00, 1.08) of CO exposure on the increased risk of term LBW during the first trimester was observed. Overall, trimester-specific exposures to the pollutants were not statistically associated with higher odds of term LBW, which were consistent with the results of entire-pregnancy-exposure models.

We evaluated whether the associations between average exposure concentrations of air pollutants during entire pregnancy and term LBW varied across subgroups defined by maternal age or neonate's sex (supplementary Fig. 16). For O_3 exposure, we observed statistically significant heterogeneity across two groups defined by maternal age, with the strongest effect (OR = 1.25, 95% CI: 1.05, 1.48) appeared among pregnant women equal to or older than 35 years old. All sensitivity analyses suggested that the results were not disturbed by the variation of parameter value in the IDW algorithm, potential misclassification of exposure, Han ethnicity or the varied gestational age (supplementary Fig. 18). In addition, when adjusting ambient temperature as a nonlinear term in the model, the associations between the exposures to air pollutants and term LBW, as previously discovered, had not changed in essence (supplementary Fig. 18).

3.4. Air pollution and birth weight

Fig. 4 shows that in single-pollutant models, for per IQR increase of CO, O_3, PM_{10}, and $PM_{2.5}$ exposure levels over the whole pregnancy, there was 3.52 g to 7.78 g reduction in birth weight (e.g., −3.52 g (95% CI: −6.23, −0.81) for O_3, −5.93 g (95% CI: −8.36, −3.49) for $PM_{2.5}$, −5.95 g (95% CI: −8.01, −3.89) for CO, and −7.78 g (95% CI:

Table 1
Characteristics of the study population (n = 2,567,457) and distribution of pregnancy outcomes and air pollutant exposures.

Variable	Number	Mean term birth weight (g)	Term LBW (%)	Term SGA (%)	Average concentration during pregnancy					
					CO	NO_2	O_3	SO_2	PM_{10}	$PM_{2.5}$
Total population	2,567,457	3174	2.3	13.7	0.92	26.3	54.6	12.7	51.9	33.2
Neonate's sex										
Male	1,359,066	3225	1.7	13.5	0.92	26.3	54.5	12.7	51.9	33.2
Female	1,208,391	3117	2.9	14.0	0.92	26.3	54.6	12.7	51.9	33.2
Birth season										
Winter	780,388	3167	2.3	14.3	0.88	24.9	54.7	11.9	48.3	30.4
Spring	579,775	3187	2.1	12.6	0.92	24.3	55.7	13.2	50.4	31.7
Summer	583,698	3182	2.2	13.3	0.96	28.0	55.1	13.4	56.1	36.5
Autumn	623,596	3163	2.4	14.5	0.94	28.3	52.8	12.7	53.9	34.8
Birth year										
2014	510,407	3172	2.3	14.5	1.00	27.3	55.4	15.6	58.7	38.4
2015	856,434	3172	2.3	13.9	0.92	24.2	52.3	12.4	49.5	31.7
2016	995,349	3178	2.2	13.1	0.90	27.5	55.4	11.8	51.5	32.6
2017	205,267	3165	2.4	14.0	0.83	26.5	57.8	11.1	47.3	28.8
Maternal age (years)										
< 35	2,307,313	3168	2.3	14.2	0.92	25.9	54.8	12.8	51.9	33.1
≥35	260,144	3232	2.1	9.7	0.92	30.0	52.6	12.2	52.2	33.3
Maternal ethnicity										
Han	2,541,821	3174	2.3	13.7	0.92	26.2	54.6	12.7	51.9	33.1
Ethnic minority	25,636	3208	2.0	11.7	0.95	31.0	51.1	13.7	53.2	34.3
Maternal cigarette smoking status										
Yes	1536	3174	2.5	13.4	0.93	22.5	53.7	13.2	49.9	32.2
No	2,565,921	3174	2.3	13.7	0.92	26.3	54.6	12.7	51.9	33.2
Mode of delivery										
Cesarean	652,558	3228	2.3	11.0	0.92	28.7	53.1	12.8	52.5	33.6
Vaginal	1,914,899	3155	2.3	14.6	0.92	25.5	55.1	12.6	51.7	33.0
Gravidity										
Primigravida	896,948	3123	3.0	17.7	0.92	25.5	54.9	12.8	51.8	33.1
Multigravida	1,670,509	3202	1.9	11.6	0.92	26.7	54.3	12.7	52.0	33.2

SGA = small for gestational age; LBW = low birth weight (< 2500 g).
Three pregnancy outcomes were assessed including term birth weight, term birth of SGA and term birth of LBW.

−10.41, −5.16) for PM_{10}, respectively) among term births. Reduced term birth weight was consistently associated with the above-mentioned pollutants in the two air pollutant adjusted models. Results of trimester specific exposure models demonstrated that the reductions of birth weight attributed to $PM_{2.5}$ and PM_{10} exposures in the first trimester were stronger than those in second and third trimesters (supplementary figures 12 to 14). Conversely, per IQR increase of average exposure concentration in O_3 during the second or third trimester was associated with reduced birth weight, and the strongest effect occurred in the second trimester. Similarly, per IQR increase of

Table 2
Air pollutant exposures in different gestational period of the study population and their correlations.

