

Acute effects of air pollutants on adverse birth outcomes in Changsha, China

A population data with time-series analysis from 2015 to 2017

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Abstract

Evidence for the acute effects of air pollutants on adverse birth outcomes is not yet conclusive. Furthermore, there are no investigations relating to the association between air pollutants and macrosomia. The aim of this study was to determine the relationship between air pollutants and low birth weight, preterm birth, and macrosomia in Changsha. Time-series analysis, using a generalized additive model was applied. Data about the adverse birth outcomes was collected from 78 midwifery institutions. Air pollution data including SO₂, NO₂, particulate matter <10 μm in diameter (PM₁₀), particulate matter <2.5 μm in diameter (PM_{2.5}), O₃, CO, and climate data were respectively collected from the Changsha Environmental Protection Agency and the Changsha Meteorological Bureau from January 2015 to December 2017. During the study period, there were 344,880 live births to be studied. In a single pollutant model, for every increase of 10 μg/m³ in PM₁₀ and PM_{2.5}, low birth weight increased by 0.12% (95% confidence interval [CI]: 0.01–0.23%) at a lag 06 and 0.44% (95% CI: 0.35–0.53%) at a lag 3, respectively. Preterm birth increased most by 1.60% (95% CI: 1.41–1.80%) at a lag 2 for every increase of 10 μg/m³ in SO₂. The highest increases in macrosomia associated with a 10 μg/m³ increase in air pollutant were 3.53% (95% CI: 3.41–3.64%) for NO₂ at lag 0, 3.33% (95% CI: 3.05–3.60%) for SO₂ at lag03. Multi-pollutant models showed that only PM₁₀ increased the low birth weight and preterm birth risk effect by 3.91% (95% CI: 3.67–4.12%) and 0.25% (95% CI: 0.14–0.37%). NO₂ increased macrosomia risk by 4.14% (95% CI: 3.97–4.31%) with a 10 μg/m³ increase. There was no association observed between the air pollutants O₃ and CO and adverse birth outcomes. Pregnant women should also take steps to limit their exposure to high levels of air pollutants during the final weeks of pregnancy.

Abbreviations: CI = confidence interval, CO = carbon monoxide, LBW = low birth weight, μg/m³ = micrograms per cubic meter, mg/m³ = milligrams per cubic meter, NAQS = national ambient air quality standard, NO₂ = nitrogen dioxide, O₃ = ozone, PM₁₀ = particulate matter <10 μm in diameter, PM_{2.5} = particulate matter <2.5 μm in diameter, RR = relative risk, SD = standard deviation, SO₂ = sulfur dioxide.

Keywords: air pollutants, low birth weight, macrosomia, preterm birth, time-series

1. Introduction

Preterm birth, defined as <37 weeks of gestations, is the 2nd largest direct cause of child deaths among children under 5 years.^[1] Preterm birth is associated with neonatal mortality and morbidity and can cause long-term adverse health consequences in life.^[2] Low birth weight (LBW), defined as a fetal birth weight <2500 g, is a most important predictor of neonatal mortality and

is associated with higher risk of infant and childhood mortality and other health problems.^[3]

Preterm birth and LBW weight have gradually become the focus of environmental epidemiology in recent years. A range of global studies have shown that exposure to air pollutants is linked to preterm birth and LBW.^[4–8] In China, there is also increasing evidence that exposure to ambient air pollutants is associated with them.^[9–13] However, the findings from western countries may not be adaptive to the county of China in which air pollutants have become an alarming problem coincident with rapid industrialization and urbanization over recent years. In addition, the relevant researches in China showed inconsistent conclusions on the association between air pollutants and preterm birth and LBW.

Macrosomia, defined as a fetal birth weight equal to or greater than 4000 g, irrespective of gestational age, is a serious public health problem worldwide due to its increasing prevalence and adverse influences on maternal and neonatal outcomes.^[14,15] The causes of macrosomia are complex, inconclusive, and difficult to interpret.^[14] However, no previous study has examined the association between maternal exposure to air pollutants and macrosomia. Studies have proved that air pollutants can change endothelial function, trigger inflammation, and insulin resistance, and are also associated with an elevated risk of hypertension.^[16,17] Air pollutants may also adversely affect blood lipid levels, which in turn, may influence blood pressure.^[18,19] Maternal serum triglyceride and high-density lipoprotein

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cholesterol levels at late gestation were related to macrosomia in women without diabetes mellitus.^[20] What is more, a recent systematic review of 200 previously published studies showed that air pollution was associated with a greater risk of type 2 diabetes mellitus.^[21] Similarly, ongoing research suggests that exposure to air pollution during pregnancy may be related to abnormal glucose regulation and the incidence of gestational diabetes mellitus among pregnant women.^[22,23] Maternal diabetes mellitus is one of the risk factors for macrosomia. These results indicated that there is association between air pollutants and macrosomia. To confirm our speculation, our present study demonstrated the association between air pollutants and macrosomia and addressed more than just LBW and preterm birth.

Daily time-series analysis is commonly used to evaluate the short-term effects of air pollutants and adverse birth outcomes.^[9,24,25] Time-series studies offer the additional advantage of being able to establish associations in which individual exposure factors that remain unchanged over time pose no bias.^[26] Furthermore, no similar studies previously published have used actual population data. Therefore, our study was based on specific population data sourced from 78 midwifery medical facilities in Changsha city in Hunan province.

The characteristics of air pollutants vary in different ways across different regions. Changsha, the capital city of Hunan province, is the economic, financial, cultural, and educational center of Hunan province. Although Changsha has experienced serious air pollution over the past few years as a result of drastic urbanization and industrial expansion, a number of appropriate measures such as low-carbon transportation and a legislation put to ban the use of fireworks for entertainment in rural and urban areas. Most previous studies focused on heavily polluted areas, such as Shanghai and Guangzhou.^[9,11] Associations between air pollutants and health topics in the central cities of China have received far less research attention. Therefore, this study aimed to evaluate the risk of adverse birth outcomes and its relationship with air pollutants in Changsha based on population data between 2015 and 2017.

2. Materials and methods

2.1. Air quality and meteorologic data in Changsha city

Changsha is located in the middle of China (28°12'N, 112°59'E), the capital of Hunan province, with an area of 11,820 km² and a population of 7.31 million. Changsha has a subtropical humid monsoon climate.

