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The mediating effect of maternal blood lipids on the association between maternal exposure to $PM_{2.5}$ and birth weight: a retrospective birth cohort study in Zhejiang, China

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Abstract

Background Maternal $PM_{2.5}$ exposure and lipid levels during pregnancy were independently detected associated with birth weight. Potential mediating factors still remain unclear.

Methods This study aimed to examine the association of maternal $PM_{2.5}$ exposure and birth weight, and explore the potential mediation effect of maternal blood lipids in the relationship between $PM_{2.5}$ exposure and birth weight. 5,162 pregnant women from Zhejiang, China were included in the study during 2013–2014. We measured blood lipids for each participant in the second and third trimesters. Air pollution exposure in residential districts was estimated based on satellite data for each individual throughout three trimesters in pregnancy. Linear mixed-effects models were employed to examine associations between $PM_{2.5}$ and birth weight. Using a mediation analysis approach, we decomposed the total effect of $PM_{2.5}$ on birth weight into natural direct and indirect effects via blood lipid concentration.

Results After adjusting for covariates, a 10 μg/m^3 increment in $PM_{2.5}$ during the second trimester was directly associated with an 11.65 g increase in birth weight (95% CI: 2.99, 20.31 g). The indirect effects of $PM_{2.5}$ exposure (each 10 μg/m^3 increase) on birth weight, mediated through elevated maternal lipid levels, were − 2.35 g (95% CI: -4.07, -0.63 g) for total cholesterol to high-density lipoprotein cholesterol ratio (TC: HDL ratio), -0.69 g (95% CI: -1.16, -0.22 g) for Triglycerides (TG), and − 1.80 g (95% CI: -3.19, -0.41 g) for HDL-C, during the second trimester.

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Conclusions Findings suggest prenatal $PM_{2.5}$ exposure may impact term birth weight via direct biological effects and lipid-mediated pathways, underscoring the importance of incorporating air pollution mitigation into perinatal care and advancing biomarker-driven fetal monitoring. Future research should clarify $PM_{2.5}$ component-specific effects, decode placental-fetal lipid regulatory mechanisms, and validate pollution-metabolism-outcome relationships through multi-regional cohorts to inform precision environmental health interventions and clinical risk management.

Keywords Birth weight, $PM_{2.5}$, Maternal lipids, Mediation effect

Introduction

Fine particulate matter (PM ≤ 2.5 μg in aerodynamic diameter ($PM_{2.5}$)) is an important component of air particulate matter that can enter the human body through the respiratory system and be deposited in organs and tissues throughout the body. In recent years, many epidemiological studies have confirmed the association of $PM_{2.5}$ with the occurrence of a series of diseases [1–3] and its close relationship with adverse pregnancy outcomes in pregnant individuals [4]. A robust epidemiological analysis [5] revealed significant linkages between gestational exposure to $PM_{2.5}$, atmospheric ozone, and elevated thermal conditions with heightened risks of preterm delivery, neonatal underweight, and intrauterine fetal demise. The conclusions drawn from these studies indicate a consistent association between prenatal exposure to $PM_{2.5}$ or ozone and an increased risk of low birth weight. Specifically, of the 29 studies reviewed, 25 studies, accounting for 86% of them, reported a statistically significant link between exposure to $PM_{2.5}$ or ozone and the incidence of low birth weight. Among the variables studied, birth weight is highly important because it reflects fetal growth and development. Moreover, it has been associated with the risk of developing metabolic diseases during childhood and adulthood [6, 7]. Utilizing high-resolution spatiotemporal pollution mapping, a prospective cohort study in the Eastern Massachusetts region systematically evaluated gestational $PM_{2.5}$ inhalation impacts on intrauterine growth patterns, incorporating serial ultrasonography data and parturition weight metrics. Previous studies have investigated the $PM_{2.5}$ exposure-linked variations in neonatal weight, even if the exposure magnitude is lower than the current national standard [8]. The underlying mechanism correlating birth weight with maternal exposure to $PM_{2.5}$ remains unclear despite sufficient case evidence. Possible mechanisms, such as vascular remodeling, inflammation, oxidative stress, immunity and epigenetic inheritance, have been proposed in previous studies.

Lipid metabolism in pregnant women is affected by multiple factors, which are crucial to the health of newborns [9–13]. It modulates fetal development and is closely related to fetal weight growth [14, 15]. Existing epidemiological research has established connections between ambient pollutant exposure and perturbations in lipid metabolism homeostasis [16]. Prolonged inhalation of atmospheric pollutants has shown correlations with changes in lipid profiles and the development of dyslipidemia [17]. Several epidemiological studies have investigated the effects of maternal $PM_{2.5}$ exposure on lipid metabolism. A prospective perinatal cohort analysis [18] identified elevated first-trimester $PM_{2.5}$ exposure (≥ 25 μg/m^3) as a potential risk modulator for dyslipidemia. The results were, however, statistically insignificant. The placenta, a critical interface between maternal and fetal environments, may mediate these effects through epigenetic or transcriptomic changes. In a US birth cohort [19] published in 2022, the complex interplay between maternal exposure to $PM_{2.5}$ during pregnancy and its potential impact on the placenta's genetic expression related to critical metabolic processes, specifically those involving lipid (fat) and glucose (sugar) metabolism, was investigated. Through phased urine metabolomics profiling in a Jiangsu birth cohort ($n = 1024$ gravid women), researchers mapped 1245 time-sensitive metabolic perturbations linking early-pregnancy xenobiotic mixtures (106 agents) to late-pregnancy lipidomic/amino acid dysregulation (139 biomarkers). The study suggests that changes in maternal metabolites may serve as a key mechanism linking prenatal environmental exposures to offspring health outcomes, such as birth weight, neurodevelopment, and immune disorders. This highlights that pollutant-driven alteration of the prenatal biochemical profiles may mediate the relationship between prenatal exposures and maternal-child health outcomes [20]. Additionally, $PM_{2.5}$ components, such as polycyclic aromatic hydrocarbons (PAHs), can act as ligands for aryl hydrocarbon receptors (AhR), altering the expression of genes involved in lipid metabolism. A cross-sectional metabolome-wide association analysis (MWAS) demonstrated significant correlations between polycyclic aromatic hydrocarbon (PAH) metabolites in maternal urine samples and specific metabolic profiles, with approximately 1% of neonatal metabolic characteristics and 2% of maternal metabolic parameters showing measurable associations [21].