Gestational period	Pollutant	Mean	SD	Max	75th	50th	25th	Min	IQR	CO	NO_2	O_3	PM_{10}	$PM_{2.5}$	SO_2
1st trimester	CO	0.94	0.13	2.44	1.03	0.94	0.85	0.37	0.18	1.00	0.39	−0.25	0.68	0.69	0.50
	NO_2	26.56	12.27	84.70	32.66	24.53	16.93	4.56	15.47		1.00	−0.51	0.62	0.58	0.21
	O_3	54.25	11.85	95.47	61.67	54.52	46.66	13.58	15.82			1.00	−0.03	−0.04	0.01
	PM_{10}	53.33	12.14	103.24	60.38	52.68	44.66	23.11	17.56				1.00	0.96	0.53
	$PM_{2.5}$	34.35	9.54	76.21	39.47	34.18	27.73	10.29	13.21					1.00	0.49
	SO_2	13.07	4.57	38.55	15.77	12.32	9.64	3.16	6.03						1.00
2nd trimester	CO	0.92	0.13	1.87	1.00	0.91	0.82	0.40	0.18	1.00	0.42	−0.22	0.75	0.77	0.51
	NO_2	26.12	12.35	86.61	32.14	24.27	16.44	4.60	15.94		1.00	−0.50	0.62	0.57	0.22
	O_3	54.34	11.39	94.06	61.89	54.15	46.87	13.97	14.79			1.00	−0.03	−0.04	0.02
	PM_{10}	51.52	12.48	103.37	59.01	50.50	42.73	18.88	17.42				1.00	0.96	0.55
	$PM_{2.5}$	32.79	9.78	76.63	38.63	32.36	25.84	8.58	13.58					1.00	0.51
	SO_2	12.69	4.38	38.55	15.46	11.93	9.30	3.15	5.90						1.00
3rd trimester	CO	0.90	0.13	1.66	1.00	0.89	0.81	0.41	0.19	1.00	0.42	−0.27	0.76	0.78	0.50
	NO_2	26.17	12.17	87.12	32.62	24.10	16.60	4.51	15.73		1.00	−0.50	0.60	0.55	0.21
	O_3	55.06	11.10	93.87	62.78	55.15	47.82	12.13	14.36			1.00	−0.07	−0.08	−0.02
	PM_{10}	50.98	11.83	104.16	59.00	49.99	42.55	18.49	16.29				1.00	0.96	0.54
	$PM_{2.5}$	32.36	9.28	75.19	38.67	31.88	25.54	8.29	13.18					1.00	0.50
	SO_2	12.43	4.07	38.67	14.98	11.78	9.30	3.22	5.61						1.00
Entire pregnancy	CO	0.92	0.09	1.73	0.98	0.92	0.86	0.50	0.12	1.00	0.25	−0.32	0.62	0.63	0.57
	NO_2	26.28	10.97	71.37	32.36	23.87	17.97	7.21	14.56		1.00	−0.64	0.59	0.53	0.16
	O_3	54.55	8.73	82.51	60.83	54.73	48.46	19.44	12.15			1.00	−0.26	−0.25	−0.09
	PM_{10}	51.93	7.47	82.13	56.92	51.80	46.68	31.59	10.63				1.00	0.93	0.60
	$PM_{2.5}$	33.16	5.51	53.90	36.48	32.97	29.29	15.84	7.60					1.00	0.58
	SO_2	12.73	3.85	33.28	15.29	12.01	9.83	4.34	5.36						1.00

SD = standard deviation; IQR = interquartile range.

