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Gestational $PM_{2.5}$ exposure may increase the risk of small for gestational age through maternal blood pressure and hemoglobin: A mediation analysis based on a prospective cohort in China, 2014–2018☆

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ABSTRACT

Background: Maternal gestational $PM_{2.5}$ exposure was associated with small for gestational age (SGA). Identifying potential mediating factors may help design preventive strategies to reduce this risk.
Objective: This study aimed to explore the roles of maternal blood pressure and hemoglobin may play in the $PM_{2.5}$ exposure and SGA relationship among 117,162 births in 16 counties across China during 2014–2018.
Methods: Daily $PM_{2.5}$ concentration was collected from China National Environmental Monitoring Center. According to maternal residency during pregnancy, the $PM_{2.5}$ exposure for each trimester and the whole pregnancy was assessed using an inverse-distance weighting approach. Repeated measurements of maternal blood pressure and hemoglobin during pregnancy were collected for each woman. We estimated the total effect of gestational $PM_{2.5}$ exposure on SGA, and further tested the mediation effects of maternal blood pressure and hemoglobin concentration during pregnancy.
Results: Of 117,162 included mother-infant pairs, 11,361 (9.7 %) were SGA. The odds ratios of SGA associated with $PM_{2.5}$ exposure (per 10 $\mu g/m^3$ increase) in the second trimester and the whole pregnancy were 1.023 (95 % CI: 1.009, 1.037) and 1.024 (1.001, 1.048), respectively. We identified the independent mediating effect of blood pressure and hemoglobin in the second and third trimesters, with the proportion of mediation ranging from 1.64 % to 5.78 % and 2.40 % to 8.70 %, respectively. When considering the mediators jointly, we found a stronger mediating effect with a proportion of mediation ranging from 3.93 % to 13.69 %.
Discussion: Increases in maternal blood pressure and hemoglobin in the second and third trimesters can independently and jointly mediate the effects of gestational $PM_{2.5}$ exposure on SGA. Monitoring and managing maternal blood pressure and hemoglobin during prenatal care may constitute a promising avenue to reducing SGA risk associated with gestational $PM_{2.5}$ exposure.

☆ **Author Contributions:** Zhu and Hu contributed equally to this work and are considered co-first authors. Q Wang had full access to all the study data and took responsibility for the integrity of the data and the accuracy of the data analysis.

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1. Background

Small for gestational age (SGA) is defined as newborns with a birth weight less than the 10th percentile of a birth weight reference for a given gestational age (Ding et al., 2013). SGA could increase the risk of various adverse health-related outcomes for both mother and the baby. Women who give birth to SGA infants have a higher risk of cardiovascular diseases and chronic kidney disease later in life (Bonamy et al., 2011; Horn et al., 2020; Pariente et al., 2015). SGA infants may suffer from various adverse health outcomes, such as neurodevelopmental disorders, metabolic syndrome as well as cardiovascular diseases (Kesavan and Devaskar, 2019; Sebastiani et al., 2016).

Although the exact etiology of SGA remains unclear, the cumulative evidence suggests SGA can be affected by environmental factors, especially fine particulate matter ($PM_{2.5}$). Previous epidemiological studies have consistently reported that gestational $PM_{2.5}$ exposure increased the risk of SGA (Guo et al., 2020; Hannam et al., 2014; Hyder et al., 2014; Liao et al., 2019; Melody et al., 2020; Percy et al., 2019; Stieb et al., 2016; Tapia et al., 2020). However, the mechanisms through which $PM_{2.5}$ could affect SGA risk remain unclear. Maternal blood pressure and hemoglobin concentration are two common indicators of the physiological state of a pregnant woman. They may also play roles in the association between $PM_{2.5}$ and SGA.

Ambient $PM_{2.5}$ exposure may trigger the autonomic imbalance (Brook et al., 2010) or interfere with the human body's internal intake of various metals(-loid) to elevate blood pressure (Lan et al., 2021). Some epidemiological studies have observed positive associations between maternal $PM_{2.5}$ exposure and gestational hypertension (Mandakh et al., 2020; Mobasher et al., 2013). In addition, higher maternal blood pressure has been reported to be associated with fetal growth restriction during the third trimester and increased risks of preterm birth, low birth weight, and SGA (Bakker et al., 2011; Liu et al., 2021; Scanlon, 2000). Such evidence implies that higher concentrations of $PM_{2.5}$ exposure may increase maternal BP during pregnancy, resulting in fetal growth restriction, ultimately increasing the risk of SGA.

Gestational $PM_{2.5}$ exposure can induce oxidative stress and increase red blood cells in peripheral blood (Sørensen et al., 2002). In addition, it has been reported that hemoglobin concentration in the second and third trimesters was associated with a reduction in birth weight and placental weight (Jwa et al., 2015), as well as an increased risk of SGA and LBW (Dewey and Oaks, 2017; Scanlon, 2000; Yazdani et al., 2004). Therefore, higher concentrations of $PM_{2.5}$ exposure may increase maternal hemoglobin during pregnancy and lead to a higher risk of SGA. One study in China has reported that $PM_{2.5}$ exposure during the first trimester was associated with intrauterine growth restriction and elevated maternal Hb concentration mediated this association (Liao et al., 2019). However, only 1945 pregnant women were included in that study, and the authors used fetal crown to rump length (CRL) as an indicator of fetal growth.

In addition, there is a potential association between maternal blood pressure and hemoglobin during pregnancy. Previous studies have shown that high maternal hemoglobin concentration during pregnancy is a risk factor for preeclampsia as well as gestational hypertension (Aghamohammadi et al., 2011; Phaloprakarn and Tangjitgamol, 2008; von Tempelhoff et al., 2008). Evidence from the epidemiological study also suggested that systolic and diastolic blood pressures increased with elevated hemoglobin levels (Atsma et al., 2012). Hemoglobin concentrations vary with plasma volume, and high hemoglobin concentrations reflect a failure of plasma volume expansion during pregnancy, which can be strongly associated with an increased incidence of pre-eclampsia in pregnancy and thus with fetal growth restriction (Odegard et al., 2000; Steer, 2000).

To our knowledge, no previous studies have empirically explored the potential mediating roles of maternal blood pressure and hemoglobin in the pathways for gestational $PM_{2.5}$ exposure and SGA. Clarifying the paths may help identify if monitoring and managing blood pressure and hemoglobin during prenatal care may constitute a promising clinical avenue in a context in which air pollution is associated with a substantial burden on maternal and infant health outcomes. In this study, using a prospective birth cohort across China, we aimed to clarify the effect of gestational $PM_{2.5}$ exposure on SGA and the extent to which this effect is mediated by maternal blood pressure and hemoglobin.