It is hypothesized that maternal lipid profiles mediate the association between prenatal $PM_{2.5}$ exposure and neonatal birth weight, based on evidence linking maternal $PM_{2.5}$ exposure to disruptions in lipid metabolism and adverse birth outcomes. While prior studies have identified these relationships as separate phenomena, the

present study uniquely addresses the critical knowledge gap in testing whether maternal lipids serve as a potential biological pathway connecting $PM_{2.5}$ to birth weight. This investigation leverages a representative birth cohort established in 2013–2014, prior to the implementation of China's 2013 Air Pollution Prevention and Control Action Plan (hereafter "2013 Clean Air Policy"), a nationwide initiative that reduced $PM_{2.5}$ levels by targeting coal combustion, industrial emissions, and vehicular pollution. The annual average $PM_{2.5}$ concentrations in Zhejiang Province from 2013 to 2017 were as follows: 70 μg/m³ in 2013 (exceeding the national ambient air quality standard by 100%), 53 μg/m³ in 2014, 47 μg/m³ in 2015, 41 μg/m³ in 2016, and 39 μg/m³ in 2017. In 2015, the province implemented substantial emission reduction measures, including the phase-out of over 17,000 coal-fired boilers and more than 320,000 yellow-label vehicles, which significantly reduced pollutant emissions and consequently lowered $PM_{2.5}$ concentrations. Furthermore, Zhejiang intensified air pollution control in 2016 by establishing the Time-bound Urban Air Quality Compliance Plan, a policy framework specifying timelines, roadmaps, and key projects for achieving compliance with air quality standards, thereby propelling measurable improvements in atmospheric conditions. By focusing on pregnancies occurring before this policy took full effect, this study capture prenatal $PM_{2.5}$ exposure during a period of unmitigated air pollution. This temporal design minimizes confounding from subsequent pollution control measures, enabling a clearer investigation of the relationship between maternal $PM_{2.5}$ exposure, lipid metabolism, and birth weight. Using mediation analysis, we aim to elucidate whether maternal lipids act as a possible mechanistic pathway linking $PM_{2.5}$ to fetal growth. While this work provides novel insights into metabolic mediation, future research should conduct in post-policy cohorts (where lower $PM_{2.5}$ levels may alter effect), explore additional pathways (e.g., glucose homeostasis or oxidative stress), and assess long-term child health outcomes.

Methods

Data source and preprocessing

Study participants

The study received approval from the Institutional Review Board of the Women's Hospital, Zhejiang University School of Medicine (IRB number: IRB-20220202-R). Written informed consent was obtained from all participants, and the Ethics Committee sanctioned the study. The cohort was established in 2013, with participant information collected by trained interviewers via a standardized computer-assisted personal interviewing system. The recorded maternal sociodemographic characteristics included residence district, ethnicity, maternal age at childbirth, education level, marital status, and medical insurance status. Data from 2013 to 2014 were extracted to explore the impact of changes in $PM_{2.5}$ levels on birth weight. The analysis included pregnant women who began prenatal care in the first trimester with continuous follow-up and finally delivered at the hospital between January 2013 and December 2014. Participants were eligible for inclusion if they had a term (≥ 37 weeks gestation) singleton live birth and had no preexisting health conditions such as diabetes, thyroid dysfunction, hypertension, severe kidney diseases or hepatic diseases before pregnancy. A total of 6,007 participants from 11 cities in Zhejiang Province were enrolled at baseline. Individuals who [1] lacked maternal blood samples at 20–28 weeks of gestation ($n = 0$); [2] had no maternal lipid records at 28–41 weeks of gestation ($n = 843$); or [3] had missing maternal demographic information or health outcomes ($n = 2$) were excluded. Eventually, 5,162 participants were included in the analysis.

Exposure assessment

$PM_{2.5}$ data This study retrieved ground-level $PM_{2.5}$ data covering the period from 2013 to 2014 from the Chinese China $PM_{2.5}$ dataset with high resolution and quality [22, 23]. This dataset was produced using the Space-Time Extra-Trees (STET) model, which combines ground observations, atmospheric reanalysis and emission inventories to generate national-scale seamless $PM_{2.5}$ data. The STET model has demonstrated high predictive accuracy, with a cross-validation coefficient of determination (R^2) of 0.89 and a root-mean-square error (RMSE) of 10.33 μg/m³. The spatial resolution was set at 1 km, and the temporal resolution was daily, with the concentration measured in μg/m³.

Daily $PM_{2.5}$ data were also collected from 11 national monitoring stations in Hangzhou city, covering the period from May 1 to December 31, 2014. These data were publicly available from the China National Environmental Monitoring Centre (https://air.cnemc.cn:18007/). However, the stations are concentrated in the northeastern part of the city, resulting in limited geographic representativeness for the entire urban area. In contrast, the gridded $PM_{2.5}$ dataset used in this study provided full-year daily estimates for both 2013 and 2014 at 33 evenly distributed grid points across Hangzhou. This allows for more comprehensive temporal and spatial coverage, and is the main reason to use the gridded data in the exposure assessment.

This study conducted the validation by comparing the gridded estimates with observed values from the monitoring stations during the overlapping period (May to December 2014), shown in Figure S1. The results indicate good spatial and temporal consistency. Spatially, both

datasets show similar distribution patterns, with higher concentrations in the northeast and lower concentrations in the southwest of Hangzhou (see Figure S1, panels a and b). Temporally, this study found similar trends in daily PM2.5 concentrations at the Xiasha station and the city-wide average from the gridded dataset (see Figure S1, panels c and d). Although station-based values tended to be slightly higher, the overall trend and fluctuation patterns were comparable. These findings support the reliability of the gridded data for use in this analysis.