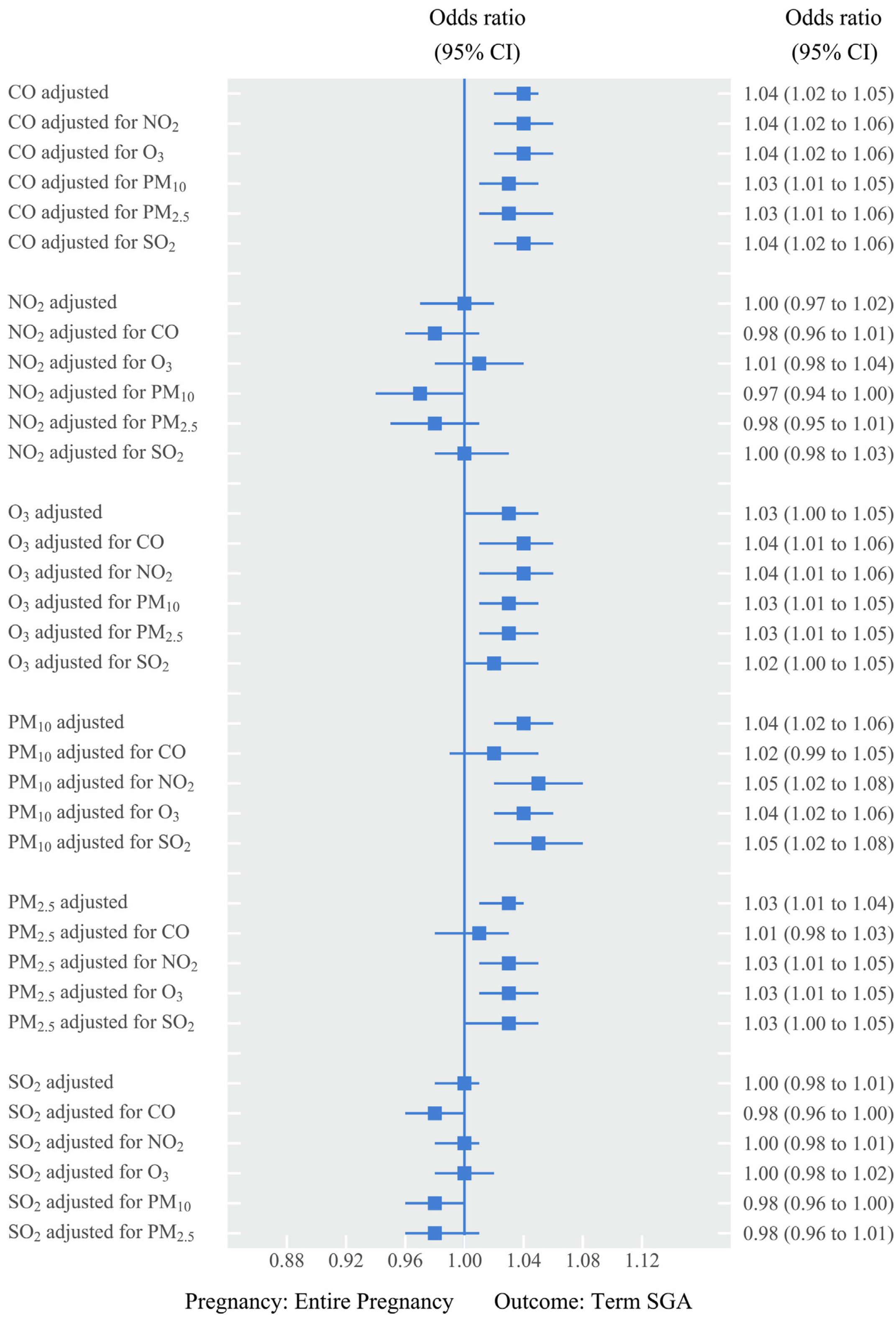

Fig. 2. Odds of term small for gestational age (SGA) associated with interquartile range (IQR) increases in air pollutant concentration during the entire pregnancy, in single and two air pollutant models. The odds ratios and corresponding 95% confidence intervals (CIs), rescaled to IQR increments specify to pollutants, were used to assess the overall effect of exposure during the period. Single pollutant models were adjusted for maternal age, maternal ethnicity, maternal cigarette smoking status, mode of delivery, gravidity, year of conception, month of conception, meteorological factors and an interaction term (pollutant exposures × month of conception). Adjusted models were adjusted for the variables considered in single pollutant models, in addition to including the air pollutant shown above. $PM_{2.5}$ and PM_{10} were not entered into the same model together as they were highly correlated.

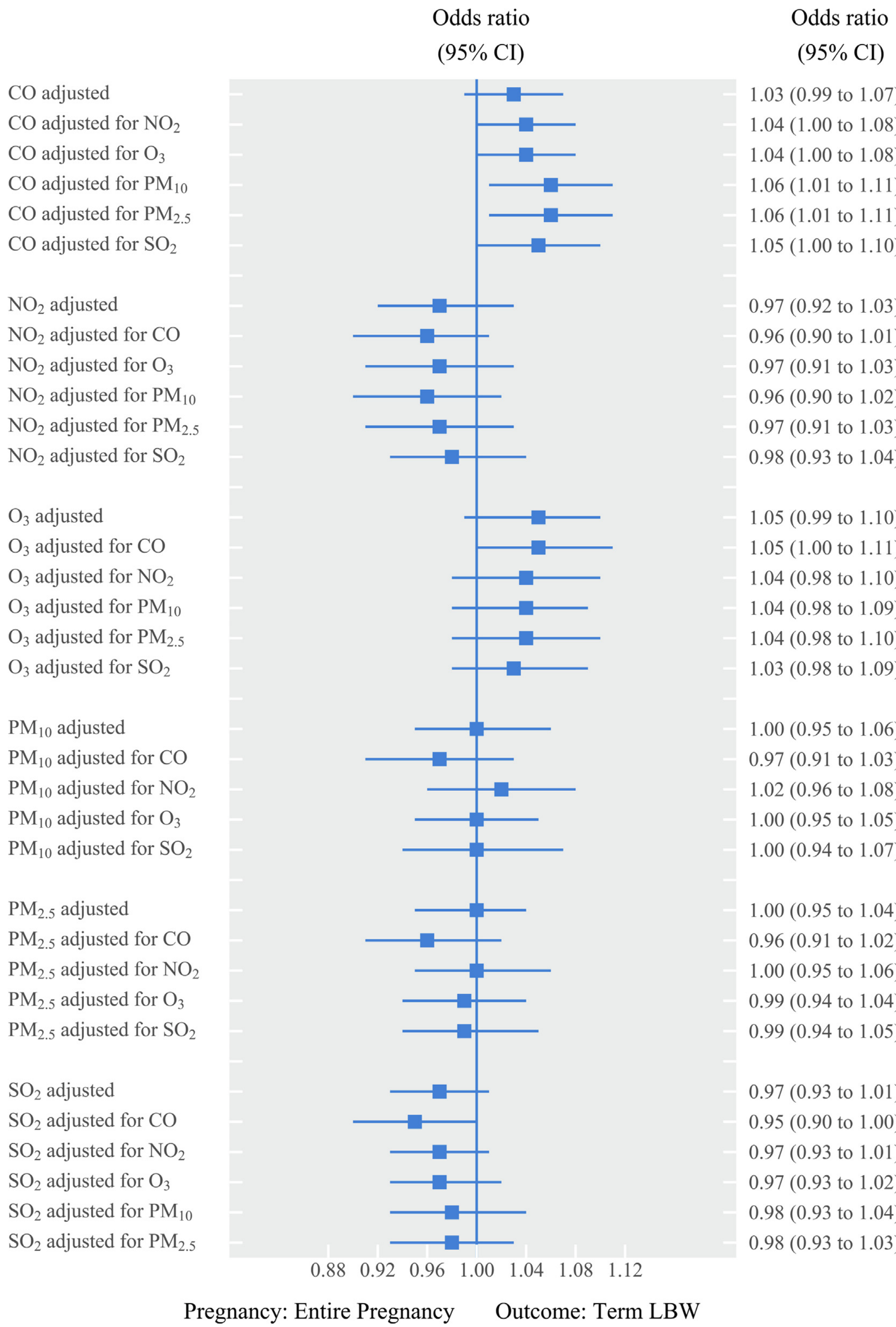

Fig. 3. Odds of term low birth weight (LBW) associated with interquartile range (IQR) increases in air pollutant concentration during the entire pregnancy, in single and two air pollutant models. The odds ratios and corresponding 95% confidence intervals (CIs), rescaled to IQR increments specify to pollutants, were used to assess the overall effect of exposure during the period. Single pollutant models were adjusted for maternal age, maternal ethnicity, maternal cigarette smoking status, mode of delivery, gravidity, year of conception, month of conception, neonate's sex, gestational age as linear and quadratic terms, meteorological factors and an interaction term (pollutant exposures × month of conception). Adjusted models were adjusted for the variables considered in single pollutant models, in addition to including the air pollutant shown above. $PM_{2.5}$ and PM_{10} were not entered into the same model together as they were highly correlated.