The daily concentrations of ambient air pollutants including sulfur dioxide (SO₂), nitrogen dioxide (NO₂), particulate matter <10 μm in diameter (PM₁₀), particulate matter <2.5 μm in diameter (PM_{2.5}), ozone (O₃), carbon monoxide (CO) from 2015 to 2017 were obtained from Changsha Environment Protection Bureau. There are 12 fixed monitoring stations distributed in 9 administrative areas in Changsha, which collect 24-hour average concentration for NO₂, SO₂, PM₁₀, PM_{2.5}, CO, and 8-hour mean concentrations of O₃ from 10:00 to 18:00. All of the air pollutants measured by the unit of milligrams per cubic meter (mg/m³), except CO, which was measured in the unit of micrograms per cubic meter (μg/m³). Daily meteorological data (temperature, atmospheric pressure, wind speed, and relative humidity) during the same period were obtained from the Changsha Meteorological Bureau. Daily values for temperature,

atmospheric pressure, wind speed, and relative humidity were calculated by averaging 24 hourly monitoring data.

2.2. Data collection for birth outcomes

The delivery information for pregnant women in all midwifery institutions in the Changsha area (N=78) was recorded in an electronic system developed by Hunan Province Maternal and Children Hospital. Because the medical certificate of birth for every new-born was based upon birth record information in the system, all information was complete and correct. Using these records, we collected a range of data for all new-borns during our study period, including birth weight, the number of gestational weeks at delivery, the birth outcomes (live births, stillbirths, and deaths within 7 days). To facilitate comparisons between the results of our study and those published in literature, we defined a birth weight <2500 g from the live births as LBW, a birth weight more than 4000 g as macrosomia, and a gestational week at delivery of 37 weeks as preterm birth. We had an initial pool of 348,044 birth records in Changsha city between January 1, 2015 and December 31, 2017, which included the permanent delivery pregnant women in Changsha. Further exclusions were made for stillbirths (N=51), dead fetuses (N=2717), deaths occurring within 7 days of birth (N=97), and extreme gestational ages above 42 weeks (N=299). Ultimately, we had 344,880 births to include in our final analyses (Fig. 1).

The study protocol was reviewed and approved by the Health Department of Hunan Province and the Institutional Review Board at Hunan province maternal and children hospital (2017-S010).

2.3. Statistical analysis

We used Microsoft Excel to establish our database. Poisson regression, using a generalized additive modeling technique, was used to analyze the associations between daily mean ambient air pollutant concentration and daily birth outcomes. The model was defined by the following equation:

$$\text{LogE}(Y_t) = \alpha + \text{Dow} + \beta X_t + S(\text{time}, \text{df}) + S(Z_t, \text{df})$$

In this equation, t refers to the day of the observation; Y_t is the observed daily birth outcome counts on day t ; $E(Y_t)$ is the expected daily birth outcomes count on day t ; α is the intercept; Dow is dummy variable for day of the week; β represents the regression coefficient for each air pollutant; X_t represents air pollutant concentrations at day t ; S is the smoothing spine function for nonlinear variables and Z_t represents meteorologic data at day t . The degrees of freedom were then selected according to the minimum value of the Akaike information criterion.^[27] In the final model, $S(\text{time}, \text{df})$ with 5 degrees of freedom for time was used to adjust the time trend,^[28] $S(Z_t, \text{df})$ with 3 degrees of freedom were used for all meteorological factors to adjust the effects of whether. The lag effects of air pollutants on birth outcomes were explored from the current day (lag 0) up to 7 days before (lag 7). We also used 2-day to 8-day (from lag 01 to lag 07) moving mean values of air pollutant concentrations to further describe the association. Additionally, to evaluate the stability of pollutant effects, a multi-pollutant model was adopted to assess the confounding effects for all pollutants. All statistical analyses were performed with R V.3.4.3 using the MGCV package (version V.1.8–17, <http://www.r-project.org>). All results were presented as the percentage change in the relative risk (RR)