Air pollution exposure assessment Individual residential addresses were geocoded as longitude and latitude coordinates, which were subsequently matched with grid-level $PM_{2.5}$ data to estimate individual exposure. This approach served as a proxy for assessing individual exposure to mitigate potential biased exposure.

Furthermore, this study calculated the average exposure concentrations for each pregnant woman in the first (weeks 1–12), second (weeks 13–27), and third trimesters (weeks 28–40). The annual average $PM_{2.5}$ concentration of the cities where the participants resided was computed.

Outcomes

Birth weight is a critical neonatal indicator that significantly influences human health from infancy through adulthood. Specifically, it is linked to a greater risk of adverse short-term pregnancy outcomes, such as stillbirth, and is also associated with an increased likelihood of developing chronic metabolic conditions, including obesity and cardiovascular diseases, later in life [24]. These health issues lead to substantial human capital losses and socioeconomic burdens. This study documented birth weight at delivery and further identified the incidence of macrosomia (≥ 4 kg) and small for gestational age (SGA). SGA was defined as a birth weight below the 10th percentile adjusted for sex and gestational age.

Blood lipid level measurements

All participating mothers received routine prenatal care at the hospital. Fasting venous blood samples were collected during mid-pregnancy (24–26 weeks) and late pregnancy (30–32 weeks) to measure lipid concentrations. The specific lipids measured included total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). The measurement methods and instruments used for lipid assays have been described in previous studies [25] and are reported in mmol/L. Specifically, TC and TG were analysed using enzymatic colorimetric assays based on the oxidase–peroxidase reaction, while HDL-C and LDL-C concentrations were determined through direct homogeneous enzymatic methods. All analyses were conducted using an automated clinical chemistry analyser with commercially available assay kits. The TC: HDL ratio, which is the ratio of HDL-C to TC, was subsequently calculated. The TC: HDL ratio is considered a good indicator of cardiovascular disease risk [26–28]. Additionally, to evaluate maternal glycemic status during pregnancy, a 75-gram oral glucose tolerance test (OGTT) was performed on all participants in the second trimester. This test measures fasting blood glucose (FBG) levels, as well as 1-hour postprandial blood glucose (PBG1h) and 2-hour postprandial blood glucose (PBG2h) levels.

Covariates

The demographics of the participants and their delivery characteristics were collected and incorporated as covariates in the analysis, including maternal age at delivery, prepregnancy body mass index (BMI) (derived from prepregnancy height and weight, categorized as underweight (< 18.5), normal weight (18.5–23.9), overweight (≥ 24.0) [29]), residence city (Hangzhou, Shaoxing, Jiaxing, Quzhou, Wenzhou, Jinhua, Huzhou, Lishui, Ningbo, Zhoushan), ethnicity (Han or minority), marital status (married and unmarried (never married, divorced, or widowed)), maternal education level (high school and below, undergraduate or equivalent, postgraduate and above), medical insurance, parity (nullipara, multiparous or primiparous), and ambient temperature and humidity exposure throughout pregnancy. Two conception season categories were generated: the warm season (from April to September) and the cold season (from October to March).

To adjust for the potential confounding effects of other ambient factors, data on daily mean temperature and relative humidity were obtained from the European Centre for Medium-Range Weather Forecasts (ECMWF) Reanalysis v5-Land (ERA5-LAND) with a spatial resolution of 9*9 km (https://www.ecmwf.int/en/forecasts/dataset/ecmwf-reanalysis-v5. Accessed 30 September 2022). Similar methods were then used to assign meteorological data (temperature and relative humidity) to each participant. The selection of covariates was guided by a directed acyclic graph (DAG) (Figure S2), which conceptualizes the presumed causal pathways among prenatal $PM_{2.5}$ exposure, maternal blood lipid levels, and birth weight. The DAG also incorporates relevant confounding variables that may influence both the mediator and outcome.

Statistical analysis

First, this study conducted descriptive analyses where continuous variables are presented as the means ± SDs, and categorical variables are presented as frequencies and percentages. Given the potential similarities among

participants within the same hospital, violating the independence assumption of regression, we utilized a mixed-effects regression model. This model was applied to estimate associations [1] between prenatal $PM_{2.5}$ exposure and blood lipids (TC, TG, LDL-C, HDL-C, and the TC: HDL ratio); [2] between prenatal $PM_{2.5}$ exposure and birth weight; and [3] between maternal blood lipid levels and birth weight. Here, in the models, the participant was considered a fixed-effect term, whereas the residential city was considered a random-effect term.

To allow for the nonlinear effects of ambient temperature and humidity, penalized smoothing splines were used, with 6 degrees of freedom (df) for the mean temperature and 3 df for the humidity. Previous studies have shown that both extremely low and high temperatures can adversely affect placental function and birth outcomes, often following U-shaped or inverse U-shaped patterns [30, 31]. The use of spline terms enables us to flexibly control for these potential nonlinear confounding effects. All exposure, mediator, and outcome variables were analysed in their original units without standardization. Specifically, $PM_{2.5}$ exposure was measured in μg/m³, blood lipid levels in mmol/L, and birth weight in grams. This approach was adopted to preserve the clinical and public health relevance and interpretability of the estimated associations.

Additionally, mediation analyses were conducted to explore how maternal blood lipids mediate the association between air pollution exposure and birth weight. The mediation analysis involved determining the total effect (TE), direct effect (DE), and indirect effect (IE), where TE represents DE plus IE, DE denotes the effect of air pollution exposure on birth weight adjusted for maternal blood lipids, and IE reflects the effect of air pollution exposure on birth weight through maternal blood lipids. Although the association between lipid levels and birth weight could not be statistically significant, the mediation analysis was still performed based on a theoretical framework suggesting that air pollution may influence fetal growth through maternal lipid metabolism. Similar mediation approaches have been widely applied in perinatal studies, even when the indirect effect is small, as long as the assumptions of the model are reasonably met [32].

Statistical analyses were performed via R version 4.0.1 for Windows, employing the "lmer" package for mixed-effects regression models and the "mediation" package for mediation analyses. A significance level of $P < 0.05$ was considered statistically significant.