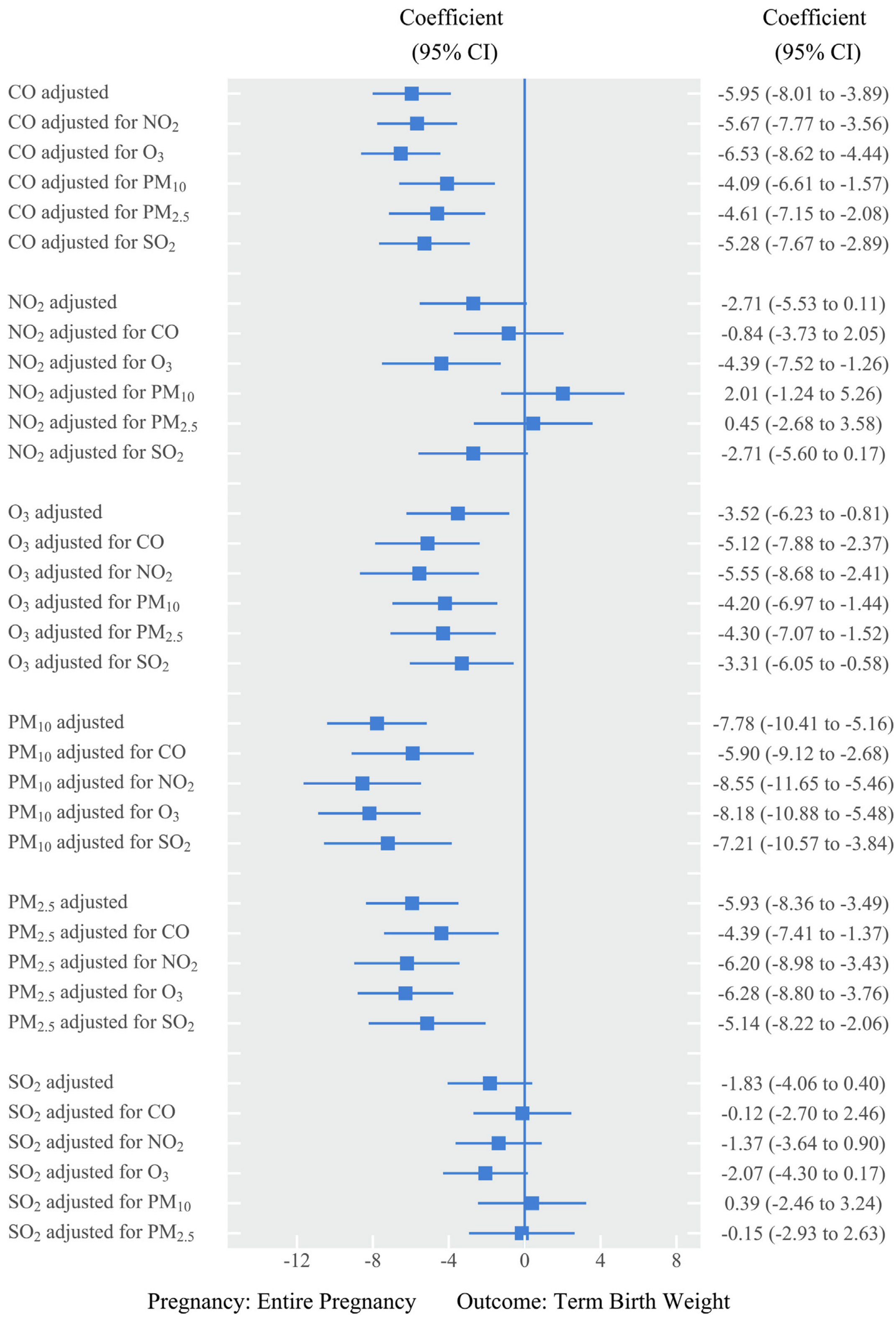

Fig. 4. The associations of term birth weight with interquartile range (IQR) increases in air pollutant concentration during the entire pregnancy, in single and two air pollutant models. The model regression coefficients rescaled to IQR increments specify to pollutants were used to assess the overall effect of exposure during the period. Single-pollutant models were adjusted for maternal age, maternal ethnicity, maternal cigarette smoking status, mode of delivery, gravidity, year of conception, month of conception, neonate's sex, gestational age as linear and quadratic terms, meteorological factors and an interaction term (pollutant exposures × month of conception). Adjusted models were adjusted for the variables considered in single pollutant models, in addition to including the air pollutant shown above. $PM_{2.5}$ and PM_{10} were not entered into the same model together as they were highly correlated.

Pregnancy: Entire Pregnancy Outcome: Term Birth Weight

Pollutants	Subgroup	Coefficient (95% CI)	P-value
CO	Sex		0.445
	Male	-6.72 (-9.60 to -3.84)	
	Female	-5.08 (-8.03 to -2.12)	
	Maternal age		0.871
	< 35	-6.07 (-8.24 to -3.91)	
	≥ 35	-5.48 (-12.34 to 1.38)	
NO_2	Sex		0.796
	Male	-2.41 (-6.34 to 1.52)	
	Female	-3.12 (-7.21 to 0.98)	
	Maternal age		0.148
	< 35	-1.44 (-4.36 to 1.49)	
	≥ 35	-7.66 (-15.56 to 0.24)	
O_3	Sex		0.929
	Male	-3.34 (-7.09 to 0.42)	
	Female	-3.62 (-7.55 to 0.32)	
	Maternal age		0.567
	< 35	-3.63 (-6.47 to -0.78)	
	≥ 35	-6.38 (-15.37 to 2.61)	
PM_{10}	Sex		0.472
	Male	-8.69 (-12.35 to -5.04)	
	Female	-6.76 (-10.54 to -2.97)	
	Maternal age		0.118
	< 35	-7.02 (-9.77 to -4.26)	
	≥ 35	-14.50 (-23.47 to -5.53)	
$PM_{2.5}$	Sex		0.039
	Male	-8.35 (-11.74 to -4.96)	
	Female	-3.20 (-6.70 to 0.30)	
	Maternal age		0.081
	< 35	-5.17 (-7.72 to -2.61)	
	≥ 35	-13.06 (-21.53 to -4.58)	
SO_2	Sex		0.454
	Male	-2.62 (-5.72 to 0.47)	
	Female	-0.92 (-4.14 to 2.31)	
	Maternal age		0.650
	< 35	-1.65 (-4.02 to 0.72)	
	≥ 35	-3.55 (-11.36 to 4.27)	