2. Methods

2.1. Participants

The National Maternal and Newborn Health Monitoring Project was initiated in 2013 by the Maternal and Child Health Center of the Chinese Center for Disease Control and Prevention. This project is a prospective birth cohort study conducted in 16 sites across eight provinces (Hubei, Hunan, Hebei, Liaoning, Guangdong, Sichuan, Yunnan, and Fujian) of China. The location of the study sites is shown in Figs. S1 and S2. More details of this project have been described in our previous study (Wu et al., 2021). The present study collected 271,720 "mother-newborn" pairs between 2013 and 2018 from the cohort. We excluded 406 stillbirths, 9234 multiple births, and 5094 births with outlier maternal age (< 13 years or > 50 years). Some stations in China started monitoring $PM_{2.5}$ regularly in 2013 or early 2014 according to the requirement of "Ambient air quality standards (GB 3095-2012) (Ministry of Environmental Protection, 2012). Therefore, the $PM_{2.5}$ surveillance data of our study areas were missing in 2013 and early 2014. By excluding those without $PM_{2.5}$ exposure measurements, the left participants (most infants were conceived since later 2014) were included ($n = 210,960$). We further excluded subjects ($n = 154$) with abnormal weight (< 500 g or > 5000 g). To define sex- and gestational age-specific birth weight (i.e., SGA, appropriate size for gestational age (AGA), and large for gestational age (LGA)), we excluded those with missing infant sex or abnormal gestational age (< 28 weeks or > 44 weeks) ($n = 284$). Since LGA may affect the effects of $PM_{2.5}$ on SGA, we excluded the LGA participants ($n = 24,367$). In addition, only subjects with at least one blood pressure test and hemoglobin test in the second and third trimesters were included. In the end, 117,162 pairs of "pregnant women-newborns" were included in the analysis. Fig. S3 shows the detailed process of participant inclusion and exclusion. This study was approved by the medical ethics committee of the School of Public Health, SunYat-sen University. All data used in the study were anonymous and excluded personally identifiable information.

2.2. Exposure measurements

We collected daily average $PM_{2.5}$, carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and the 8-hour average ozone (O_3) concentration from the China National Environmental Monitoring Center (http://www.cnemc.cn) from 2014 to 2018 at 1597 sites. Inverse distance weighting (IDW) was applied to interpolate the daily concentration for each air pollutant to a 1×1 km resolution using ArcGIS 10.5 (Environmental Systems Research Institute, Redlands, California, USA) (Roberts et al., 2014). According to the residential address of each pregnant woman, the daily air pollutant exposure level for each pregnancy was extracted and then averaged for several periods: the whole pregnancy, the first trimester (1st to 12th gestational weeks), the second trimester (13–27th gestational weeks), and the third trimester (28th gestational week to delivery).

To adjust for the potential confounding effect of ambient temperature, the daily mean temperatures during 2014–2018 were also collected for 680 sites from the China Meteorological Data Service Center (http://data.cma.cn), and the exposure was assigned to each pregnancy by the IDW interpolation technology, as we did for air pollution exposure.

2.3. Outcome and mediators

We defined SGA, AGA, and LGA based on a sex- and gestational-age-specific birth weight reference established based on the representative Chinese population (Dai et al., 2014). Blood pressure (mmHg) and hemoglobin (g/L) were treated as two mediators in this study, where BP includes systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure [MAP, MAP = (SBP − DBP)/3 + DBP], and pulse pressure (PP, PP = SBP − DBP). All BP and Hb tests (i.e., repeated measurements) during pregnancy were collected for each mother.

2.4. Covariates

According to prior knowledge and the recommendation of directed acyclic graphs (DAGs) (Textor et al., 2016) (Fig. S4), a set of covariates, including maternal age, pre-pregnancy body mass index (BMI) (calculated based on collected pre-pregnancy height and weight), province (Fujian, Guangdong, Hebei, Hubei, Hunan, Liaoning, Sichuan, Yunnan), maternal education (< 6 years, 6–9 years, 10–12 years, or over 12 years), maternal migrant status (local or migrant), year of birth (2015, 2016, 2017, 2018), parity (multiparous or primiparous) and ambient temperature exposure during the entire pregnancy were selected and adjusted in the multivariate models. Since the effect of ambient temperature on birth weight might be nonlinear, we included a natural cubic spline of ambient temperature exposure during the entire pregnancy (degree of freedom = 3) in the model (Chen et al., 2018).

2.5. Statistical analyses

We used independent samples t-test for continuous variables and a chi-square test for categorical variables to examine differences in various maternal and infant characteristics between the SGA and AGA groups. Pearson product-moment correlation coefficients were used for correlations between air pollutants.

We used logistic regression models to estimate the total effects of $PM_{2.5}$ exposure on SGA in each gestational period (including the whole pregnancy and each trimester). When evaluating the relationship between different trimester exposures and SGA, we simultaneously included three trimesters of $PM_{2.5}$ exposures in the same model (Wilson et al., 2017; Wu et al., 2021).

$$logitP(Y=1|A,C)=\beta_0 \quad +\beta_a A+\beta_c C \tag{1}$$

Where β_0 indicated the intercept, β_a represented the coefficients for the exposure, and β_c denoted the coefficients for other covariates. The total effect risk ratio can be calculated as $R^{TE}=EXP(\beta_a)$.

When estimating mediation effects, we adopted a causal mediation approach under the potential outcomes framework (VanderWeele, 2016) to decompose the total effect (TE) of $PM_{2.5}$ of SGA into natural direct effect (NDE) and natural indirect effect (NIE) via maternal BP and Hb level during pregnancy. Informed by previous studies (VanderWeele, 2016; VanderWeele and Vansteelandt, 2014), we developed a framework to show the causal relationships among variables, as illustrated in Fig. 1. We assumed $PM_{2.5}$ may affect SGA through two pathways, influencing maternal BP and Hb level during pregnancy. In addition, two mediators were positively associated, as previous studies suggested (Atsma et al., 2012). Therefore, maternal Hb and BP may work independently and jointly to mediate the association between gestational $PM_{2.5}$ exposure and SGA. Following this framework, we estimated their independent and joint mediating effects.

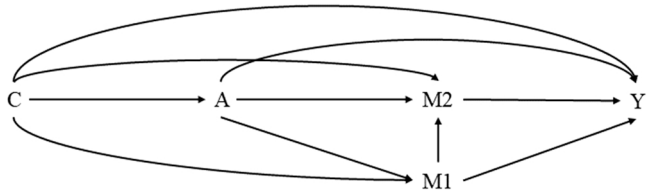

Fig. 1. Hypothetical framework for mediation analysis. Y was a binomial outcome (SGA and AGA). A denoted the exposure of interest ($PM_{2.5}$), and M(M_1 and M_2) denoted two continuous mediators (Hb and BP), respectively. C was a set of covariates, including province, pre-pregnancy body BMI, maternal education, maternal age, maternal migrant status, year of birth, parity, and the mean temperature during pregnancy.