Sensitivity analyses

To assess the robustness of the key findings, sensitivity analyses were conducted by varying the degrees of freedom (df) for the penalized smoothing splines of mean temperature (5–7 df) and relative humidity (2–4 df) within the mixed-effects models. In addition, to better explore the mediating relationship, mediation analyses for air pollution in trimester 1 and blood lipids in trimester 2 were also performed.

Results

Descriptive results

A total of 5,162 women who underwent live singleton deliveries were included in this study. The mean maternal age was 28.77 years, and the average maternal BMI was 20.39 (Table 1). Among infants born at term, 51.7% were male, and 61.8% were delivered during the warm season. The mean birth weight was 3357.45 g, with a standard deviation (SD) of 384.54 g, with SGA and macrosomia proportions of 5.3% and 5.9%, respectively.

The mean (SD) concentration of $PM_{2.5}$ for participant women during the first, second, and third trimesters was 67. 04 (21.49) μg/m³, 64.86 (19.38) μg/m³, 56.86 (16.24) μg/m³ (Table 2). A strong negative correlation was detected between $PM_{2.5}$ and temperature, with coefficients ranging from – 0.914 to -0.830 (Table S1).

Associations between air pollution and blood lipid levels

The changes in maternal blood lipid levels (mmol/L) during trimester 2 and trimester 3 for each 10 μg/m³ increment in $PM_{2.5}$ exposure are displayed in Table 3. Notably, lower $PM_{2.5}$ exposure in the first trimester correlated with elevated levels of HDL-C in the third trimester.

$PM_{2.5}$ was associated with increased blood lipid levels during trimester 2 and trimester 3. Each 10 μg/m³ increase in $PM_{2.5}$ during trimester 1 was associated with a 0.125 mmol/L (95% CI: 0.029, 0.221 mmol/L) increase in TG during trimester 3. An increase of 10 μg/m³ in average $PM_{2.5}$ levels throughout pregnancy was related to a 0.171 mmol/L (95% CI: 0.095, 0.247 mmol/L) increase in HDL-C and a -0.229 mmol/L (95% CI: -0.443, -0.015 mmol/L) decrease in the TC: HDL ratio during trimester 3. However, no statistically significant associations were observed between $PM_{2.5}$ and TC or LDL-C.

Gender-specific analyses revealed stronger effects of $PM_{2.5}$ on blood lipids in women with male fetuses during the third trimester and stronger effects in those with female fetuses during the second trimester (Table S2). For example, each 10 μg/m³ increase in $PM_{2.5}$ was associated with a 0.230 mmol/L (95% CI: 0.122, 0.338 mmol/L) increase in 3rd-trimester HDL-C and a 0.063 mmol/L (95% CI: 0.020, 0.106 mmol/L) increase in 2nd-trimester HDL-C for participants with male and female fetuses, respectively.

Associations between $PM_{2.5}$ and birth weight

Table 4 summarizes the associations between prenatal $PM_{2.5}$ exposure and birth weight. Air pollution exposure

Table 1 Descriptive statistics of study population

Maternal Characteristics	**(*n* = 5,162)**
Maternal age (mean (SD), years)	28.77 (3.21)
Maternal Education (%)	
Under college	222 (4.3)
College or equivalent	4,295 (83.2)
Above college	645 (12.5)
Medical insurance (%)	
Yes	4,969 (96.3)
No	193 (3.7)
Marital status (%)	
Married	5,121 (91.2)
Unmarried	41 (0.8)
Ethnicity (%)	
Han	5,128 (99.3)
Others	34(0.7)
Gravidity (mean (SD))	1.53 (0.85)
Gravidity (%)	
1	3,269 (63.3)
≥ 2	1,893 (36.7)
Parity (%)	
Nullipara	522 (10.1)
Primipara	4,640 (89.9)
Maternal weight gain (mean (SD), kg)	14.74 (3.91)
Height (mean (SD), m)	1.61 (0.05)
Prepregnancy weight (mean (SD, kg)	52.92 (7.11)
Predelivery weight (mean (SD, kg)	67.66 (7.80)
Maternal prepregnancy BMI (mean (SD), kg/m^2)	20.39 (2.51)
Maternal prepregnancy BMI (%)	
<18.5	1,172 (22.7)
18.5–24.9	3,559 (68.9)
≥25	431 (8.3)
Anemia (%)	1,748 (33.9)
Delivery way (%)	
Normal labor	3,499 (67.8)
Cesarean section	1,663 (32.2)
Fetal Characteristics	
Fetal gender (%)	
Male	2,668 (51.7)
Female	2,494 (48.3)
Gestational week (mean (SD))	39.70 (1.05)
Season of conception (%)	
Warm	1974 (38.2)
Cold	3188 (61.8)
Birth weight (mean (SD), g)	3357.45 (384.54)
Apgar1 (mean (SD))	9.89 (0.60)
Apgar5 (mean (SD))	9.97 (0.23)
SGA (%)	272 (5.3)
Macrosomia (%)	288 (5.6)
Biological testing	
2nd -trimester TC (mean (SD), mmol/L)	6.21 (1.02)
2nd -trimester TG (mean (SD), mmol/L)	2.19 (0.81)
2nd -trimester HDL-C(mean (SD), mmol/L)	2.40 (0.51)
2nd -trimester LDL-C (mean (SD), mmol/L)	3.43 (0.86)
3rd -trimester TC(mean (SD), mmol/L)	6.73 (1.86)

Table 1 (continued)

Maternal Characteristics	(*n* = 5,162)
3rd -trimester TG (mean (SD), mmol/L)	3.38 (1.66)
3rd -trimester HDL-C (mean (SD), mmol/L)	2.17 (0.60)
3rd -trimester LDL-C (mean (SD), mmol/L)	3.71 (1.74)
2nd -trimester TC: HDL ratio (mean (SD), mmol/L)	2.66 (0.54)
3rd -trimester TC: HDL ratio (mean (SD), mmol/L)	3.25 (1.65)
ALB (mean (SD), g/L)	38.37 (2.22)
FBG (mean (SD), g/L)	4.39 (0.32)
PBG1h (mean (SD), g/L)	7.55 (1.31)
PBG2h (mean (SD), g/L)	6.45 (0.99)