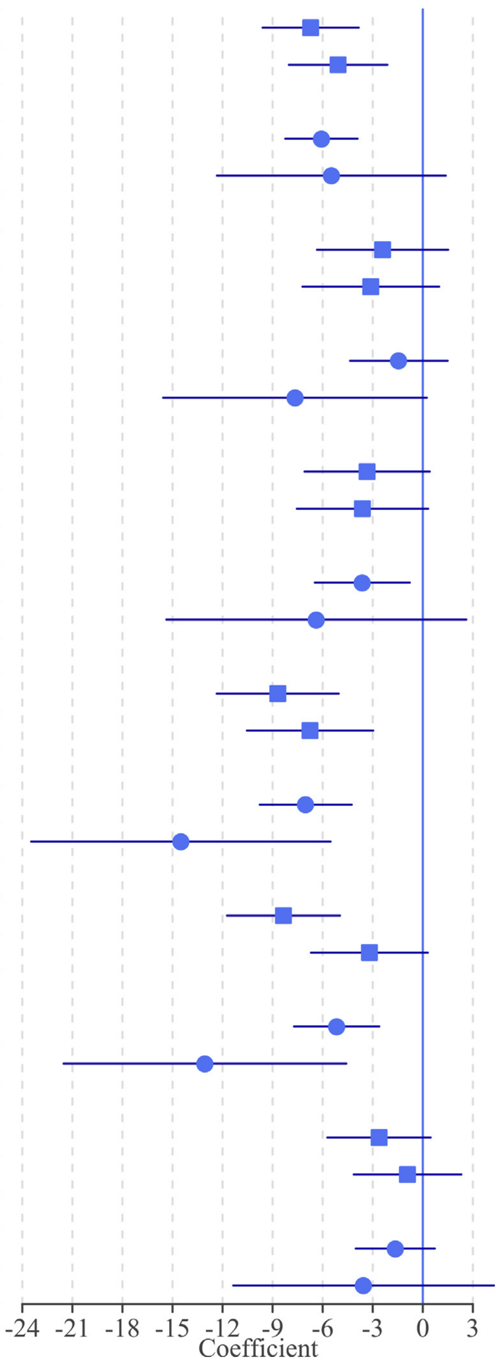

Fig. 5. The associations of term birth weight with interquartile range (IQR) increases in air pollutant concentration over the entire pregnancy, stratified by potential modifiers (maternal age or neonate's sex). The model's regression coefficients and corresponding 95% confidence intervals (CIs), rescaled to IQR increments specify to pollutants, were used to assess the overall effect of exposure during entire pregnancy in each subgroup. *P*-values for heterogeneity in the subgroups were estimated by using the DerSimonian-Laird method. Generalized estimating equation model were adjusted for maternal age, maternal ethnicity, maternal cigarette smoking status, mode of delivery, gravidity, year of conception, month of conception, neonate's sex, gestational age as linear and quadratic terms, meteorological factors and an interaction term (pollutant exposures × month of conception).

average concentrations in CO during the second trimester was associated with the largest reduction of birth weight (supplementary Fig. 13).

We also evaluated whether reduced term birth weight varied according to the defined subgroups during the entire pregnancy (Fig. 5). Results of $PM_{2.5}$ stratified by infant sex showed that the largest reduction (−8.35 g, 95% CI: −11.74, −4.96) in term birth weight was observed among male infants. Although it was not statistically significant (*P*-value = 0.081), a boundary modification effect of maternal age on the association between $PM_{2.5}$ exposure and reduced term birth weight was observed. We did not observe heterogeneity in the associations between reduced term birth weight and the exposures to other pollutants across different subgroups defined by maternal age or infant sex. Results were not materially different across sensitivity analyses (supplementary Fig. 19).

4. Discussion

4.1. Key findings

Our study included around 2.57 million singleton term live-births across 123 districts and counties in China. To our knowledge, this is the largest population-based study performed in China so far, concerning the associations between maternal exposure to different air pollutants during pregnancy and multiple markers of fetal growth. By using home permanent addresses, we estimated personal-adjusted condition of air pollutants for pregnant women. We found that average exposure concentrations of CO during the entire pregnancy were associated with lower fetal growth as evidenced by higher risk in term SGA and the decrement in term birth weight. These associations occurred steadily in the second and third trimesters of pregnancy. Per IQR increase of O_3, $PM_{2.5}$, and PM_{10} during the entire pregnancy was significantly associated with a decrement of 3.52 g, 5.93 g, and 7.78 g in birth weight, respectively. Our findings add the evidence that maternal exposure to ambient air pollution during pregnancy is associated with lower fetal growth.