A mediator model was fitted to estimate the effect of $PM_{2.5}$ exposure on BP or Hb in each gestational period. Given both mediators, BP and Hb, were measured repeatedly during the pregnancy, we used generalized estimating equations (GEE) with linear regression and an autoregressive structure for effect estimation. The model is as follows:

$$E(M_i|A,C)=\alpha_{0,i}+\alpha_{a,i}A+\alpha_{c,i}C, \text{ for } i= \quad 1, \quad 2 \tag{2}$$

For mediators M_i, $\alpha_{0,i}$ represented the intercept, $\alpha_{a,i}$ and $\alpha_{c,i}$ were coefficients for $PM_{2.5}$ and other covariates, respectively.

Then, we fitted the outcome model to estimate the direct effects of $PM_{2.5}$ exposure on SGA and estimated indirect effects of $PM_{2.5}$ exposure on SGA (i.e. mediating effects of maternal BP and Hb) by using the products from both the mediator model and outcome model (VanderWeele, 2016). Both independent and joint mediating effects of maternal BP and Hb were estimated.

When estimating the independent mediating effect of Hb ($M = M_1$), we fitted the outcome model shown as the model (3):

$$logitP(Y=1|A,M,C)=\beta'_0 \quad +\beta'_a A+\beta'_{m,1}M_1+\beta'_c C \tag{3}$$

Then the natural indirect effect risk ratio could be calculated as $R^{NIE}=EXP(\beta'_{m,1}\alpha_{a,1})$, and the natural direct effect can be calculated as $R^{NDE}=EXP(\beta'_a)$. Considering the operability, we included averaged maternal hemoglobin of each gestation period in the model.

When estimating the independent mediating effect of BP ($M = M_2$), we first tested the association between blood pressure and hemoglobin in each trimester and did find maternal BP levels were affected by hemoglobin levels. Therefore, Hb was treated as a mediator-outcome confounder affected by $PM_{2.5}$ exposure. We additionally included Hb in the outcome model, as shown in model (4) to accurately identify the mediating role of BP.

$$logitP(Y=1|A,M,C)=\beta''_0 \quad +\beta''_a A+\beta''_{m,1}M_1+\beta''_{m,2}M_2+\beta''_c C \tag{4}$$

In this case: $R^{NIE}=EXP(\beta''_{m,2}\alpha_{a,2})$, $R^{NDE}=EXP(\beta''_a)$.

When estimating the joint mediating effect of BP and Hb [$M = (M_1, M_2)$], a previous study suggested including all of the mediators under consideration in the outcome model (VanderWeele and Vansteelandt, 2014). It should be exactly the model (4). Then the joint natural indirect effect and direct effect can be calculated as $R^{NIE}=EXP\left(\beta''_{m,1}\alpha_{a,1}+\beta''_{m,2}\alpha_{a,2}\right)$, $R^{NDE}=EXP(\beta''_a)$, respectively.

If the estimated NDE and NIE were in the same direction (Yu et al., 2019), the proportion of mediation (PM) could be calculated as $R^{NDE}*(R^{NIE}-1)/(R^{TE}-1)$. The 95 % confidence intervals (CIs) for NIE and PM were estimated by bootstrapping with 500 replications (Efron, 1987).

Finally, we estimated the annual number of SGA attributable to gestational $PM_{2.5}$ exposure and those mediated by maternal blood pressure and hemoglobin. Based on the latest health statistics (China Statistical Yearbook 2021) launched by the National Bureau of Statistics (www.stats.gov.cn/tjsj./ndsj/), the number of SGA infants with an incidence rate of 10 % was estimated. Multiplying this with attributable risk [$AR=(OR-1)/OR$], we estimated the number of SGA attributable to gestational $PM_{2.5}$ exposure ($Number_{SGA\ attributable\ to\ gestatiowerenal\ PM2.5exposure}=Number_{SGA}*AR$). Here odds ratio (OR) and 95 % confidence interval (CI) were used as the estimated total effects of $PM_{2.5}$ exposure on SGA per 10 μg/m^3 increment in $PM_{2.5}$. Then the number of SGA attributable to gestational $PM_{2.5}$ exposure and mediated by blood pressure and hemoglobin was estimated as

$Number_{SGA\ mediated\ by\ BP\ and\ Hb} = Number_{SGA\ attributable\ to\ gestational\ PM2.5exposure} * Proportion\ of\ Mediation$.

All statistical analyses were completed with R Version 4.0.5.

2.6. Additional analyses

We performed the following sensitivity analyses to check the robustness of our results. First, we repeated our analyses by adjusting for the natural cubic spline of mean ambient temperature exposure during pregnancy with a degree of freedom (df) from 4 to 6 to test the influence of df selection on the confounding effects of ambient temperature. Second, we adjusted for confounding effects of other air pollutants. Considering the strong correlation between $PM_{2.5}$ and other pollutants such as CO, NO_2, and SO_2 (Table S1), we only performed a two-pollutant model that included both $PM_{2.5}$ and O_3. Third, we restricted the subjects to those with a gestational age greater than or equal to 37 weeks and reestimated the association between $PM_{2.5}$ and SGA to assess the impact of the length of exposure in the third trimester. Fourth, since not all counties in our study had at least one air pollution monitoring station, we repeated our analyses by restricting subjects to six counties with air pollution monitoring stations to assess the impact of exposure assessment on the effect estimation.

3. Results

The characteristics of mothers and newborns for SGA and AGA are shown in Table 1. Among the 117,162 newborns included in this study, 11,361 (9.70 %) were SGA, and 105,801 (90.30 %) were AGA. The average birth weight of SGA and AGA newborns was 2589.09 g and 3267.25 g, respectively. The mean (standard deviation, SD) concentration of $PM_{2.5}$ for SGA and AGA during the whole pregnancy was 51.04 (25.52) μg/m^3 and 51.96 (25.26) μg/m^3, respectively (Table 2). Table 3 shows the mean (SD) levels of SBP, DBP, and Hb over the whole pregnancy for SGA and AGA were 109.61 (8.77) mmHg and 109.27 (8.02) mHg, 68.81 (6.45) mmHg and 68.30 (5.78) mmHg, 118.92 (9.61) g/L and 118.02 (9.10) g/L, respectively.

As shown in Table 4, we observed that $PM_{2.5}$ exposure in the second trimester and the whole pregnancy were associated with an increased risk of SGA. For each 10 μg/m^3 increase in $PM_{2.5}$ exposure, ORs of SGA were 1.023 (95 % CI: 1.008, 1.037) and 1.025 (95 % CI: 1.002, 1.048), respectively. With per 10 μg/m^3 increase in second trimester $PM_{2.5}$, the SBP, DBP, MAP, and Hb in the second trimester increased by 0.092 mmHg, 0.083 mmHg, 0.087 mmHg, and 0.060 g/L, respectively; the SBP, DBP, MAP, PP, and Hb in the third trimester increased by 0.095 mmHg, 0.028 mmHg, 0.049 mmHg, 0.069 mmHg, and 0.116 g/L, respectively. $PM_{2.5}$ exposure in the whole pregnancy increased SBP, PP, and Hb in the third trimester by 0.107 mmHg, 0.122 mmHg, and 0.118 g/L, respectively. We also observed higher SBP, DBP, and Hb levels in the third trimester and the whole pregnancy were associated with an increased risk of SGA **(**Table S2**).**

We examined the associations between BP and Hb during the second and third trimesters as well as whole pregnancy and found two mediators were positively associated **(**Table S3**).** During the second trimester, with per 1 g/L increase in Hb, the SBP and DBP in the second trimester increased by 0.057 and 0.094 mmHg, respectively; during the third trimester, SBP and DBP increased by 0.059 and 0.088 mmHg, respectively. In the whole pregnancy, per 1 g/L increase in Hb increased SBP and DBP by 0.073 and 0.096 mmHg, respectively.