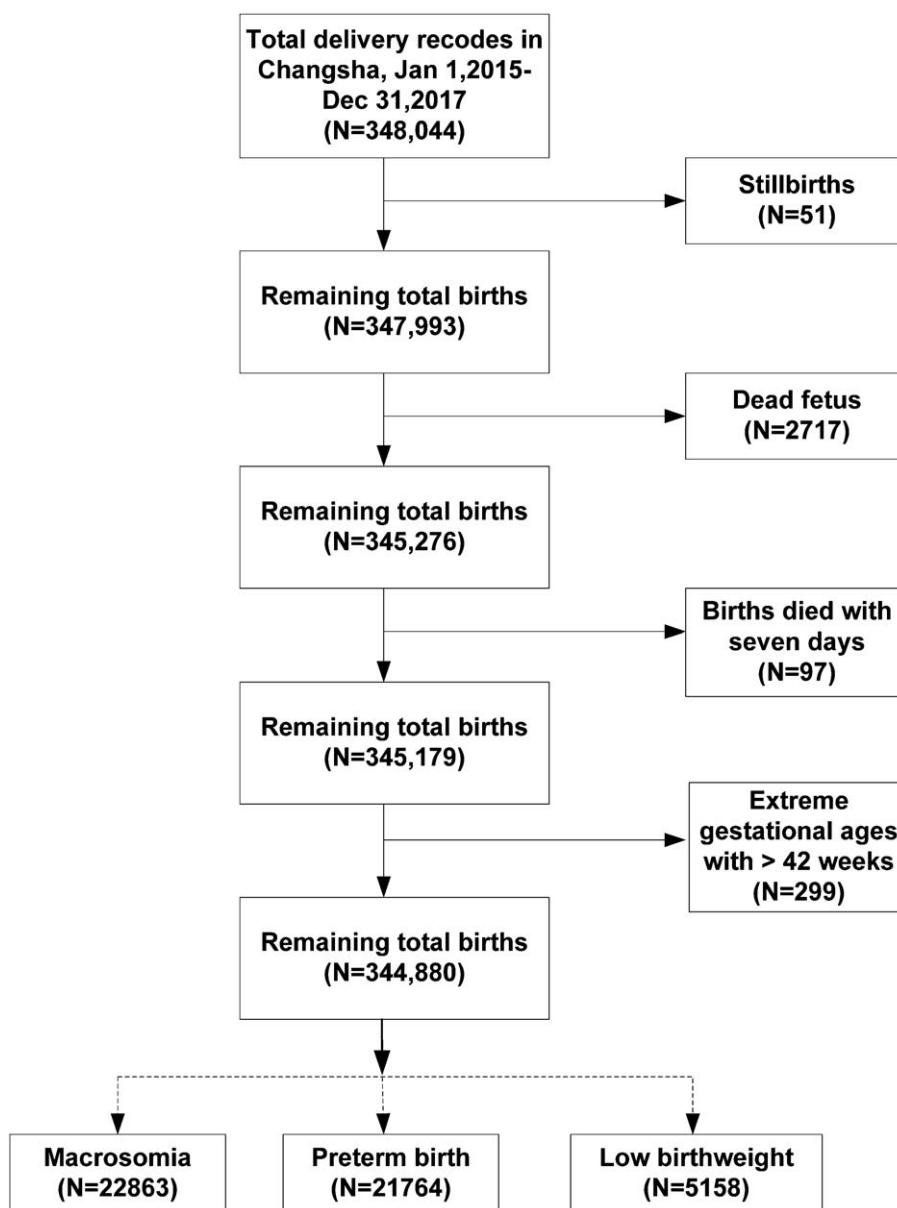


Figure 1. Flow chart showing how the study population was selected.

of birth outcomes along with 95% confidence intervals (CIs) in association with a $10\text{-}\mu\text{g}/\text{m}^3$ increase in daily air pollutants.

3. Results

2.4. Description of data

Table 1 shows the summary statistics of daily birth outcomes, air pollutants, and meteorologic data from January 1, 2015 to December 31, 2017 in the Changsha area. During the study period, there were 4 LBW newborns, 21 premature births and 29 live births with macrosomia delivered every day. The daily mean concentrations of NO_2 ranged from 11 to $109\ \mu\text{g}/\text{m}^3$, with a mean concentration of $34\ \mu\text{g}/\text{m}^3$. The daily mean concentrations of SO_2 ranged from 4 to $71\ \mu\text{g}/\text{m}^3$, with a mean concentration of $14\ \mu\text{g}/\text{m}^3$. The daily mean concentrations of PM_{10} ranged from 4 to $338\ \mu\text{g}/\text{m}^3$, with a mean concentration of $65\ \mu\text{g}/\text{m}^3$. The daily

mean concentrations of $\text{PM}_{2.5}$ ranged from 3 to $263\ \mu\text{g}/\text{m}^3$, with a mean concentration of $46\ \mu\text{g}/\text{m}^3$. The daily mean concentrations of O_3 ranged from 6 to $230\ \mu\text{g}/\text{m}^3$, with a mean concentration of $80\ \mu\text{g}/\text{m}^3$. The daily mean concentrations of CO ranged from 0.4 to $2.3\ \text{mg}/\text{m}^3$, with a mean concentration of $0.9\ \text{mg}/\text{m}^3$. The mean daily air pressure, wind speed, relative humidity, and temperature were 1001.5 kPa, 2.65 m/s, 80.96% and 17.52°C , respectively.

2.5. Spearman correlation

Table 2 shows the Spearman rank correlation coefficients between air pollutants and meteorologic factors in Changsha during the study period. Wind speed, relative humidity, and temperature were negatively correlated with the 6 air pollutants. Of the 6 air pollutants, NO_2 , SO_2 , PM_{10} , and $\text{PM}_{2.5}$ were strongly correlated with each other, with PM_{10} and $\text{PM}_{2.5}$

Table 1

Descriptive summary of daily air pollution, meteorological factors and birth outcomes in Changsha, China, between 2015 and 2017.

Variables	Mean	SD	Min	P ₂₅	P ₅₀	P ₇₅	Max
Air pollution							
SO ₂ , μg/m ³	15.62	7.92	4	10	14	19	71
NO ₂ , μg/m ³	38.39	17.06	11	25	34	48	109
PM ₁₀ , μg/m ³	72.48	39.18	4	44	65	95.25	338
PM _{2.5} , μg/m ³	55.39	35.54	3	30	46	70	263
O ₃ , μg/m ³	84.4	46.38	6	48	80	113	230
CO, mg/m ³	0.94	0.27	0.4	0.7	0.9	1.1	2.3
Meteorologic factors							
Air pressure, kPa	1001.5	8.71	985.2	994	1001	1008.4	1029.7
Wind speed, m/s	2.65	1.41	0	1.6	2.43	3.5	8.45
Relative humidity, (%)	80.96	13.44	72	72	83	92.25	100
Temperature, °C	17.52	8.31	-0.88	10.04	18.27	24.46	32.70
Birth outcomes							
LBW	4.71	2.97	0	3	4	6	35
Macrosomia	19.86	6.20	6	15	19	24	41
Preterm birth	20.86	7.41	3	15	21	26	44

LBW=low birth weight, mg/m³=milligrams per cubic meter, μg/m³=micrograms per cubic meter, SD=standard deviation.

showing the highest correlation coefficient of 0.893. All correlations were statistically significant ($P < .01$) except the correlation between PM_{2.5} and O₃, CO and relative humidity, and SO₂ and temperature ($P > .05$).

2.6. Time-series analysis

Table 3 shows the increased risk and associated 95% CIs (at different lags) of 3 birth outcomes with every 10 μg/m³ increase of each air pollutant; these were evaluated by controlling the influence of meteorologic factors and day of the week. The highest increases in LBW associated with a 10 μg/m³ increase in air pollutants were 0.44% (95% CI: 0.35–0.53%) for PM_{2.5} at lag 3. The highest increases in preterm birth associated with a 10 μg/m³ increase in air pollutants were 1.60% (95% CI: 1.41–1.80%) for SO₂ at lag 2. For overall macrosomia, the highest increases in macrosomia associated with a 10 μg/m³ increase in each air pollutant were 3.53% (95%CI: 3.41–3.64%) for NO₂ at lag 0, 3.33% (95% CI: 3.05–3.60%) for SO₂ at lag 03, 0.37% (95% CI: 0.33–0.41%) for PM₁₀ at lag 6, 0.64% (95% CI: 0.60–0.68%) for PM_{2.5} at lag 6.

Table 4 summarizes the increased risk and associated 95% CIs of 3 birth outcomes in multiple pollutant models. In terms of

LBW and preterm birth, only PM₁₀ increased the risk effect by 3.91% (95% CI: 3.67–4.12%) and 0.25% (95% CI: 0.14–0.37%), respectively, with a 10 μg/m³ increase. However, NO₂ increased the risk of macrosomia by 4.14% (95% CI: 3.97–4.31%) with a 10 μg/m³ increase in the multiple pollutant model.