SD, standard deviation; SGA, small for gestational age; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALB, albumin; FBG, fasting blood glucose; PBG1h, 1-hour postprandial blood glucose; PBG2h, 2-hour postprandial blood glucose

Table 2 Descriptive statistics of air pollutants (μg/m^3) and meteorological factors during trimester 1 to trimester 3

Trimester	Environmental exposure	Mean	SD	Percentiles			Minimum	Maximum
				25th	50th	75th		
Trimester 1	$PM_{2.5}$ (μg/m^3)	67.40	21.49	50.87	62.18	83.83	24.96	107.33
	Temperature (°C)	20.07	7.97	13.34	17.77	27.04	9.44	33.95
	Relative humidity (%)	70.92	3.60	67.93	71.70	74.02	61.36	85.14
Trimester 2	$PM_{2.5}$ (μg/m^3)	64.86	19.38	48.45	58.72	78.59	19.84	105.73
	Temperature (°C)	20.74	6.31	14.56	21.95	26.91	9.42	33.26
	Relative humidity (%)	74.79	4.29	71.79	74.53	77.45	64.40	87.64
Trimester 3	$PM_{2.5}$ (μg/m^3)	56.86	16.24	44.24	54.47	60.86	24.66	107.01
	Temperature (°C)	21.90	6.28	16.86	23.87	27.52	9.06	29.14
	Relative humidity (%)	77.10	3.93	74.03	77.15	80.19	67.07	85.27
Whole term	$PM_{2.5}$ (μg/m^3)	63.04	8.11	54.06	66.63	69.95	27.85	73.97
	Temperature (°C)	20.90	1.77	19.23	21.13	22.66	17.04	24.66
	Relative humidity (%)	74.27	3.10	71.68	74.46	77.30	65.82	82.33

SD, standard deviation

during pregnancy, particularly $PM_{2.5}$ during trimester 2, was significantly associated with increased birth weight, with each 10 μg/m^3 increase correlating with a 27.320 g (95% CI: 6.003, 48.637 g) increase in birth weight.

Associations between blood lipid levels and birth weight

Table S3 presents the associations between maternal blood lipid levels and birth weight. Each 1 mmol/L increase in 2nd-trimester blood lipid levels (TC, TG, HDL-C, LDL-C) was significantly associated with 15.656 g (95% CI: 6.185, 25.127 g), 44.038 g (95% CI: 31.960, 56.116 g), -20.971 g (95% CI: -40.208, -1.734 g), and 24.007 g (95% CI: 12.827, 35.187 g) variations in birth weight, respectively.

Furthermore, these associations appeared to be stronger for participants who delivered male births in terms of TG levels and the TC: HDL ratio. Specifically, a 1-unit increase in the 2nd-trimester TC: HDL ratio was associated with a 53.265 g (95% CI: 25.547, 80.983 g) increase in birth weight for mothers with male fetuses, whereas a 44.882 g (95% CI: 21.364, 68.400 g) increase was observed for mothers with female fetuses.

Mediation analyses of maternal blood lipids in prenatal air pollution and birth weight associations

Mediation analyses were conducted to explore whether maternal blood lipids mediate the relationship between prenatal air pollution exposure and birth weight outcomes (Table 5). These findings indicate that higher air pollution levels may affect birth weight through alterations in maternal lipid profiles, with the magnitude of this effect ranging from 9.19 g to 9.34 g for the TC: HDL ratio, TG, and HDL-C. For example, the indirect effects of $PM_{2.5}$ (each 10 μg/m^3 increment) during trimester 2 on birth weight were – 2.35 g (95% CI: -4.07, -0.63 g), -0.69 g (95% CI: -1.16, -0.22 g), and – 1.80 g (95% CI: -3.19, -0.41 g) by the TC: HDL ratio, TG, and HDL-C during trimester 2, respectively. The direct effects of $PM_{2.5}$ (each 10 μg/m^3 increment) during trimester 2 on birth weight were 11.65 g (95% CI: 2.99, 20.31 g), 10.03 g (95% CI: 1.54, 18.52 g), and 10.99 g (95% CI: 2.13, 19.85 g), respectively.

Discussion

This study contributes to the growing body of evidence on the relationship between prenatal air pollution exposure and fetal development. Here's a summary of the key findings. Using a retrospective birth cohort design, an

Table 3 Changes in blood lipid levels (mmol/L) during trimester 2 and trimester 3 per 10 μg/m^3 increase in air pollutants

Trimester	Lipids	Differences in blood lipids (mmol/L) (95% CI)	
		Trimester 2	Trimester 3
1st -trimester $PM_{2.5}$	TC	0.034 (-0.025, 0.093)	0.016 (-0.092, 0.124)
	TG	0.018 (-0.029, 0.065)	**0.125 (0.029, 0.221)**
	HDL-C	-0.027 (-0.056, 0.002)	-0.006 (-0.041, 0.029)
	LDL-C	0.039 (-0.012, 0.090)	0.049 (-0.051, 0.149)
	TC: HDL ratio	0.029 (-0.002, 0.060)	0.016 (-0.080, 0.112)
2nd -trimester $PM_{2.5}$	TC	-0.002 (-0.063, 0.059)	-0.017 (-0.129, 0.095)
	TG	-0.026 (-0.075, 0.023)	-0.050 (-0.150, 0.050)
	HDL-C	0.030 (-0.001, 0.061)	0.010 (-0.025, 0.045)
	LDL-C	-0.022 (-0.075, 0.031)	-0.072 (-0.176, 0.032)
	TC: HDL ratio	-0.027 (-0.060, 0.006)	-0.042 (-0.142, 0.058)
3rd -trimester $PM_{2.5}$	TC	-	-0.038 (-0.183, 0.107)
	TG	-	0.074 (-0.053, 0.201)
	HDL-C	-	0.027 (-0.020, 0.074)
	LDL-C	-	0.020 (-0.115, 0.155)
	TC: HDL ratio	-	-0.091 (-0.220, 0.038)
Whole term $PM_{2.5}$	TC	-	0.091 (-0.150, 0.332)
	TG	-	0.041 (-0.173, 0.255)
	HDL-C	-	**0.171 (0.095, 0.247)**
	LDL-C	-	0.163 (-0.060, 0.386)
	TC: HDL ratio	-	**-0.229 (-0.443, -0.015)**