We observed independent mediation effects of BP and Hb in the second and third trimesters on the $PM_{2.5}$ and SGA association. Elevated blood pressure in the second and third trimesters mediated 1.64–5.78 % of the effect of $PM_{2.5}$ exposure on SGA. And elevated hemoglobin in the second and third trimesters mediated 2.40–8.70 % of the effect of $PM_{2.5}$ exposure on SGA (Table 5). However, we failed to find any mediating effect of pulse pressure in the association of $PM_{2.5}$ with SGA in the second trimester and whole pregnancy. As shown in Table 6, the joint mediation effects of maternal BP and Hb were stronger. Of the association between second-trimester $PM_{2.5}$ exposure and SGA, 3.93–13.69 % were mediated by the combination of BP and Hb in the second and third trimesters. In the third trimester, BP worked jointly with Hb to mediate 6.16–13.34 % of the whole pregnancy $PM_{2.5}$ exposure and SGA association. According to our estimation, the annual number of SGA attributable to $PM_{2.5}$ exposure per 10 μg/m3 increment was approximately 2.70 million (95 % CI: 1.07 million, 4.29 million). Among these, 106,110–369,630 SGA could be mediated by BP and Hb.

Table 1
Characteristics of mothers and newborns for SGA and AGA.

Variables		SGA	AGA	*P*
Total births, N (%)		11,361 (9.70)	105,801 (90.30)	< 0.001
Birth weight, Mean (SD), g		2589.09 (246.28)	3267.25 (292.97)	< 0.001
Gestational weeks, Mean (SD)		39.11 (1.30)	39.06 (1.29)	< 0.001
Maternal age, Mean (SD)		32.83 (6.73)	33.91 (6.42)	< 0.001
Infant sex, N (%)	Male	5549 (48.84)	56,016 (52.94)	< 0.001
	Female	5812 (51.16)	49,785 (47.06)	
Pre-pregnancy BMI, N(%)	< 18.5 kg/m^2	2703 (23.79)	14,951 (14.13)	< 0.001
	18.5–24 kg/m^2	6936 (61.05)	68,967 (65.19)	
	> 24 kg/m^2	1685 (14.83)	21,586 (20.4)	
	Unknown	37 (0.33)	297 (0.28)	
Province, N (%)	Hubei	923 (8.12)	8129 (7.68)	< 0.001
	Hunan	1986 (17.48)	19,611 (18.54)	
	Hebei	2064 (18.17)	19,989 (18.89)	
	Liaoning	612 (5.39)	9733 (9.20)	
	Guangdong	744 (6.55)	3536 (3.34)	
	Sichuan	1098 (9.66)	8951 (8.46)	
	Yunnan	1711 (15.06)	13,887 (13.13)	
	Fujian	2223 (19.57)	21,965 (20.76)	
Maternal education, N (%)	< 6 years	482 (4.24)	3547 (3.35)	< 0.001
	6–9 years	3906 (34.38)	33,591 (31.75)	
	10–12years	3391 (29.85)	30,857 (29.17)	
	> 12 years	3290 (28.96)	34,821 (32.91)	
	Unknown	292 (2.57)	2985 (2.82)	
Maternal migrant status, N (%)	Local	10,498 (92.40)	98,242 (92.86)	< 0.001
	Migrant	709 (6.24)	6717 (6.35)	
	Unknown	154 (1.36)	842 (0.80)	
Year of birth, N (%)	2015	2580 (22.71)	23,867 (22.56)	< 0.001
	2016	3461 (30.46)	33,664 (31.82)	
	2017	3096 (27.25)	28,706 (27.13)	
	2018	2224 (19.58)	19,564 (18.49)	
Parity, N(%)	Multiparous	6662 (58.64)	55,076 (52.06)	< 0.001
	Primiparous	4692 (41.30)	50,714 (47.93)	
Season of conception, N (%)	Spring	2810 (24.73)	26,558 (25.10)	0.78
	Summer	3117 (27.44)	28,731 (27.16)	
	Fall	2876 (25.31)	26,569 (25.11)	
	Winter	2558 (22.52)	23,943 (22.63)	

Table 2
Distribution of $PM_{2.5}$ (μg/m^3) concentration and ambient temperature (℃) during pregnancy.

Pregnancy period	Mean (SD)	Percentiles		
		25th	50th	75th
SGA				
$PM_{2.5}$_WP[a]	51.04 (25.52)	28.83	47.49	66.46
$PM_{2.5}$_T1[a]	51.20 (31.57)	28.56	42.37	65.06
$PM_{2.5}$_T2[a]	51.24 (30.97)	29.81	40.93	64.27
$PM_{2.5}$_T3[a]	50.62 (32.24)	30.07	40.15	62.69
Temperature[b] (℃)	17.10 (3.73)	15.13	17.32	19.94
AGA				
$PM_{2.5}$_WP[a]	51.96 (25.26)	29.33	49.05	67.11
$PM_{2.5}$_T1[a]	52.24 (31.58)	29.80	44.09	65.99
$PM_{2.5}$_T2[a]	52.00 (30.43)	30.46	42.41	65.33
$PM_{2.5}$_T3[a]	51.60 (32.56)	30.78	41.18	63.14
Temperature[b] (℃)	16.74 (3.97)	14.87	17.07	19.78

[a] $PM_{2.5}$_WP: average maternal $PM_{2.5}$ exposure during the whole pregnancy; $PM_{2.5}$_T1: average maternal $PM_{2.5}$ exposure in the first trimester; $PM_{2.5}$_T2: average maternal $PM_{2.5}$ exposure in the second trimester; $PM_{2.5}$_T3: average maternal $PM_{2.5}$ exposure in the third trimester.
[b] Temperature: the mean temperature of the whole pregnancy.

Table 3
Blood pressure (mmHg) and hemoglobin concentration (g/L) during pregnancy.