4.2. Exposures to air pollutants and term SGA

Previous studies have reported the risks of preterm delivery associated with prenatal exposure to ambient air pollutants (Ritz et al., 2000; Leem et al., 2006). Although some studies have supported small effects of ambient air pollution on SGA (Maisonet et al., 2004; Brauer et al., 2008), evidence is still limited on the impact of long-term exposures to air pollution on term birth of SGA. In addition, it is important for targeting public health interventions to identify critical periods of susceptibility during pregnancy. Our study established trimester specific models to examine the impact of ambient air pollution on birth outcomes. This study showed term SGA births were predominant in all SGA births, and the number of term SGA births was far greater than that of preterm SGA births (data not shown), indicating that it was vital to study the relationship between air pollution exposure and term SGA. We found a statistically significant association between CO exposure and term SGA, which was consistent with a previous study (Le et al., 2012). The study of 164,905 singleton births in Detroit, Michigan occurring from 1990 to 2001 reported that CO was positively associated with term SGA for all exposure windows used in single pollutant models (Le et al., 2012). However, a previous study in Brisbane, Australia found that trimester-specific exposures were not significantly associated with an increased risk of term SGA (Hansen et al., 2007). It is noteworthy that, according to Hansen et al., Brisbane's average concentrations of air pollutants (e.g., average of PM_{10} 19.6 $\mu g/m^3$, IQR 14.6–22.7) in Brisbane (Hansen et al., 2007) were quite different from our research (e.g., average of PM_{10} 51.9 $\mu g/m^3$, IQR 46.7–56.9). These differences may partly contribute to the disparity in the studies. In view of China's growing level of industrialization and the identified adverse effects of ambient air pollutants, it is necessary to pay more attention to the term birth of SGA related to air pollution. In particular, we found that the estimated prevalence of SGA in term infants in Guangdong was higher than the rate estimated by a retrospective study in 14 provinces and autonomous regions in China (Chen et al., 2017). We speculate that this may be due to that fetal-growth is relatively small in Guangdong, compared to whole nation. It suggests that in addition to air pollutant exposures, other factors causing the relatively high prevalence of SGA cannot be ignored in the study area.

If the causal relationships between adverse pregnancy outcomes and air pollutants are identified, a research priority will be to determine the critical time point of pregnancy that is susceptible to air pollution exposure (Dugandzic et al., 2006). In the study we didn't observe term SGA was statistically associated with NO_2, SO_2, or O_3, in either entire-pregnancy or trimester-specific exposure models. However, the results suggested that the first trimester PM_{10} exposure had the strongest impact on term SGA, which was consistent with a recent population-based cohort study in London (Smith et al., 2017). We also found that $PM_{2.5}$ exposures in the first trimester increased the risk of term SGA, but the border effect (OR = 1.03, 95% CI: 1.00, 1.06) after controlling for CO in the model was observed (supplementary Fig. 6). According to the findings of Smith et al., an elevated risk of term SGA was also associated with $PM_{2.5}$ exposure of the first trimester (Smith et al., 2017). China still lacks large-scale population studies to investigate the association between maternal exposure to air pollution during pregnancy and fetal growth. A recent study suggested that prenatal exposure to high concentration of PM_{10} increased the risk of abnormal fetal growth, based on data of 8877 pregnant women from 2010 to 2012 in Lanzhou, China (Zhao et al., 2018). In addition, a more recent Chinese study indicated that a 10 $\mu g/m^3$ increment in $PM_{2.5}$ concentration was related to premature SGA in the whole gestation (Li et al., 2019). Our findings revealed the adverse impact between maternal exposure to air pollution and term SGA, and contributed to understand the extent of the hazard impact of particular pollutants and critical exposure-periods of susceptibility during pregnancy. In general, SGA is regarded as a failure of a fetus that is unable to realize its genetic growth potential because of lack of nutrition (Jan et al., 2011), and both short- and long-term macro and micronutrient status of women of childbearing age is thought to mainly affect SGA (Christian et al., 2014). In particular, SGA was found to be associated with higher risk of brain dysfunction, neurodevelopment impairment, renal function impairment and somatic growth failure in fetuses (Baschat et al., 2004; Cosmi et al., 2011; Yalin et al., 2016). Nutritional intervention in women of childbearing age before and during pregnancy may be an effective strategy to improve the adverse consequences of SGA.

4.3. Exposures to air pollutants and birth weight

We found that prenatal exposure to air pollution during the entire pregnancy was not associated with risk of term LBW, but they were associated with a small decrement in birth weight at term. Our results suggest modest-magnitude associations between reduced birth weight and pollutants of CO, O_3, PM_{10}, and $PM_{2.5}$ in this study. Our results of associations between air pollution and a reduction of birth weight were supported by a number of previous studies performed in different countries (Mannes et al., 2005; Geer et al., 2012; Dadvand et al., 2013). For example, a study across 14 centers from 9 countries (Dadvand et al., 2013), which used a random-effects *meta*-analysis, found that per increase of 10 $\mu g/m^3$ in PM_{10} exposure during the whole pregnancy was associated with reduced term birth weight (−8.9 g, 95% CI: −13.2, −4.6). The result was consistent with our study. Another study reported that per 12 PPB (part per billion) increase in average O_3 concentration over the entire pregnancy was associated with 47.2 g reduction (95% CI: −27.4, −67.0) of birth weight, which was the most robust for exposures during the second and third trimesters (Salam et al., 2005). Our result was in agreement with the finding of exposure to O_3 during the second and third trimesters associating with a lower birth weight for term neonates. Additionally, our results were supported by a previous study indicating that maternal exposure to $PM_{2.5}$ was associated decreased birth weight after adjustment for co-pollutants (Li et al., 2019) from Ningbo city, China. However, our study also has some inconsistent findings with the results they reported. For example, we didn't identify the adverse effect of SO_2 on birth weight. One potential explanation for this is that there are differences in the concentrations and emission source of specific air pollutants between the two regions. For the adverse perinatal outcome of LBW, a prior study

(Fleischer et al., 2014) indicated that outdoor air pollutants' concentrations were positively associated with LBW, whereas our study failed to find that association. In particular, our study demonstrated a modest worsening of fetal growth metrics with increased exposure to air pollutants, and indicated that maternal exposure to ambient air pollution results in lower birth weight for term neonates.