Note: Results from linear mixed-effects regression models after adjustment for maternal age, prepregnancy BMI, education, marital status, conception season, temperature, and humidity

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CI, confidence interval

Table 4 Change in birth weight (g) per 10 μg/m^3 increase in air pollutants

Pollutant	Differences in birth weight (g) (95% CI)
1st -trimester $PM_{2.5}$	-12.781 (-33.310, 7.748)
2nd -trimester $PM_{2.5}$	**27.320 (6.003, 48.637)**
3rd -trimester $PM_{2.5}$	-7.678 (-35.202, 19.846)
Whole term $PM_{2.5}$	-7.669 (-53.404, 38.066)

Note: Results from linear mixed-effects regression models after adjustment for maternal age, prepregnancy BMI, education, marital status, gestational age, birth sex, conception season, temperature, and relative humidity

CI, confidence interval

association between prenatal exposure to $PM_{2.5}$ and birth weight was observed, adding to the growing evidence linking air pollution to adverse birth outcomes. Notably, the present analysis identified maternal TC and HDL-C levels during the second trimester as potential mediators in the observed association between $PM_{2.5}$ exposure and birth weight. These findings suggest that disruptions in maternal lipid metabolism, which plays an important role in supplying energy and essential lipids to the developing fetus, may partially account for the effects of $PM_{2.5}$ on fetal growth. Based on available evidence, this is the first study to empirically examine lipid-mediated pathways in the $PM_{2.5}$–birth weight relationship, providing preliminary evidence for a plausible biological mechanism. Further research is needed to confirm these findings and explore additional pathways through which air pollution may influence developmental outcomes.

Previous epidemiological studies have predominantly reported inverse associations between prenatal $PM_{2.5}$ exposure and birth weight. A meta-analysis [33], encompassing 14 centers across nine countries, found that a 10 μg/m^3 increase in prenatal $PM_{2.5}$ exposure was associated with a higher risk of term low birth weight. The results revealed that term low birth weight was positively associated with a 10 μg/m^3 increase in PM_{10} and $PM_{2.5}$ exposure during the entire pregnancy. These findings align with later studies in diverse regions, which suggest that air pollution impacts fetal growth through mechanisms such as placental insufficiency, oxidative stress, or inflammation. However, this study observed a positive association between second-trimester $PM_{2.5}$ exposure and birth weight, contrasting with most existing literature. In the aforementioned meta-analysis, the median $PM_{2.5}$ concentrations across included studies ranged from 3.98 to 20.3 μg/m^3, which is substantially lower than the exposure levels observed in the present study cohort (mean: ~65 μg/m^3). This substantial disparity likely reflects differences in regional pollution profiles, as the meta-analysis predominantly incorporated data from North American and European populations residing in low-to-moderate pollution settings. In contrast, this cohort study represents a high-exposure context typical of industrial regions in China, where $PM_{2.5}$ levels frequently exceed 60 μg/m^3. A Chinese cohort study [34] involving 177,841 mother-neonate pairs from 1 January 2010 to 31 December 2012 (14,598 large-for-gestational-age [LGA] cases, 8.2%; 163,243 normal birth weight infants, 91.8%) further aligns with our findings on $PM_{2.5}$-associated fetal overgrowth. The mean prenatal $PM_{2.5}$ exposure was 74.9 ± 22.3 μg/m^3. Logistic regression analysis revealed significant trimester-specific associations: each 10 μg/m^3 increase in $PM_{2.5}$ exposure corresponded to elevated LGA risks, with adjusted odds ratios (95% CI) of 1.045 (1.037–1.052) in the first trimester, 1.035

Table 5 Mediation effect of blood lipids on the associations between air pollution and birth weight