Pregnancy period	Mean (SD)		
	Number of tests	SGA	AGA
SBP_WP[a]	7.94 (2.77)	109.61 (8.77)	109.27 (8.02)
SBP_T1[a]	0.77 (0.61)	105.83 (10.96)	105.79 (10.46)
SBP_T2[a]	2.82 (1.03)	107.67 (9.62)	107.65 (9.17)
SBP_T3[a]	4.36 (2.06)	111.76 (10.33)	111.01 (9.08)
DBP_WP[b]	7.94 (2.77)	68.81 (6.45)	68.30 (5.78)
DBP_T1[b]	0.77 (0.61)	67.5 (7.98)	67.31 (7.56)
DBP_T2[b]	2.82 (1.03)	67.26 (6.94)	67.00 (6.53)
DBP_T3[b]	4.36 (2.06)	70.2 (7.81)	69.39 (6.72)
Hb_WP[c]	4.53 (1.56)	118.92 (9.61)	118.02 (9.10)
Hb_T1[c]	0.68 (0.51)	126.15 (12.32)	126.11 (11.84)
Hb_T2[c]	1.88 (0.85)	118.65 (10.33)	118.01 (10.04)
Hb_T3[c]	1.98 (1.04)	116.82 (10.80)	115.36 (10.35)

[a] SBP_WP: maternal SBP during the whole pregnancy; SBP_T1: maternal SBP in the first trimester, SBP_T2: maternal SBP in the second trimester; SBP_T3: maternal SBP in the third trimester.
[b] DBP_WP: maternal DBP during the whole pregnancy; DBP_T1: maternal DBP in the first trimester, DBP_T2: maternal DBP in the second trimester; DBP_T3: maternal DBP in the third trimester.
[c] Hb_WP: maternal Hb during the whole pregnancy; Hb_T1: maternal Hb in the first trimester; Hb_T2: maternal Hb in the second trimester; Hb_T3: maternal Hb in the third trimester.

In additional analyses, by changing the degrees of freedom for natural cubic spline of ambient temperature exposure from 4 to 6, the effect estimates of $PM_{2.5}$ exposure on SGA were similar (Table S4). When $PM_{2.5}$ and O_3 were included in a two-pollutant model, we still found consistent effects of $PM_{2.5}$ exposure during pregnancy on SGA, BP, and Hb (Table S5). When restricting the subjects to the pregnant women with term-born infants (n = 113,794), we observed similar associations between $PM_{2.5}$ exposure in different trimesters and SGA (Table S6). By restricting subjects to six counties with air pollution monitoring stations, 36,161 individuals (30.86 % of subjects ultimately included in the analysis) remained. We still observed similar results that second-trimester $PM_{2.5}$ exposure was associated with SGA, although the effect was nonsignificant for the whole pregnancy $PM_{2.5}$ exposure. The mediating effects of BP and Hb on the association between second-trimester $PM_{2.5}$ exposure and SGA were consistent with the main results (Table S7; Table S8).

Table 4
Estimated effects of ambient $PM_{2.5}$ (each 10 ug/m^3 increase) on SGA, blood pressure (mmHg), and hemoglobin (g/L).

Exposure	Outcome	
		OR (95 % CI)[a]
$PM_{2.5}$_WP	SGA	1.025 (1.002, 1.048)
$PM_{2.5}$_T1	SGA	1.004 (0.993, 1.016)
$PM_{2.5}$_T2	SGA	1.023 (1.008, 1.037)
$PM_{2.5}$_T3	SGA	0.997 (0.987, 1.008)
		β (95 % CI)[a]
$PM_{2.5}$_T2	SBP_T2	0.092 (0.061, 0.123)
	DBP_T2	0.083 (0.061, 0.105)
	MAP_T2	0.087 (0.064, 0.110)
	PP_T2	0.008 (− 0.013, 0.030)
	Hb_T2	0.060 (0.027, 0.092)
$PM_{2.5}$_T2	SBP_T3	0.095 (0.064, 0.126)
	DBP_T3	0.028 (0.004, 0.051)
	MAP_T3	0.049 (0.025, 0.073)
	PP_T3	0.069 (0.048, 0.091)
	Hb_T3	0.116 (0.083, 0.149)
$PM_{2.5}$_WP	SBP_T3	0.107 (0.048, 0.167)
	DBP_T3	-0.010 (− 0.055, 0.034)
	MAP_T3	0.028 (− 0.019, 0.074)
	PP_T3	0.122 (0.081, 0.163)
	Hb_T3	0.118 (0.055, 0.181)

[a] Adjusted for maternal age, pre-pregnancy body BMI, province, maternal education, maternal migrant status, year of birth, parity, and the mean temperature over the same gestational period as the exposure.

4. Discussion

Based on this large sample prospective birth cohort study, we found robust findings that exposure to $PM_{2.5}$ was associated with an increased risk of SGA, especially during the second trimester. One novel finding in the present study is that we observed maternal BP and Hb in the second and third trimesters independently and jointly mediated the effects of $PM_{2.5}$ exposure on SGA. As far as we know, this is the first study to empirically assess the role of elevated maternal BP and Hb on the pathways of $PM_{2.5}$ exposure and SGA. The findings could be beneficial to better understanding mechanisms underlying the association between air pollution and adverse birth outcomes. Furthermore, our findings could have important implications in supporting the monitoring and management of maternal BP and Hb during prenatal care, which may potentially reduce the risk of adverse birth outcomes associated with air pollution.

Blood pressure during pregnancy could be affected by maternal $PM_{2.5}$ exposure. It is well documented that air pollution may result in oxidative stress. When pregnant women are exposed to higher concentrations of $PM_{2.5}$, the induced placental oxidative stress may release antiangiogenic factors into the maternal circulation, which can lead to some maternal inflammatory responses, including endothelial dysfunction and increased blood pressure (Kingdom and Kaufmann, 1997; Macdonald-Wallis et al., 2014). In this study, we also observed that $PM_{2.5}$ exposure in the second trimester and the whole pregnancy were associated with elevated blood pressure in the later pregnancy, which was consistent with the findings of some previous epidemiological studies (Lan et al., 2021; Mandakh et al., 2020; Mobasher et al., 2013). Yet, increased blood pressure may adversely affect the development of the placental villous tree, leading to decreased placental function and reduced placental transport of oxygen and nutrients, which may result in intrauterine growth restriction (Kingdom and Kaufmann, 1997). Based on those mentioned above and epidemiological evidence, it's plausible that maternal blood pressure may play a role in the pathway of maternal $PM_{2.5}$ exposure and SGA. However, no previous study has provided direct evidence to show how maternal blood pressure could link $PM_{2.5}$ exposure and SGA. A previous study suggested that blood pressure may mediate the association between air pollution and adverse birth outcomes, but the magnitude of the mediation effect and mediation

Table 5
Estimates of the independent mediating effects of BP and Hb on the association between exposure to $PM_{2.5}$ and SGA during pregnancy.