Our findings of an effect of $PM_{2.5}$ and PM_{10} with the first trimester exposure were supported by previous studies suggesting that early pregnancy exposures might be the critical time point (Lee et al., 2003; Liu et al., 2003). Although likely multifactorial, one suggested mechanism for reduced birth weight is the transplacental exposures to the polycyclic aromatic hydrocarbons (PAH) component of PM in ambient air in early pregnancy (Perera et al., 1998). Furthermore, our study suggests that reduced infant birth weight consequent upon maternal exposure to CO and O_3 during the latter part of the pregnancy. It was consistent with the finding that babies whose mothers exposed to higher levels of ambient CO during the last trimester of pregnancy tended to have lower birth weight (Ritz et al., 1999). Some biological mechanisms that CO might influence birth weight have been discussed. Boy et al. suggested that once CO is inhaled, it crosses the placental barrier and combines with hemoglobin to form carboxyhemoglobin, which is a more stable compound that does not easily release O_2 to fetuses (Boy et al., 2002). This process may have detrimental effects on intrauterine growth for the fetuses. More studies are needed to shed light on the direct toxic effects of CO in future. Our study exhibited modest decreases in birth weight ranging from 3.5 g to 7.7 g per IQR increases in individual pollutants. Our study result was in agreement with the finding from a study indicating maternal exposure to ambient air pollution results in modestly lower birth weight in term infants in California (Morello-Frosch et al., 2010). In addition, the effects due to ambient air pollution exposures were generally smaller than other exposures, such as smoking and indoor wood fuel use. For example, England et al. found that the mean birth weight of infants of smokeless tobacco users was reduced by 331 g in infants of smokers (England et al., 2012). Although the effect was less than many other exposures, such as smoking, precautionary efforts to reduce pollutants may be beneficial for infant health from a population perspective, in particular when the ubiquity of air pollution exposures and the potential increase in the level of air pollutants related to sustainable industrial development in China were considered.

4.4. Effect modification

Our study determined whether the relationship between maternal exposure to air pollution and fetal growth was modified by maternal age or infant sex. This is because some populations may have disproportionate burdens from air pollution caused by elevated susceptibility of pollutants due to maternal characteristics. In our study a border effect modification (P-value = 0.066) by maternal age of the relation between NO_2 exposure and term SGA was observed. The risk of term SGA attributable to NO_2 exposure was slightly greater among pregnant women of advanced age ($\geq$35 years). In addition, we found that women of advanced age at pregnancy had a greater increase in risk of term LBW due to O_3 exposure (P-value = 0.040), indicating that there was a significant interaction between older maternal age and O_3 exposure for birth weight. In general, our results of maternal age as an effect modifier for the impact of maternal air pollution exposure on adverse pregnancy outcomes were in accordance with the findings of a prior study (Han et al., 2018). Our results suggested that the impact of maternal exposure to $PM_{2.5}$ on the risk of term LBW did not differ by infant sex or maternal age (Ng et al., 2017). In addition, our results were consistent with a previous study, which found no interaction between infant sex and maternal exposure to nitrogen oxides on the risk of term LBW or SGA (Franklin et al., 2019). Male infants in previous studies have been identified as a group at high risk for reduced birth weight in association with air pollutant effects (Lakshmanan et al., 2015). Similar sex-specific modification effects were also observed in our study. Our study demonstrated that infant sex was an effective modifier on the relationship. The effects of maternal exposure to $PM_{2.5}$ on term birth weight were differential for infants of different genders. The relationship between $PM_{2.5}$ exposure and reduced birth weight was most pronounced in male infants. In general, effect modification by maternal age or infant sex reflects the elevated susceptibility to the adverse effects of air pollution as a result of differing biological susceptibility, disparity of individual behavior, and environmental inequality (Smith et al., 2017). Early evidence suggests that utero-placental dysfunction is a biological mechanism for susceptibility to fetal growth restriction with advanced maternal age (de Vries et al., 2012; Lean et al., 2017). It provides the biological plausibility of effect modification by maternal age of the relation between air pollution exposure and reduced fetal growth.

4.5. Implication for interventions

This study focused on the impacts of ambient air pollution on markers of fetal growth that contributed to a better understanding of the vulnerable time periods during pregnancy and ability to design interventions at the policy and personal levels. We found that maternal exposures to ambient air pollution are positively associated with lower fetal growth. There was heterogeneity among prior studies for the association between maternal exposure to ambient air pollution and reduction of fetal growth. Some studies showed that the heterogeneity among researches could be partially explained by the differences in population characteristics, study design, sample size, exposure assessment method used, number of pollutants examined, socio-economic condition and climatic conditions (Stieb et al., 2012; Sun et al., 2019). Although some heterogeneity was observed existing among prior studies for the association, the ubiquity of air pollution exposures, relatively high levels of the pollutants, exposure of very large numbers of pregnant women, and potential toxic effects of short-term or long-term exposure on human body implies that the benefit for infant health could be very substantial when taking preventive measures to reduce pollutants. Although there are gaps in our knowledge of the underlying physiologic mechanisms by which air pollution may affect fetal growth, there will be implications for individuals and regulators to take effective interventions. Pregnant women can benefit from legislation on air pollution prevention and control reducing their exposure to potentially harmful pollutants (Requejo et al., 2013). Where affordable, policy needs to actively support the transition of clean fuels from solid fuels to reduce the air pollution-related risk of adverse pregnancy outcomes in the population (Bruce et al., 2013). Because the nutritional status of pregnant women has an impact on fertility that cannot be ignored, nutritional intervention in women before and during pregnancy may effectively improve the consequences of adverse reproductive health outcomes. Moreover, targeted strategies, such as wearing a breathing outdoors, especially on high pollution days or adding an air ventilation system indoors should be adopted to reduce personal exposure levels of air pollution for pregnant women.