Trimester/$PM_{2.5}$	Trimester/lipids	Effect	Effect (95% CI)	*P*-values
Trimester 1	Trimester 2 TC: HDL ratio	Total	-1.70 (-7.64, 4.24)	0.574
		Direct	-1.97 (-7.89, 3.95)	0.515
		Indirect	0.26 (-0.09, 0.61)	0.141
Trimester 2	**Trimester 2 TC: HDL ratio**	Total	**9.30 (0.85, 17.75)**	**0.031**
		Direct	**11.65 (2.99, 20.31)**	**0.008**
		Indirect	**-2.35 (-4.07, -0.63)**	**0.008**
Trimester 2	Trimester 3 TC: HDL ratio	Total	8.80 (0.29, 17.31)	**0.042**
		Direct	9.57 (1.10, 18.04)	**0.027**
		Indirect	-0.77 (-1.93, 0.39)	0.194
Trimester 3	Trimester 3 TC: HDL ratio	Total	-6.49 (-15.35, 2.37)	0.151
		Direct	-5.46 (-14.26, 3.34)	0.224
		Indirect	-1.03 (-2.46, 0.40)	0.156
Trimester 1	Trimester 2 TC	Total	-2.87 (-8.83, 3.09)	0.345
		Direct	-2.84 (-8.80, 3.12)	0.351
		Indirect	-0.03 (-0.15, 0.09)	0.635
Trimester 2	Trimester 2 TC	Total	9.41 (0.96, 17.86)	**0.029**
		Direct	9.25 (0.80, 17.70)	**0.032**
		Indirect	0.17 (-0.10, 0.44)	0.234
Trimester 2	Trimester 3 TC	Total	9.34 (0.83, 17.85)	**0.031**
		Direct	9.35 (0.84, 17.86)	**0.031**
		Indirect	-0.01 (-0.13, 0.11)	0.917
Trimester 3	Trimester 3 TC	Total	-6.08 (-15.15, 2.99)	0.189
		Direct	-6.09 (-15.16, 2.98)	0.188
		Indirect	0.00 (-0.08, 0.08)	0.915
Trimester 1	Trimester 2 TG	Total	-2.79 (-9.02, 3.44)	0.380
		Direct	-2.68 (-8.91, 3.55)	0.398
		Indirect	-0.11 (-0.42, 0.20)	0.493
Trimester 2	**Trimester 2 TG**	Total	**9.34 (0.83, 17.85)**	**0.031**
		Direct	10.03 (1.54, 18.52)	**0.021**
		Indirect	-0.69 (-1.16, -0.22)	**0.005**
Trimester 2	Trimester 3 TG	Total	9.28 (1.03, 17.53)	**0.028**
		Direct	8.92 (0.73, 17.11)	**0.033**
		Indirect	0.36 (-0.40, 1.12)	0.358
Trimester 3	Trimester 3 TG	Total	-5.58 (-15.09, 3.93)	0.250
		Direct	-5.98 (-15.43, 3.47)	0.215
		Indirect	0.41 (-0.32, 1.14)	0.266
Trimester 1	Trimester 2 HDL-C	Total	-1.99 (-7.95, 3.97)	0.514
		Direct	-2.25 (-8.19, 3.69)	0.458
		Indirect	0.26 (-0.03, 0.55)	0.078
Trimester 2	**Trimester 2 HDL-C**	Total	**9.19 (0.53, 17.85)**	**0.038**
		Direct	10.99 (2.13, 19.85)	**0.015**
		Indirect	-1.80 (-3.19, -0.41)	**0.011**
Trimester 2	Trimester 3 HDL-C	Total	6.63 (-2.05, 15.31)	0.134
		Direct	8.78 (0.16, 17.40)	**0.046**
		Indirect	-2.15 (-2.95, -1.35)	**0.000**
Trimester 3	Trimester 3 HDL-C	Total	-7.50 (-16.56, 1.56)	0.105
		Direct	-4.12 (-13.16, 4.92)	0.371
		Indirect	-3.38 (-4.52, -2.24)	**0.000**
Trimester 1	Trimester 2 LDL-C	Total	-3.02 (-9.02, 2.98)	0.325
		Direct	-3.12 (-9.12, 2.88)	0.308
		Indirect	0.10 (-0.12, 0.32)	0.369
Trimester 2	Trimester 2 LDL-C	Total	9.40 (0.89, 17.91)	**0.030**
		Direct	9.13 (0.64, 17.62)	**0.035**

Table 5 (continued)

Trimester/$PM_{2.5}$	Trimester/lipids	Effect	Effect (95% CI)	*P*-values
		Indirect	0.27 (-0.02, 0.56)	0.074
Trimester 2	Trimester 3 LDL-C	Total	9.31 (0.65, 17.97)	**0.035**
		Direct	9.67 (1.01, 18.33)	**0.029**
		Indirect	-0.37 (-0.76, 0.02)	0.069
Trimester 3	Trimester 3 LDL-C	Total	-6.43 (-15.66, 2.80)	0.173
		Direct	-6.35 (-15.58, 2.88)	0.178
		Indirect	-0.08 (-0.26, 0.10)	0.387

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CI, confidence interval

(1.028–1.043) in the second trimester, 1.033 (1.026–1.039) in the third trimester, and 1.049 (1.041–1.058) for whole-pregnancy exposure. Subgroup analyses stratified by infant sex and maternal age demonstrated robustness of these associations. Notably, dose-response curves indicated a plateau in LGA risk when $PM_{2.5}$ concentrations exceeded 100 μg/m³ during all trimesters, suggesting potential threshold effects in high-exposure scenarios. Such elevated baseline exposures may overwhelm physiological detoxification pathways and induce nonlinear dose-response relationships [35–37], potentially explaining mechanistic divergences between the findings and those from lower-exposure settings. This discrepancy may further arise from regional differences in $PM_{2.5}$ chemical composition and coexposure patterns, combined with methodological variability in exposure assessment. Specifically, $PM_{2.5}$ in high-exposure regions such as China is often enriched with metals (e.g., lead, cadmium) and organic compounds (e.g., polycyclic aromatic hydrocarbons), compared to sulfate-dominated particles co mmonly observed in North American and European contexts. Additionally, coexposure to elevated levels of other pollutants, such as nitrogen dioxide (NO2) and ozone, in industrial settings may synergistically amplify $PM_{2.5}$ toxicity through inflammatory or epigenetic pathways, complicating direct comparisons with studies in cleaner environments. Methodological variations including inconsistent adjustment for confounders like maternal dietary patterns, socioeconomic disparities, or indoor air pollution sources—could further bias effect estimates or mask true biological associations, contributing to the observed inconsistencies across studies. These findings underscore the complexity of $PM_{2.5}$ effects on birth outcomes, which may vary by population, exposure profile, and analytical approach. Further research integrating chemical-speciated $PM_{2.5}$ data, placental biomarkers, and advanced causal inference methods is needed to reconcile these inconsistencies and elucidate context-dependent mechanisms.

Studies assessing the effects of exposure to $PM_{2.5}$ or other air pollutants exposure during pregnancy on maternal lipid metabolism are limited. In a recent population-based study [16], $PM_{2.5}$ was found to be positively correlated with LDL-C and TC and negatively correlated with TG, which excluded people with abnormal blood lipid concentrations. The study by Yang [17] contributes valuable insights into the health impacts of long-term exposure to $PM_{2.5}$ and its chemical components on blood lipid profiles in a Chinese context. This multicity investigation extends understanding of the relationship between air pollution and cardiovascular health risks by specifically focusing on dyslipidemia, a condition characterized by abnormal levels of lipids in the blood, including increased total cholesterol (TC) and triglycerides (TG), which are risk factors for cardiovascular diseases. One previous study [18] showed that exposure to high levels of $PM_{2.5}$ (≥ 25 μg/m³) in early pregnancy resulted in increased odds of high cholesterol, but not statistically significant. While evidence suggests air pollution may influence blood lipid profiles in the general population, studies examining these effects specifically in pregnant individuals remain limited. Further investigation into how air pollution alters maternal lipid metabolism during pregnancy is warranted, given the potential implications for fetal development and birth outcomes. Expanding research on pregnant populations could improve understanding of the interactions between air pollution, maternal lipid dynamics, and pregnancy health, particularly given the unique metabolic demands of gestation.