4. Discussion

This study explored the association between birth outcome data (LBW, preterm birth, and macrosomia) obtained from Hunan Province Maternal and Children Hospital and a range of air pollutants (NO₂, SO₂, PM₁₀, PM_{2.5}, O₃, CO) in Changsha, China, between 2015 and 2017, using a time-series model. Our findings showed that there was a weak positive association between LBW and short-term exposure to particulate matter. NO₂, SO₂, PM₁₀, and PM_{2.5} were weakly but positively associated with preterm birth. There was an association between macrosomia and cumulative exposure from 0 to 3 days before birth to NO₂ and SO₂ pollution in the ambient air and an association between macrosomia and particulate matter especially at lag 6 to lag 7 days. Furthermore, 2- to 8-day (from lag 01 to lag 07) moving mean values of NO₂, SO₂, PM₁₀, and PM_{2.5} concentrations were all associated with an increased risk of

Table 2

Spearman correlation between air pollutants and meteorologic factors in Changsha, China, between 2015 and 2017.

Air pollutants	SO ₂	NO ₂	PM ₁₀	PM _{2.5}	O ₃	CO	Air pressure	Wind speed	Relative humidity
NO ₂	0.553								
PM ₁₀	0.684	0.731							
PM _{2.5}	0.537	0.706	0.893						
O ₃	0.202	-0.096	0.204	-0.049*					
CO	0.372	0.686	0.586	0.717	-0.318				
Air pressure	0.142	0.522	0.327	0.472	-0.422	0.413			
Wind speed	-0.312	-0.438	-0.312	-0.182	-0.240	-0.236	0.096		
Relative humidity	-0.568	-0.349	-0.536	-0.274	-0.546	0.037*	-0.096	0.202	
Temperature	-0.029*	-0.442	-0.188	-0.415	0.619	-0.474	-0.894	-0.164	-0.126

All Spearman's correlations between air pollutants and meteorologic factors were statistically significant with P -values $< .01$ but those labeled with "*" with P -value $> .05$.

Table 3

Increased risk change and 95% confidence intervals (CIs) for each 10 µg/m³ increase in air pollutants showing associations between air pollutants and birth outcomes.

Lag, d	RR changes % (95% CI)-LBW					
	NO ₂	SO ₂	PM ₁₀	PM _{2.5}	O ₃	CO
0	-1.43 (-1.68 to -1.17)	0.37 (-0.14 to 0.89)	-0.06 (-0.15 to 0.03)	-0.78 (-0.88 to -0.69)	-0.62 (-0.71 to -0.53)	0.03 (-12.50 to 12.57)
1	-2.76 (-2.96 to -2.56)	-6.03 (-6.48 to -5.59)	-0.72 (-0.80 to -0.64)	-0.75 (-0.84 to -0.66)	-1.19 (-1.27 to -1.10)	-0.11 (-12.17 to 11.95)
2	-2.16 (-2.35 to -1.96)	-3.13 (-3.54 to -2.72)	0.07 (-0.01 to -0.14)	0.22 (0.13 to 0.31)	-0.77 (-0.85 to -0.70)	-0.06 (-12.37 to 12.25)
3	-0.74 (-0.93 to -0.54)	-4.02 (-4.43 to -3.62)	0.38 (-0.30 to -0.46)	0.44 (0.35 to 0.53)	-0.75 (-0.82 to -0.68)	0.01 (-12.52 to 12.54)
4	-0.07 (-0.26 to 0.12)	-2.05 (-2.44 to -1.66)	0.03 (-0.04 to -0.11)	0.04 (-0.06 to 0.13)	-0.32 (-0.39 to -0.24)	0.01 (-12.66 to 12.68)
5	-1.27 (-1.46 to -1.07)	-1.01 (-1.40 to -0.62)	-0.11 (-0.18 to -0.03)	-0.09 (-0.19 to 0.00)	-0.61 (-0.68 to -0.53)	-0.02 (-12.73 to 12.69)
6	-1.13 (-1.32 to -0.94)	-1.13 (-1.53 to -0.73)	-0.10 (-0.18 to -0.02)	-0.47 (-0.57 to -0.38)	-0.45 (-0.52 to -0.38)	-0.11 (-12.89 to 12.67)
7	-2.11 (-2.30 to -1.91)	-2.71 (-3.11 to -2.31)	-0.91 (-0.99 to -0.83)	-1.30 (-1.40 to -1.21)	-0.61 (-0.68 to -0.54)	-0.20 (-13.16 to 12.75)
01	-2.52 (-2.77 to -2.28)	-4.09 (-4.63 to -3.55)	-0.52 (-0.62 to -0.43)	-0.85 (-0.95 to -0.75)	-1.25 (-1.35 to -1.14)	-0.04 (-13.42 to 13.34)
02	-2.67 (-2.91 to -2.43)	-4.32 (-4.87 to -3.77)	-0.27 (-0.37 to -0.17)	-0.47 (-0.58 to -0.37)	-1.32 (-1.42 to -1.22)	-0.04 (-14.27 to 14.18)
03	-2.27 (-2.52 to -2.03)	-5.04 (-5.61 to -4.47)	0.00 (-0.10 to 0.10)	-0.17 (-0.28 to -0.06)	-1.36 (-1.47 to -1.26)	-0.02 (-15.13 to 15.09)
04	-1.81 (-2.07 to -1.56)	-4.77 (-5.36 to -4.19)	0.07 (-0.03 to 0.17)	-0.07 (-0.19 to 0.05)	-1.22 (-1.33 to -1.12)	0.01 (-15.98 to 15.98)
05	-1.82 (-2.08 to -1.56)	-4.11 (-4.71 to -3.51)	0.09 (-0.02 to 0.20)	-0.01 (-0.13 to 0.12)	-1.24 (-1.34 to -1.13)	0.01 (-16.74 to 16.77)
06	-1.79 (-2.06 to -1.53)	-3.66 (-4.28 to -3.04)	0.12 (0.01-0.23)	-0.05 (-0.18 to 0.07)	-1.21 (-1.31 to -1.10)	0.01 (-17.45 to 17.45)
07	-2.01 (-2.28 to -1.73)	-3.71 (-4.35 to -3.07)	-0.08 (-0.20 to -0.03)	-0.28 (-0.41 to -0.15)	-1.24 (-1.35 to -1.13)	-0.03 (-18.12 to -18.07)