Exposure	Mediator	R^{TE} (95 % CI)[a]	R^{NDE} (95 % CI)[a]	R^{NIE} (95 % CI)[a]	PM (%)[a]
$PM_{2.5}$_T2	SBP_T2	1.023 (1.008, 1.037)	1.023 (1.009, 1.037)	1.0004 (1.0003, 1.0005)	1.64 (1.36, 2.19)
	DBP_T2		1.022 (1.008, 1.037)	1.0010 (1.0009, 1.0014)	4.69 (4.24, 6.12)
	MAP_T2		1.022 (1.008, 1.037)	1.0009 (1.0008, 1.0012)	3.97 (3.60, 5.40)
	PP_T2		1.023 (1.009, 1.038)	1.0000 (0.9999, 1.0001)	–
	Hb_T2		1.023 (1.009, 1.038)	1.0005 (1.0003, 1.0008)	2.40 (1.55, 3.55)
$PM_{2.5}$_T2	SBP_T3	1.023 (1.008, 1.037)	1.024 (1.009, 1.038)	1.0012 (1.0009, 1.0014)	5.57 (3.87, 6.13)
	DBP_T3		1.025 (1.011, 1.039)	1.0006 (1.0002, 1.0009)	2.91 (0.68, 3.84)
	MAP_T3		1.024 (1.010, 1.039)	1.0011 (1.0006, 1.0012)	4.82 (2.70, 5.41)
	PP_T3		1.023 (1.009, 1.038)	1.0000 (0.9998, 1.0002)	–
	Hb_T3		1.023 (1.009, 1.038)	1.0019 (1.0017, 1.0025)	8.70 (7.44, 11.20)
$PM_{2.5}$_WP	SBP_T3	1.025 (1.002, 1.048)	1.022 (0.999, 1.046)	1.0013 (1.0007, 1.0016)	5.78 (2.80, 6.68)
	DBP_T3		1.024 (1.001. 1.047)	0.9998 (0.9988, 1.0000)	–
	MAP_T3		1.023 (1.000, 1.047)	1.0006 (0.9997, 1.0008)	2.48 (− 1.25, 3.32)
	PP_T3		1.023 (1.000, 1.047)	1.0000 (0.9996, 1.0004)	–
	Hb_T3		1.023 (1.000, 1.047)	1.0019 (1.0011, 1.0028)	8.13 (4.64, 11.67)

[a] R^{TE}: total effect risk ratio; R^{NDE}: natural direct effect risk ratio; R^{NIE}: natural indirect effect risk ratio; PM: proportion mediated.

Table 6
Estimates of the joint mediating effects of BP and Hb on the association between exposure to $PM_{2.5}$ and SGA during pregnancy.

Exposure	Mediators[a]	R^{TE} (95 % CI)[a]	R^{NDE} (95 % CI)[a]	R^{NIE} (95 % CI)[a]	PM (%)[a]
$PM_{2.5}$_T2	SBP_T2 and Hb_T2	1.023 (1.008, 1.037)	1.023 (1.009, 1.037)	1.0008 (1.0007, 1.0012)	3.93 (3.16, 5.35)
	DBP_T2 and Hb_T2		1.022 (1.008, 1.037)	1.0015 (1.0013, 1.0020)	6.79 (5.92, 9.04)
	MAP_T2 and Hb_T2		1.022 (1.008, 1.037)	1.0014 (1.0012, 1.0018)	6.12 (5.40, 8.09)
$PM_{2.5}$_T2	SBP_T3 and Hb_T3	1.023 (1.008, 1.037)	1.024 (1.009, 1.038)	1.0030 (1.0025, 1.0035)	13.69 (11.36, 15.83)
	DBP_T3 and Hb_T3		1.025 (1.011, 1.039)	1.0024 (1.0017, 1.0028)	10.61 (7.77, 12.82)
	MAP_T3 and Hb_T3		1.0024 (1.010, 1.039)	1.0028 (1.0022, 1.0032)	12.57 (9.91, 14.42)
$PM_{2.5}$_WP	SBP_T3 and Hb_T3	1.025 (1.002, 1.048)	1.022 (0.999, 1.046)	1.0032 (1.0019, 1.0039)	13.34 (8.07, 16.15)
	DBP_T3 and Hb_T3		1.024 (1.001. 1.047)	1.0014 (1.0001, 1.0022)	6.16 (0.59, 9.10)
	MAP_T3 and Hb_T3		1.023 (1.000, 1.047)	1.0023 (1.0013, 1.0026)	9.69 (5.40, 10.80)

[a] R^{TE}: total effect risk ratio; R^{NDE}: natural direct effect risk ratio; R^{NIE}: natural indirect effect risk ratio; PM: proportion mediated.

proportion was not reported (Lee et al., 2012). In the present study, we first estimated the mediation proportions ranging from 1.64 % to 5.78 % for maternal blood pressure at different gestational periods in the association between $PM_{2.5}$ and SGA.

In parallel, we also found a mediating role of maternal hemoglobin in the association between $PM_{2.5}$ exposure and SGA. Previous studies have found that exposure to higher concentrations of ambient $PM_{2.5}$ increased reticulocyte levels in peripheral blood, stimulated the bone marrow to release erythropoietin, and was associated with increased hemoglobin concentrations (Medeiros et al., 2004; Sørensen et al., 2002). In this study, we similarly observed that $PM_{2.5}$ exposure during pregnancy increased maternal hemoglobin concentrations. Excessive hemoglobin concentration may increase blood viscosity and affect placental blood flow, which could, in turn, interfere with uteroplacental circulation and adversely affects fetal growth and development (Dewey and Oaks, 2017; Rasmussen and Oian, 1993). At the same time, the reduction in hemoglobin concentration during pregnancy is a proxy for increased plasma volume during pregnancy, which could decrease the risk of adverse birth outcomes, including LBW and SGA (Jwa et al., 2015). Our study further confirmed these findings, where we observed higher hemoglobin levels in mid to late pregnancy and the whole pregnancy were associated with an increased risk of SGA. We further found high hemoglobin in the later pregnancy mediated the effects of $PM_{2.5}$ exposure on SGA. Another study from Wuhan, China, reported that $PM_{2.5}$ exposure in early pregnancy was associated with intrauterine growth restriction, and elevated maternal hemoglobin concentrations mediated the association (Liao et al., 2019) with a proportion of 12.1 % (without reporting 95 % confidence intervals for proportion of mediation). In our study, the estimated mediation proportion of maternal hemoglobin was 2.40–8.70 %, lower than that reported in Liao et al.'s study. The difference may be partly because the two studies used different indicators for intrauterine growth restriction. The Wuhan study measured fetal crown-to-rump length (CRL) at 11–14 gestational weeks, while we used SGA as a measure of fetal growth during the whole pregnancy. Therefore, they examined the mediating effect of hemoglobin in early gestation, but we were able to explore it by trimesters.

Furthermore, we observed the joint mediation effect of maternal BP and Hb during the second and third trimesters on the $PM_{2.5}$ exposure and SGA relationship. Previous studies have found that high hemoglobin was associated with a higher risk of subsequent preeclampsia (Hachey et al., 2020; Mogaddam et al., 2019), and maternal hemoglobin concentrations were negatively associated with birth weight (Amburgey et al., 2009). On the other hand, both preeclampsia and gestational hypertension have been reported to increase the risk of SGA (McCowan and Horgan, 2009; Odegard et al., 2000). One of the conditions for the development of preeclampsia is an increase in capillary endothelial permeability, which will lead to a decrease in blood volume and a consequent increase in maternal hemoglobin concentration (Aghamohammadi et al., 2011). And, free hemoglobin and hemoglobin released into the placental vascular lumen are potent toxins that may cause endothelial damage and inflammation, which will further promote the development of preeclampsia (Centlow et al., 2008). Thus high hemoglobin can be used to predict the development of hypertensive disorders during pregnancy. This suggests that increased blood pressure and high hemoglobin levels are closely related and may jointly contribute to

placental dysfunction.