The observations provide critical insight into the complex relationship between prenatal $PM_{2.5}$ exposure and fetal development. The observed mediating effect of maternal blood lipid levels during the second and third trimesters in the association between $PM_{2.5}$ exposure and birth weight merits attention. This mediation analysis approach is supported by previous studies, including evidence from a recent U.S. birth cohort [19] demonstrating gestational $PM_{2.5}$ exposure may directly affect placental function. Experimental evidence suggests $PM_{2.5}$ particles may cross the placental barrier, with analyses of placental gene expression indicating that pregnancy exposure could influence genes regulating key biological processes including inflammation, lipid transport, cell communication, and invasion. These molecular changes might impair placental capacity to regulate glucose and lipid metabolism, potentially affecting nutrient and

oxygen transfer essential for fetal growth. This biological mechanism helps contextualize the present finding regarding the mediating role of maternal lipids, particularly during the second trimester. The mediation analysis methodology applied in this study has been previously validated for examining associations between maternal air pollution exposure and birth outcomes [38]. This approach enables estimation of both direct and indirect exposure effects while identifying potential mechanistic pathways. The present results align with the hypothesis that $PM_{2.5}$ exposure might disrupt metabolic pathways through intermediate effects on maternal physiology, which could contribute to adverse pregnancy outcomes. Further research is needed to confirm these observed relationships and elucidate the underlying biological mechanisms.

While air pollution levels have shown marked improvement following China's 2013 Clean Air Policy, annual average $PM_{2.5}$ concentrations remain elevated compared to the WHO guideline value of 10 μg/m^3 [39]. Given persistent exposure risks, prenatal environmental pollutant exposure represents an ongoing public health challenge in China. This mediation analysis suggests potential biological mechanisms linking $PM_{2.5}$ exposure with fetal development, particularly through maternal lipid metabolism pathways. These findings carry potential public health implications if maternal blood lipid regulation demonstrates effectiveness in mitigating $PM_{2.5}$-associated birth outcomes. Implementing targeted emission reduction policies could further improve air quality, which might reduce adverse birth outcomes while yielding socioeconomic benefits through improved population health. Further longitudinal studies are required to validate these observations and assess intervention feasibility.

Strengths and limitations

This study has several methodological strengths. First, the investigation of maternal blood lipids as potential mediators between prenatal $PM_{2.5}$ exposure and term birth weight represents a novel approach, providing empirical support for understanding gestational exposure mechanisms and suggesting potential biological pathways. Second, the exclusion of participants with diabetes and pregnancy complications, combined with adjustment for key confounders, strengthens the specificity of observed associations. Third, the $PM_{2.5}$ exposure assessment model incorporated three trimester-specific exposure windows with 1 km×1 km grid resolution, enhancing spatiotemporal precision beyond conventional monitoring approaches. Methodological rigor was further ensured through sensitivity analyses examining potential confounding factors and model stability. Notably, the use of TC: HDL ratio as a composite lipid marker offers methodological advantages over isolated TC or HDL-C measurements, as this ratio has been associated with cardiovascular risk profiles in epidemiological studies through its reflection of atherogenic LDL-C and protective HDL-C balance.

Several study limitations warrant consideration. First, $PM_{2.5}$ exposure assessment relied on ambient concentration data matched to community-level residential addresses, without accounting for indoor pollution sources or individual mobility patterns during pregnancy. This approach may lead to measurement error due to unrecorded time-activity patterns and microenvironmental exposure variations. However, such exposure misclassification is generally considered nondifferential in observational studies, which would bias effect estimates toward the null. Second, the exclusive inclusion of uncomplicated pregnancies introduces selection bias concerns. The exclusion of pregnancies with complications may limit generalizability and potentially introduce residual confounding if omitted factors simultaneously influence both complication risk and birth weight. This design feature precludes examination of potential effect modification by pregnancy complications.Future studies incorporating personal monitoring devices and detailed time-activity records could improve exposure assessment accuracy, while inclusive sampling frameworks encompassing complicated pregnancies would enhance result generalizability.

Conclusions

Key findings suggest prenatal $PM_{2.5}$ exposure shows an association with term birth weight, with maternal lipid levels potentially mediating this relationship. These observations extend current understanding of gestational air pollution effects by identifying plausible biological pathways linking environmental exposure to fetal growth outcomes. The methodological framework could inform three key domains: [1] maternal health monitoring protocols incorporating lipid profile tracking [2], air quality standards refinement considering vulnerable populations, and [3] prenatal care guidelines addressing environmental health risks. From a global health perspective, these findings underscore the importance of evaluating air quality interventions as potential dual-purpose strategies for environmental protection and perinatal health improvement. Future investigations should prioritize: [1] replication in multi-regional birth cohorts with enhanced exposure assessment methods [2], mechanistic studies elucidating lipid-mediated pathways using longitudinal biomarker data, and [3] intervention trials assessing whether lipid regulation modifies $PM_{2.5}$-related birth outcomes. Such evidence would strengthen causal inference while guiding targeted prevention strategies.While these findings contribute to environmental epidemiology

literature, their translation into clinical or policy applications requires validation through implementation research and health impact assessments.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions
All authors contributed to the study conception and design. The study was designed by QL and HH, who also supervised the study. HC and QC were responsible for conceiving the study idea, proposing the study protocol and drafting the paper. HC, QC, DW, ML, FX and YC collected the data. HC and QC cleaned, calibrated and verified the data. HC performed the statistical analysis. HC, QC, LW and QL contributed to the interpretation of results and editing the paper. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The dataset generated and analyzed during this study is available from the corresponding authors upon reasonable request.

Declarations

Consent for publication
Not applicable. Information is anonymized and the submission does not include images that may identify the person.

Competing interests
The authors declare no competing interests.

Ethical approval
The study received approval from the Institutional Review Board of the Women's Hospital, Zhejiang University School of Medicine (IRB number: IRB-20220202-R).

Consent to participate
Written informed consent was obtained from all participants.

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