Lag, d	RR changes % (95% CI) - preterm birth					
	NO ₂	SO ₂	PM ₁₀	PM _{2.5}	O ₃	CO
0	0.70 (0.58-0.82)	0.38 (0.13-0.63)	0.11 (0.07-0.15)	0.07 (0.02-0.11)	-0.15 (-0.19 to -0.11)	0.09 (-5.73 to 5.90)
1	0.58 (0.49-0.67)	-0.15 (-0.36 to 0.06)	0.00 (-0.04 to 0.04)	-0.01 (-0.05 to 0.04)	-0.05 (-0.09 to -0.01)	0.06 (-5.51 to 5.62)
2	0.13 (0.04-0.22)	1.60 (1.41-1.80)	-0.03 (-0.07 to 0.00)	-0.19 (-0.23 to -0.15)	-0.24 (-0.28 to -0.21)	0.05 (-5.66 to 5.75)
3	-0.14 (-0.23 to -0.05)	-1.03 (-1.22 to -0.84)	-0.39 (-0.42 to -0.35)	-0.64 (-0.68 to -0.59)	-0.53 (-0.57 to -0.50)	-0.01 (-5.87 to 5.85)
4	0.31 (0.02-0.40)	-1.07 (-1.26 to -0.88)	-0.20 (-0.24 to -0.17)	-0.20 (-0.24 to -0.15)	-0.21 (-0.24 to -0.18)	0.03 (-5.89 to 5.95)
5	0.03 (-0.06 to 0.12)	-1.45 (-1.64 to -1.26)	-0.10 (-0.14 to -0.07)	0.12 (0.08-0.16)	-0.07 (-0.10 to -0.03)	0.03 (-5.90 to 5.95)
6	-0.34 (-0.43 to -0.25)	-1.26 (-1.45 to -1.06)	-0.15 (-0.18 to -0.11)	-0.03 (-0.08 to 0.01)	-0.06 (-0.09 to -0.02)	0.02 (-5.90 to 5.95)
7	-1.05 (-1.14 to -0.96)	-2.08 (-2.28 to -1.89)	-0.29 (-0.33 to -0.26)	-0.16 (-0.20 to -0.12)	-0.07 (-0.11 to -0.04)	-0.01 (-6.01 to 6.00)
01	0.75 (0.64-0.87)	0.13 (-0.14 to 0.39)	0.06 (0.02-0.10)	0.04 (-0.01 to 0.09)	-0.13 (-0.18 to -0.08)	0.08 (-6.12 to 6.29)
02	0.57 (0.46-0.68)	1.15 (0.88 to -1.42)	0.03 (-0.02 to 0.07)	-0.05 (-0.10 to -0.00)	-0.24 (-0.29 to -0.19)	0.09 (-6.53 to 6.70)
03	0.39 (0.28-0.51)	0.36 (0.08-0.64)	-0.15 (-0.19 to 0.10)	-0.28 (-0.33 to -0.23)	-0.46 (-0.51 to -0.41)	0.07 (-6.99 to 7.13)
04	0.42 (0.31-0.54)	-0.25 (-0.54 to 0.04)	-0.21 (-0.26 to -0.16)	-0.32 (-0.37 to -0.26)	-0.47 (-0.52 to -0.42)	0.07 (-7.44 to 7.58)
05	0.36 (0.23-0.48)	-0.92 (-1.22 to -0.62)	-0.23 (-0.28 to -0.18)	-0.27 (-0.32 to -0.21)	-0.43 (-0.48 to -0.38)	0.07 (-7.85 to 7.99)
06	0.18 (0.05-0.31)	-1.44 (-1.75 to -1.13)	-0.27 (-0.33 to -0.22)	-0.27 (-0.33 to -0.21)	-0.40 (-0.45 to -0.35)	0.07 (-8.24 to 8.38)
07	-0.13 (0.26-0.00)	-2.14 (-2.46 to -1.81)	-0.35 (-0.40 to -0.29)	-0.31 (-0.37 to -0.24)	-0.39 (-0.44 to -0.34)	0.06 (-8.63 to 8.75)

Lag (Days)	RR changes % (95% CI)- macrosomia					
	NO ₂	SO ₂	PM ₁₀	PM _{2.5}	O ₃	CO
0	3.53 (3.41-3.64)	3.03 (2.78-3.27)	0.13 (0.09-0.18)	0.14 (0.10-0.19)	-0.76 (-0.81 to -0.72)	0.12 (-5.72 to 5.93)
1	1.82 (1.73-1.91)	1.50 (1.29-1.71)	0.30 (0.26-0.34)	0.21 (0.17-0.26)	-0.35 (-0.39 to -0.30)	0.05 (-5.59 to 5.70)
2	1.34 (1.25-1.43)	1.63 (1.44-1.83)	0.07 (0.03-0.11)	0.13 (0.08-0.17)	-0.42 (-0.45 to -0.38)	0.05 (-5.74 to 5.85)
3	1.39 (1.31-1.48)	2.44 (2.25-2.63)	0.22 (0.19-0.26)	0.28 (0.23-0.32)	-0.29 (-0.33 to -0.26)	0.07 (-5.84 to 5.98)
4	0.37 (0.28-0.46)	0.62 (0.43-0.81)	0.04 (0.01-0.08)	0.09 (0.05-0.14)	-0.23 (-0.27 to -0.20)	0.00 (-6.03 to 6.02)
5	0.65 (0.56-0.74)	-0.18 (-0.37 to 0.01)	0.08 (0.05-0.12)	0.23 (0.18-0.27)	-0.43 (-0.46 to -0.39)	0.04 (-5.98 to 6.06)
6	0.96 (0.87-1.05)	0.97 (0.78-1.16)	0.37 (0.33-0.41)	0.64 (0.60-0.68)	-0.17 (-0.20 to -0.13)	0.11 (-5.89 to 6.11)
7	0.48 (0.39-0.58)	0.31 (0.12-0.50)	0.26 (0.22-0.29)	0.45 (0.41-0.49)	-0.01 (-0.04 to 0.03)	0.07 (-6.03 to 0.03)
01	2.78 (2.68-2.89)	2.77 (2.51-3.04)	0.20 (0.16-0.25)	0.18 (0.13-0.23)	-0.77 (-0.82 to -0.72)	0.0 (-7.00 to 7.21)
02	2.52 (2.41-2.62)	2.77 (2.51-3.04)	0.20 (0.16-0.25)	0.18 (0.13-0.23)	-0.77 (-0.82 to -0.72)	0.0 (-7.00 to 7.21)
03	2.51 (2.40-2.62)	3.33 (3.05-3.60)	0.24 (0.19-0.29)	0.23 (0.18-0.28)	-0.75 (-0.80 to -0.70)	0.10 (-7.00 to 7.21)
04	2.25 (2.13-2.36)	2.94 (2.65-3.22)	0.20 (0.15-0.25)	0.21 (0.15-0.27)	-0.72 (-0.77 to -0.67)	0.08 (-7.46 to 7.63)
05	2.17 (2.05-2.29)	2.34 (2.05-2.64)	0.19 (0.14-0.24)	0.23 (0.17-0.29)	-0.78 (-0.83 to -0.73)	0.08 (-7.86 to 8.03)
06	2.21 (2.09-2.34)	2.36 (2.06-2.67)	0.27 (0.22-0.33)	0.37 (0.31-0.43)	-0.74 (-0.79 to -0.69)	0.10 (-8.20 to 8.41)
07	2.15 (2.02-2.28)	2.26 (2.20-2.31)	0.32 (0.27-0.38)	0.45 (0.38-0.51)	-0.67 (-0.72 to -0.62)	0.11 (-8.54 to 8.77)