Although ambient $PM_{2.5}$ concentrations in China have been decreasing in recent years, they are still above the WHO guideline value of 10 μg/m^3. Moreover, with China's large population size and the implementation of the three-child policy launched in 2021 (Tatum, 2021), we expect the number of newborns will increase shortly. Adverse birth outcomes (including SGA) attributed to $PM_{2.5}$ exposure during pregnancy will be a significant public health problem. While monitoring blood pressure and hemoglobin provides an opportunity for managing the harmful effect of $PM_{2.5}$ exposure during pregnancy.

We investigated for the first time the potential mediating role of maternal blood pressure and hemoglobin in the relationship between $PM_{2.5}$ and SGA. Based on a prospective cohort study with relatively large sample size, we provided convincing evidence for understanding the effects of gestational $PM_{2.5}$ exposure and adverse birth outcomes and the potential causal pathways. Our findings may inform public health interventions, environmental policies, and prenatal care. Some limitations should be acknowledged. First, we collected pregnant women's residency addresses at a sub-district level and used inverse distance weighting to assess individuals' exposure. However, we did not collect maternal activity status and residential mobility during pregnancy. We were unable to measure their indoor $PM_{2.5}$ exposure either. Without taking into account, these factors could lead to exposure to misclassification. However, the exposure misclassification is more likely non-differential and usually results in underestimation of effects. In addition, we used a mass concentration of $PM_{2.5}$ as the exposure. $PM_{2.5}$ is a mixture of chemical components that may cause different health impacts. However, we were unable to distinguish the various possible effects due to the lack of data on $PM_{2.5}$ chemical components. And some important confoundings, such as pregnant women smoking, alcohol, diet, exercise, etc., were unavailable; without adjusting for them, the estimation could be biased.

5. Conclusions

In conclusion, $PM_{2.5}$ exposure in the second trimester and the whole pregnancy was associated with an increased risk of SGA, and maternal blood pressure and hemoglobin during the second and third trimester mediated this association. Our findings can strengthen the evidence on maternal $PM_{2.5}$ exposure and SGA, and also add to our understanding of the causal pathways of $PM_{2.5}$ exposure during pregnancy and SGA. These findings may have important public health and clinical implications in informing public health interventions, environmental policies, and prenatal care.

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CRediT authorship contribution statement

Zhenghong Zhu, Qiong Wang: Conceptualization. **Qiong Wang:** Funding acquisition. **Tarik Benmarhnia, Zhoupeng Ren, Jiajun Luo:** Methodology, Validation. **Wei Zhao, Sidi Chen:** Investigation. **Kaipu Wu, Xiaoxin Zhang, Liyun Wang:** Data curation. **Zhenghong Zhu, Huanqing Hu:** Software, Formal analysis, Visualization, Writing – original draft. **Zhenghong Zhu, Qiong Wang:** Writing – review & editing. **Jiangli Di, Cunrui Huang:** Project administration, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2022.113836.

References

Aghamohammadi, A., Zafari, M., Tofighi, M., 2011. High maternal hemoglobin concentration in first trimester as risk factor for pregnancy induced hypertension. Casp. J. Intern. Med. 2, 194–197.
Amburgey, O., Ing, E., Badger, G., et al., 2009. Maternal hemoglobin concentration and its association with birth weight in newborns of mothers with preeclampsia. J. Matern.-Fetal Neonatal. Med. 22, 740–744.
Atsma, F., Veldhuizen, I., de Kort, W., et al., 2012. Hemoglobin level is positively associated with blood pressure in a large cohort of healthy individuals. Hypertension 60, 936–941.
Bakker, R., Steegers, E.A., Hofman, A., et al., 2011. Blood pressure in different gestational trimesters, fetal growth, and the risk of adverse birth outcomes: the generation R study. Am. J. Epidemiol. 174, 797–806.
Bonamy, A.K., Parikh, N.I., Cnattingius, S., et al., 2011. Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth. Circulation 124, 2839–2846.
Brook, R.D., Rajagopalan, S., Pope III, C.A., et al., 2010. Particulate matter air pollution and cardiovascular disease an update to the scientific statement from the american heart association. Circulation 121, 2331–2378.
Centlow, M., Carninci, P., Nemeth, K., et al., 2008. Placental expression profiling in preeclampsia: local overproduction of hemoglobin may drive pathological changes. Fertil. Steril. 90, 1834–1843.
Chen, G., Guo, Y., Abramson, M.J., et al., 2018. Exposure to low concentrations of air pollutants and adverse birth outcomes in Brisbane, Australia, 2003–2013. Sci. Total Environ. 622, 721–726.
Dai, L., Deng, C., Li, Y., et al., 2014. Birth weight reference percentiles for Chinese. PLoS One 9, e104779.
Dewey, K.G., Oaks, B.M., 2017. U-shaped curve for risk associated with maternal hemoglobin, iron status, or iron supplementation. Am. J. Clin. Nutr. 106, 1694S–1702S.
Ding, G., Tian, Y., Zhang, Y., et al., 2013. Application of a global reference for fetal-weight and birthweight percentiles in predicting infant mortality. BJOG 120, 1613–1621.
Efron, B., 1987. Better bootstrap confidence intervals. J. Am. Stat. Assoc. 82, 171–185.
Guo, P., Chen, Y., Wu, H., et al., 2020. Ambient air pollution and markers of fetal growth: a retrospective population-based cohort study of 2.57 million term singleton births in China. Environ. Int. 135, 105410.
Hachey, S., Alderfer, K., Anasti, J.N., et al., 2020. Elevated early third trimester hemoglobin as a predictor of preeclampsia. Obstet. Gynecol. 135, 128S.
Hannam, K., McNamee, R., Baker, P., et al., 2014. Air pollution exposure and adverse pregnancy outcomes in a large UK birth cohort: use of a novel spatio-temporal modelling technique. Scand. J. Work Environ. Health 40, 518-30.
Horn, J., Haug, E.B., Markovitz, A.R., et al., 2020. Life course trajectories of maternal cardiovascular risk factors according to offspring birthweight: the HUNT study. Sci. Rep. 10, 1–12.
Hyder, A., Lee, H.J., Ebisu, K., et al., 2014. PM2.5 exposure and birth outcomes: use of satellite- and monitor-based data. Epidemiology 25 (58–67).
Jwa, S.C., Fujiwara, T., Yamanobe, Y., et al., 2015. Changes in maternal hemoglobin during pregnancy and birth outcomes. BMC Pregnancy Childbirth 15, 80.
Kesavan, K., Devaskar, S.U., 2019. Intrauterine growth restriction: postnatal monitoring and outcomes. Pediatr. Clin. N. Am. 66, 403–423.
Kingdom, J.C.P., Kaufmann, P., 1997. Oxygen and placental villous development: origins of fetal hypoxia. Placenta 18, 613–621.
Lan, C., Liu, Y., Li, Q., et al., 2021. Internal metal(loid)s are potentially involved in the association between ambient fine particulate matter and blood pressure: A repeated-measurement study in north China. Chemosphere 267, 129146.
Lee, P.-C., Talbott, E.O., Roberts, J.M., et al., 2012. Ambient air pollution exposure and blood pressure changes during pregnancy. Environ. Res. 117, 46–53.