4.6. Strengths and limitations

The principal strength of this study was the size of the cohort with more than 2.5 million singleton term live-births from 123 districts across Guangdong province. A considerably large sample size provided sufficient statistical power for exploring the relationship between air pollution and fetal growth. In addition, air pollution exposures were estimated based on actual home addresses of mother recorded prior to conception, pregnancy follow-up, and postpartum follow-up records, which provided accurate estimates of individual exposure levels and helped minimize potential exposure misclassifications due to mother mobility. Another strength of our study was to assess individual exposure levels of air pollutants using inverse distance weighted average concentrations at all nearest monitoring stations of each mother' actual home addresses. By contrast, many previous studies frequently used air pollutant concentrations averaged across a city to represent an individual's actual exposure to pollutants, which did not account for variations in pollutant concentrations across a city. Furthermore, several sensitivity analyses were performed to examine the robustness of the results. Our results from two pollutant models suggested that the associations between maternal ambient air pollutants and markers of fetal growth did not change materially after adjustment for other pollutants. The results were not materially different across sensitivity analyses in relation to the varied parameters in IDW algorithm, potential misclassification of exposure or restricted subgroup of Han's ethnicity. Our study suggested that maternal exposure to ambient air pollution during pregnancy tended to decrease fetal growth. We identified that the effects of ambient air pollutants were more pronounced in certain periods of pregnancy.

Nonetheless, we acknowledged several limitations of this study. First, although the IDW-based spatial interpolation method was believed to provide accurate estimates of individual-level exposures, there was a tradeoff to choose an optimal combination of the two main parameters (inverse distance weighting power and nearest observations numbers) in the approach. A relatively large range of initial value of the parameter for the grid search means that there is a greater probability of getting the global optimal value and produce better exposure estimate, while this can increase the time of computing. Considering that the amount of data we analyzed was very large, we chose a reasonable range of initial value of the parameter and then determine the optimal combination using 10-fold cross validation. In this study, the performance of exposure assessments for all air pollutants was generally high or moderate. However, the performance of the exposure assessment for CO needed to be further improved. We should look cautiously at the validation result of CO. Second, although this study included a large number of ground-level monitors of air pollutants across Guangdong province, the exposure misclassification due to the spatial distance between ground-level monitors and air pollutant emission sources may also have an impact on the results of the IDW approach. Third, residual confounding by potential misclassification of exposures cannot be ruled out. Micro-environmental factors might cause bias in exposure assessment, for example, the indoor and outdoor activity patterns, time staying next to the vehicle, personal habits of using wood-burning stoves and passive inhalation of secondhand smoke (Clayton et al., 1993). Potential exposure misclassification due to mobility may also influence the associations because exposure misclassification was likely occurring without tracking personal behavior pattern. Fourth, although we adjusted for a wide range of covariates, we cannot eliminate the possibility of residual confounding from other factors. For example, personal information of socioeconomic status was not obtained and controlled for in the models, which may also have an impact on the magnitude of the associations for the pollutants. Fifth, due to the relatively large sample, we cannot eliminate the possibility that hospital staff or pregnant women accidentally reported inaccurate information (Guo et al., 2019). Last, our analysis was based on a large sample across 123 districts and counties, and in order to account for the nested structure of the data when estimating the impact of ambient air pollution on birth outcomes (Fleischer et al., 2014), we used the GEE model to obtain reliable effect estimates. However, bias may be introduced without methodologically taking into account the varying gestational age in the model. Additional analysis of LBW or SGA using the time-to-event approach (Chang et al., 2012; Chang et al., 2015) to examine effects of exposure may be informative. We should also cautiously extrapolate the results of this present study to other countries with different exposure levels and profiles, as well as ethnic backgrounds.

5. Conclusions

In this study of a large sample size (> 2.5 million term births), we found a relationship between maternal exposure to ambient air pollution during pregnancy and risk of term SGA and changes in birth weight, both of which are vital markers of fetal growth. We found that maternal exposure to CO during the entire pregnancy was significantly associated with lower birth weight and higher risk of term SGA, and the harmful effects of CO exposure were most pronounced during the later pregnancy. In addition, we found PM_{10} exposure during the first trimester increased odds of term SGA. The results suggest CO, O_3, PM_{10} and $PM_{2.5}$ could be risk factors associated with birth weight reduction of newborns in Guangdong province of China; however, the current levels of the pollutants were not the risk factor to increase the chance of LBW among term infants. Moreover, our results gave a clear indication as to which trimester could be most influential with respect to air pollution and fetal growth. In view of the ubiquity of air pollution exposures as well as the spatial heterogeneity of air pollution in China, our results have important clinical and public health implications. Further studies are warranted to integrate these findings and take effective interventions in pregnancy. And promoting environmental health policy to reduce ambient air pollutants may be beneficial for fetal growth.

CRediT authorship contribution statement

Pi Guo: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing - original draft, Writing - review & editing. **Yuliang Chen:** Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Writing - original draft, Visualization. **Haisheng Wu:** Data curation, Formal analysis, Methodology, Software, Validation. **Jing Zeng:** Investigation. **Zhisheng Zeng:** Investigation. **Weiping Li:** Formal analysis. **Qingying Zhang:** Formal analysis. **Xia Huo:** Writing - review & editing. **Wenru Feng:** Investigation, Methodology. **Jiumin Lin:** Writing - review & editing. **Huazhang Miao:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing - original draft, Writing - review & editing. **Yingxian Zhu:** Conceptualization, Investigation, Project administration, Resources, Supervision, Writing - review & editing.

Declaration of Competing Interest

None.

Acknowledgements

We thank China National Meteorological Data Service Center and PM25.in platform for providing open monitoring data of meteorological factors and air quality. We thank the editor and the three anonymous reviewers for their professional suggestions which have greatly improved the manuscript.

Funding

The study was funded by the National Natural Science Youth Fund of China (No. 81703323). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105410.

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