CI=confidence intervals, LBW=low birth weight, RR=relative risk.

macrosomia. However, there was no association between O₃ and CO and adverse birth outcomes. PM₁₀ increased the risk of LBW and preterm birth in all pollutant models, while NO₂ increased the risk of macrosomia in all pollutant models. This represents the 1st study to investigate the association between air pollutants and birth outcomes, including macrosomia, in Changsha.

The daily mean concentration of PM_{2.5} and PM₁₀ was higher than the national ambient air quality standard (NAQS) primary standard, but lower than the secondary standard accordingly. The daily mean concentrations of SO₂, NO₂, O₃, and CO were all lower than their respective NAQS primary standard. The daily mean concentrations of PM₁₀, SO₂, and NO₂ in Changsha area between 2015 and 2017 were lower than the PM₁₀ (105.91 µg/m³), SO₂ (20.57 µg/m³), NO₂ (30.93 µg/m³) in Hefei city between 2010, and 2015. Hefei city is the capital of Anhui province and is located in the east of China (31°52'N, 117°17'E).^[29] Similarly, the daily mean concentrations of

PM₁₀, SO₂, and NO₂ in Changsha were lower than the PM₁₀ (115.60 µg/m³), SO₂ (53.21 µg/m³), NO₂ (53.08 µg/m³) in Wuhan city between 2006 and 2009. Wuhan city is the capital of Hubei province and located at the center of China (30°33'N, 114°19'E).^[30] Although economic development has been achieved at the expense of the environment over the last few years, the government has been working hard to come up with policies and measures to tackle air pollution. Therefore, the concentration of air pollutions is starting to decrease. Reducing the concentration of particulate matters is a specific target for the Changsha government in the future.

In the present study, we found that air pollutants were negatively associated with LBW in single pollutant models except for PM₁₀ at lag 06 day and PM_{2.5} at lag 2 and lag 3 days. PM₁₀ showed the highest risk of LBW in the all pollutant model. A previous study, involving 22 countries in the World Health Organization Global Survey on Maternal and Perinatal Health

Table 4**Association between a 10 $\mu\text{g}/\text{m}^3$ increases in air pollutants with birth outcomes using an all pollutants model for data collected between 2015 and 2017.**

Air pollutant	LBW		Preterm birth		Macrosomia	
	RR Changes %	95% CI	RR changes %	95% CI	RR changes %	95% CI
NO ₂	-4.094	-4.450 to -3.738	-0.274	-0.442 to -0.105	4.141	3.972-4.309
SO ₂	0.535	-0.101 to -1.172	-1.046	-1.357 to -0.736	-0.352	-0.665 to -0.039
PM ₁₀	3.906	3.674 to -4.139	0.252	0.138-0.366	-0.001	-0.116 to -0.114
PM _{2.5}	-4.467	-4.699 to -4.236	-0.730	-0.842 to -0.618	-0.177	-0.288 to -0.065
O ₃	-0.733	-0.831 to -0.636	0.000	-0.045 to 0.045	-0.428	-0.474 to -0.382
CO	0.213	-18.140 to -18.567	0.146	-8.353 to 8.644	0.089	-8.530 to 8.707

CI=confidence interval, LBW=low birth weight, RR=relative risk.

from 2004 to 2008, found higher PM_{2.5} levels were associated with a higher risk of LBW; this relationship was identified by using generalized estimation equations.^[31] A total of 23 studies published before July 2016 were collected and analyzed; the authors concluded that PM_{2.5} exposure throughout pregnancy may increase the risk of term low birth weight.^[32] In this present study, our results showed that exposure to particulate matters increased the risk of LBW. A plausible explanation for this might be that a low placenta weight is related to birth weight during pregnancy; the placenta is a vital organ as it supports the nourishment, growth and development of the embryo.^[33] During pregnancy, exposure to maternal particulate matter may represent an important risk factor for intrauterine inflammation which could then affect the growth, development, and function of the placenta.^[34] In this present study, a weak positive association between short-term exposure to particulate matters and LBW was observed for the reason of low concentration. Additional research is now needed to gain a better understanding of the impacts of air pollution on LBW, including the identification of susceptible sub-populations, the effects of multiple pollutants, and the effect of different types of weather, time periods, and differential study designs.^[35]