Liao, J., Li, Y., Wang, X., et al., 2019. Prenatal exposure to fine particulate matter, maternal hemoglobin concentration, and fetal growth during early pregnancy: associations and mediation effects analysis. Environ. Res. 173, 366–372.
Liu, Y., Li, N., An, H., et al., 2021. Impact of gestational hypertension and preeclampsia on low birthweight and small-for-gestational-age infants in China: a large prospective cohort study. J. Clin. Hypertens. 23, 835–842.
Macdonald-Wallis, C., Tilling, K., Fraser, A., et al., 2014. Associations of blood pressure change in pregnancy with fetal growth and gestational age at delivery: findings from a prospective cohort. Hypertension 64, 36–44.
Mandakh, Y., Rittner, R., Flanagan, E., et al., 2020. Maternal exposure to ambient air pollution and risk of preeclampsia: a population-based cohort study in Scania. Swed. Int. J. Environ. Res. Public Health 17, 1744.
McCowan, L., Horgan, R.P., 2009. Risk factors for small for gestational age infants. Best Pract. Res. Clin. Obstet. Gynaecol. 23, 779–793.
Medeiros Jr., N., Rivero, D.H., Kasahara, D.I., et al., 2004. Acute pulmonary and hematological effects of two types of particle surrogates are influenced by their elemental composition. Environ. Res. 95, 62–70.
Melody, S., Wills, K., Knibbs, L.D., et al., 2020. Adverse birth outcomes in Victoria, Australia in association with maternal exposure to low levels of ambient air pollution. Environ. Res. 188, 109784.
Ministry of Environmental Protection, 2012. Ambient Air Quality Standards (GB 3095-2012) (Available online: ⟨https://www.mee.gov.cn/ywgz/fgbz/bz/bzwb/dqhjbh/dqhjzlbz/201203/W020120410330232398521.pdf⟩, (Accessed 20 May 2022)).
Mobasher, Z., Salam, M.T., Goodwin, T.M., et al., 2013. Associations between ambient air pollution and hypertensive disorders of pregnancy. Environ. Res. 123, 9–16.
Mogaddam, M.R., Ardebili, N.S., Kariman, N., 2019. The relation between the incidence rate of second and third trimester hemoglobin and the incidence of preeclampsia and gestational diabetes: a cohort study. Crescent J. Med. Biol. Sci. 6, 85–90.
Odegard, R.A., Vatten, L.J., Nilsen, S.T., et al., 2000. Preeclampsia and fetal growth. Obstet. Gynecol. 96, 950–955.
Pariente, G., Shoham Vardi, I., Kessous, R., et al., 2015. Delivery of an SGA neonate as an independent risk factor for long-term maternal chronic kidney disease. Am. J. Obstet. Gynecol. 212, S387.
Percy, Z., DeFranco, E., Xu, F., et al., 2019. Trimester specific PM2.5 exposure and fetal growth in Ohio, 2007–2010. Environ. Res. 171, 111–118.
Phaloprakarn, C., Tangjitgamol, S., 2008. Impact of high maternal hemoglobin at first antenatal visit on pregnancy outcomes: a cohort study. J. Perinat. Med. 36, 115–119.
Rasmussen, S., Oian, P., 1993. First- and second-trimester hemoglobin levels. Relation to birth weight and gestational age. Acta Obstet. Gynecol. Scand. 72, 246–251.
Roberts, J.D., Voss, J.D., Knight, B., 2014. The association of ambient air pollution and physical inactivity in the United States. PLoS One 9, e90143.
Scanlon, K., 2000. High and low hemoglobin levels during pregnancy: differential risks for preterm birth and small for gestational age. Obstet. Gynecol. 96, 741–748.
Sebastiani, G., Diaz, M., Bassols, J., et al., 2016. The sequence of prenatal growth restraint and post-natal catch-up growth leads to a thicker intima-media and more pre-peritoneal and hepatic fat by age 3–6 years. Pediatr. Obes. 11, 251–257.
Sørensen, M., Daneshvar, B., Hansen, M., et al., 2002. Personal PM2.5 exposure and markers of oxidative stress in blood. Environ. Health Perspect. 111, 161–165.
Steer, P.J., 2000. Maternal hemoglobin concentration and birth weight. Am. J. Clin. Nutr. 71, 1285S–1287S.
Stieb, D.M., Chen, L., Beckerman, B.S., et al., 2016. Associations of pregnancy outcomes and PM2.5 in a National Canadian study. Environ. Health Perspect. 124, 243–249.
Tapia, V.L., Vasquez, B.V., Vu, B., et al., 2020. Association between maternal exposure to particulate matter (PM2.5) and adverse pregnancy outcomes in Lima, Peru. J. Expo. Sci. Environ. Epidemiol. 30, 689–697.
Tatum, M., 2021. China's three-child policy. Lancet 397, 2238.
Textor, J., van der Zander, B., Gilthorpe, M.S., et al., 2016. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. Int. J. Epidemiol. 45, 1887–1894.
VanderWeele, T.J., 2016. Mediation analysis: a practitioner's guide. Annu. Rev. Public Health 37, 17–32.
VanderWeele, T.J., Vansteelandt, S., 2014. Mediation analysis with multiple mediators. epidemiol. Methods 2, 95–115.
von Tempelhoff, G.-F., Heilmann, L., Rudig, L., et al., 2008. Mean maternal second-trimester hemoglobin concentration and outcome of pregnancy: a population-based study. Clin. Appl. Thromb./Hemost. 14, 19–28.
Wilson, A., Chiu, Y.M., Hsu, H.L., et al., 2017. Potential for bias when estimating critical windows for air pollution in children's health. Am. J. Epidemiol. 186, 1281–1289.
Wu, K., Hu, H., Ren, Z., et al., 2021. Effects of maternal exposure to fine particulate matter on birth weight in 16 counties across China: a quantile regression analysis. Environ. Res. Lett. 16, 055014.
Yazdani, M., Tadbiri, M., Shakeri, S., 2004. Maternal hemoglobin level, prematurity, and low birth weight. Int. J. Gynaecol. Obstet. 85, 163–164.
Yu, Y., Liew, Z., Wang, A., et al., 2019. Mediating roles of preterm birth and restricted fetal growth in the relationship between maternal education and infant mortality: a Danish population-based cohort study. PLoS Med. 16, e1002831.