In the present study, we found that NO₂ was associated with preterm birth in single pollutant models at lag 0 to lag 2 days, lag 4 and lag 5 days, and lag 01 to lag 06 days. SO₂ was associated with preterm birth at lag 0, lag 2, and lag 01 to lag 03 days in single pollutant models. PM₁₀ was associated with preterm birth at lag 0 and lag 01 days in single pollutant models, while PM_{2.5} was associated with preterm birth at lag 0 and lag 5 days. There was no association between O₃ and CO and preterm birth in our single pollutant models. Previous studies regarding the specific pollutants linked to preterm birth have been very inconsistent. A study in the Middle East, which took place between 2015 and 2018 showed that significant relationship between each 10-unit increase in NO₂ and CO, and premature birth in lag 0; this relationship was identified by conducting a time-series study adjusted by trend, seasonality, temperature, relative humidity, weekdays, and holidays.^[36] Another study conducted a time-series analysis of metropolitan Atlanta between 1994 and 2004 and showed that PM_{2.5} was associated with preterm birth in the final week of gestation.^[37] One large study of London, covering 13 years between 1988 and 2000, and using time-series regression techniques, suggested that there was no association between preterm births and cumulative exposure from 0 to 6 days before birth to ambient air pollution of PM₁₀ and O₃ or recent changes in the weather.^[25] In another study, Zhao et al reported a 0.7% increased risk of preterm birth associated with each 10 $\mu\text{g}/\text{m}^3$ increase in PM₁₀ on day 4 of the week before delivery in

Cuangzhou, China.^[10] Evidence also suggests that inflammatory pathways, as well as implantation errors in early pregnancy, play a role in preterm birth, although the pathophysiology of preterm birth remains poorly understood.^[2] Air pollutants could increase the risk of preterm birth by affecting these 2 pathways. The levels of air pollutants in the weeks following conception could disrupt implantation and placentation, and the high levels of air pollution during late pregnancy could activate either an acute or sustained inflammatory response, thus leading to the initiation of early labor.^[37] Most of our present results showed a weak relationship between air pollutants and preterm birth. This may have been related to that we investigated ambient concentrations in the preceding week of birth and not the weeks following conception. We found the increased risk of low birth weight and preterm birth associated to cumulative exposure to PM₁₀ is not significant in a single pollutant model if compared to the increased risk detected in the multi-pollutant model. A study in Hefei city had also found similar phenomenon, in which one pollutant showed robust effect after other pollutants entered into the model.^[29] It suggested the PM₁₀ might be more important in air pollution mixture.

In the present study, we also found that the air pollutants NO₂, SO₂, PM₁₀, and PM_{2.5} were associated with macrosomia in single pollutant models. NO₂ and SO₂ were associated with macrosomia at lag 0 to lag 7 days and lag 01 to lag 07 days, except for SO₂ at lag 5. NO₂ showed the highest risk of macrosomia in our all pollutants model. However, many studies have reported an association between air pollution and diabetes mellitus. For example, a systematic review in Europe and north America synthesized the results of studies on type 1 and type 2 diabetes mellitus, and gestational diabetes, and showed that PM_{2.5} and NO₂ increased the risk of diabetes mellitus by 8% to 10% per 10 $\mu\text{g}/\text{m}^3$ increase in exposure.^[38] Available evidence from other systematic reviews and meta-analyses supports a prospective association of NO₂ and PM_{2.5} with an increased risk for diabetes mellitus.^[39,40] This present study found higher levels of NO₂ to be significantly associated with increasing risk of macrosomia after introducing other air pollutants. Other studies have also observed that the effect of NO₂ was enhanced when all air pollutants were assessed together.^[41-43] The biological mechanisms that link air pollution to the development of macrosomia remain unclear, although one possible explanation for this is that air pollution causes maternal diabetes, which represents a pathological factor which could lead to macrosomia. Another pathway might be the systemic inflammation caused by air pollutants that results in metabolic dysfunction.^[17] Furthermore, obesity and over-nutrition, risk factors for the development of diabetes, may render women more susceptible to the effects of air pollution^[44] and also promote the development of macrosomia

during pregnancy. In future similar studies, it will be necessary to explore the relationship between air pollution and macrosomia after 1st considering maternal diabetes status.

This study had multiple strengths. First, the use of population data allowed for the inclusion of all births in the Changsha area, whereas most previous studies included only components of data from the city being studied. Second, the birth information used in our analyses was all correct and complete because it was linked to the birth certificate, which is a legal document supervised by the public security department. Third, this was the 1st study to examine whether air pollutants are associated with macrosomia.

This study also had some limitations. First, our analyses were not adjusted for infant gender, maternal age, race, maternal smoking status, and maternal health status due to lack of these individual risk factors. Future studies could focus on personal risk factors especially time varying factors such as maternal smoking status and maternal health status to confirm our findings. Second, the potential issue of linearity was not considered in this study; this may have led to some instability in our multiple models. Third, the exposure levels provided by outdoor monitors may not fully represent individual exposure levels. Nonetheless, even a small increase in the risk for advanced birth outcomes could have a major effect on public health following ubiquitous exposure. This concept requires further investigation.

5. Conclusion

The results obtained in this study indicated that during the study period, particulate matter was weakly associated with low birth weight and that both SO₂ and NO₂ influenced the incidence of preterm birth and macrosomia in Changsha. Despite the low levels of air pollutants in Changsha, pregnant women should make a specific effort to limit their exposure to high levels of air pollutants during the final weeks of pregnancy.

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References

- [1] Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth. *Lancet* (London, England) 2008;371:75–84.
- [2] Behrman RE, Butler AS. Preterm birth: causes, consequences, and prevention. The National Academies Press, Washington, DC:2007.
- [3] McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. *N Engl J Med* 1985;2:82–90.
- [4] Xu X, Sharma RK, Talbott EO, et al. PM10 air pollution exposure during pregnancy and term low birth weight in Allegheny County, PA, 1994–2000. *Int Arch Occup Environ Health* 2011;84:251–7.
- [5] Woodruff TJ, Parker JD, Adams K, et al. International Collaboration on Air Pollution and Pregnancy Outcomes (ICAPPO). *Int J Environ Res Public Health* 2010;7:2638–52.
- [6] Wilhelm M, Ritz B. Local variations in co and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA. *Environ Health Perspect* 2005;113:1212–21.
- [7] Malley CS, Kuylenstierna JC, Vallack HW, et al. Preterm birth associated with maternal fine particulate matter exposure: a global, regional and national assessment. *Environ Int* 2017;101:173–82.
- [8] Arroyo V, Diaz J, Ortiz C, et al. Short term effect of air pollution, noise and heat waves on preterm births in Madrid (Spain). *Environ Res* 2016;145:162–8.
- [9] Jiang LL, Zhang YH, Song GX, et al. A time series analysis of outdoor air pollution and preterm birth in Shanghai, China. *Biomed Environ Sci* 2007;20:426–31.
- [10] Zhao N, Qiu J, Zhang Y, et al. Ambient air pollutant PM10 and risk of preterm birth in Lanzhou, China. *Environ Int* 2015;76:71–7.
- [11] Zhao Q, Liang Z, Tao S, et al. Effects of air pollution on neonatal prematurity in Guangzhou of China: a time-series study. *Environ Health* 2011;10:
- [12] Sun X, Luo X, Zhao C, et al. The association between fine particulate matter exposure during pregnancy and preterm birth: a meta-analysis. *BMC Pregnancy Childbirth* 2015;15:300.
- [13] He JR, Liu Y, Xia XY, et al. Ambient temperature and the risk of preterm birth in Guangzhou, China (2001–2011). *Environ Health Perspect* 2016;124:1100–6.
- [14] Koyanagi A, Zhang J, Dagvadorj A, et al. Macrosomia in 23 developing countries: an analysis of a multicountry, facility-based, cross-sectional survey. *Lancet* (London, England) 2013;381:476–83.
- [15] Alsammani MA, Ahmed SR. Fetal and maternal outcomes in pregnancies complicated with fetal macrosomia. *N Am J Med Sci* 2012;4:283–6.
- [16] Schulz M, Romppel M, Grande G. Built environment and health: a systematic review of studies in Germany. *J Public Health* 2018;40:8–15.
- [17] Rajagopalan S, Brook RD. Air pollution and type 2 diabetes mechanistic insights. *Diabetes* 2012;61:3037–45.
- [18] Poursafa P, Mansourian M, Motlagh ME, et al. Is air quality index associated with cardiometabolic risk factors in adolescents? The CASPIAN-III Study. *Environ Res* 2014;134:105–9.
- [19] Wang M, Zheng S, Nie Y, et al. Association between short-term exposure to air pollution and dyslipidemias among type 2 diabetic patients in northwest China: a population-based study. *Int J Environ Res Public Health* 2018;15:631.
- [20] Wang X, Guan Q, Zhao J, et al. Association of maternal serum lipids at late gestation with the risk of neonatal macrosomia in women without diabetes mellitus. *Lipids Health Dis* 2018;17:78.
- [21] Dendup T, Feng X, Clingan S, Astell-Burt T. Environmental risk factors for developing type 2 diabetes mellitus: a systematic review. *Int J Environ Res Public Health* 2018;15:78.
- [22] Shen HN, Hua SY, Chiu CT, et al. Maternal Exposure to Air Pollutants and Risk of Gestational Diabetes Mellitus in Taiwan. *Int J Environ Res Public Health* 2017;14:1604.
- [23] Robledo CA, Mendola P, Yeung E, et al. Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus. *Environ Res* 2015;137:316–22.
- [24] Liang Z, Lin Y, Ma Y, et al. The association between ambient temperature and preterm birth in Shenzhen, China: a distributed lag non-linear time series analysis. *Environ Health* 2016;15:84.
- [25] Lee SJ, Hajat S, Steer PJ, et al. A time-series analysis of any short-term effects of meteorological and air pollution factors on preterm births in London, UK. *Environ Res* 2008;106:185–94.
- [26] Recio A, Linares C, Banegas JR, et al. Road traffic noise effects on cardiovascular, respiratory, and metabolic health: an integrative model of biological mechanisms. *Environ Res* 2016;146:359–70.
- [27] Akaike H. Factor analysis and AIC. *Psychometrika* 1987;52:317–32.
- [28] Bretnier S, Wolf K, Peters A, et al. Short-term effects of air temperature on cause-specific cardiovascular mortality in Bavaria, Germany. *Heart* 2014;100:1272–80.
- [29] Zhang C, Ding R, Xiao C, et al. Association between air pollution and cardiovascular mortality in Hefei, China: a time-series analysis. *Environ Pollut* 2017;229:790–7.
- [30] Liu Y, Chen X, Huang S, et al. Association between air pollutants and cardiovascular disease mortality in Wuhan, China. *Int J Environ Res Public Health* 2015;12:3506–16.

- [31] Fleischer NL, Merialdi M, van Donkelaar A, et al. Outdoor air pollution, preterm birth, and low birth weight: analysis of the world health organization global survey on maternal and perinatal health. *Environ Health Perspect* 2014;122:425–30.
- [32] Li X, Huang S, Jiao A, et al. Association between ambient fine particulate matter and preterm birth or term low birth weight: an updated systematic review and meta-analysis. *Environ Pollut* 2017;227:596–605.
- [33] Payam D, Jennifer P, Bell ML, et al. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. *Environ Health Perspect* 2013;121:367–73.
- [34] Massa NR, Mao G, Zhang X, et al. Intrauterine inflammation and maternal exposure to ambient PM_{2.5} during preconception and specific periods of pregnancy: the Boston birth cohort. *Environ Health Perspect* 2016;124:1608–15.
- [35] Bell ML, Ebisu K, Belanger K. The relationship between air pollution and low birth weight: effects by mother's age, infant sex, co-pollutants, and pre-term births. *Environ Res Lett* 2008;3:44003.
- [36] Dastoorpoor M, Idani E, Goudarzi G, et al. Acute effects of air pollution on spontaneous abortion, premature delivery, and stillbirth in Ahvaz, Iran: a time-series study. *Environ Sci Pollut Res Int* 2017;25:1–2.
- [37] Darrow LA, Klein M, Flanders WD, et al. Ambient air pollution and preterm birth: a time-series analysis. *Epidemiology* 2009;20:689–98.
- [38] Eze IC, Hemkens LG, Bucher HC, et al. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. *Environ Health Perspect* 2015;123:381.
- [39] Balti EV, Echouffo-Tcheugui JB, Yako YY, et al. Air pollution and risk of type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2014;106:161–72.
- [40] Wang B, Xu D, Jing Z, et al. Effect of long-term exposure to air pollution on type 2 diabetes mellitus risk: a systemic review and meta-analysis of cohort studies. *Eur J Endocrinol* 2014;171:173–82.
- [41] Coogan PF, White LF, Jerrett M, et al. Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles. *Circulation* 2012;125:767–72.
- [42] Coogan PF, White LF, Yu J, et al. Long term exposure to NO₂ and diabetes incidence in the black women's health study. *Environ Res* 2016;148:360.
- [43] Krämer U, Herder C, Sugiri D, et al. Traffic-related air pollution and incident type 2 diabetes: results from the SALIA cohort study. *Environ Health Perspect* 2010;118:1273–9.
- [44] Sun Q, Yue P, Deulius JA, et al. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. *Circulation* 2009;119:538–46.