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Maternal metabolomics linking prenatal exposure to fine particulate matter and birth weight: a cross-sectional analysis of the MADRES cohort

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Abstract

Background Prenatal exposure to air pollution has been associated with an increased risk of low birth weight. Disrupted metabolism may serve as an underlying mechanism, but the specific metabolic pathways involved remain unclear.

Methods In the Maternal and Developmental Risks from Environmental and Social Stressors (MADRES) study, 382 third-trimester maternal serum samples were analyzed for untargeted metabolomics using liquid chromatography with Fourier transform high-resolution mass spectrometry. Ambient concentrations of fine particulate matter ($PM_{2.5}$), particulate matter ≤ 10 µm in diameter (PM_{10}), nitrogen dioxide (NO_2), and ozone (O_3) were estimated using inverse-distance-squared weighted spatial interpolation based on daily residential histories. Birth weight was retrieved from medical records. Linear regression identified metabolomic features associated with air pollution exposure or birth weight, followed by Mummichog pathway enrichment and mediation analyses for the selected features.

Results Second-trimester $PM_{2.5}$ exposure was associated with lower birth weight. Fourteen metabolic pathways were significantly associated with second-trimester $PM_{2.5}$ exposure, with C21-steroid hormone biosynthesis and metabolism showing the most significant association. Sixteen metabolic pathways were significantly associated with birth weight, with vitamin A (retinol) metabolism being the most significantly enriched pathway. Seven pathways were associated with both $PM_{2.5}$ exposure and birth weight, including C21-steroid hormone biosynthesis and metabolism, bile acid biosynthesis, tyrosine metabolism, ascorbate (vitamin C) and aldarate metabolism, vitamin D3 (cholecalciferol) metabolism, vitamin A (retinol) metabolism, and pyrimidine metabolism. Overweight or obese women exhibited more metabolomic features and metabolic pathways associated with $PM_{2.5}$ exposure compared to underweight or normal-weight women. No associations were observed between PM_{10}, NO_2, or O_3 and birth weight.

Conclusions Maternal metabolic pathways involving steroid metabolism, oxidative stress and inflammation, vitamin metabolism, and DNA damage may link prenatal $PM_{2.5}$ exposure to lower birth weight, with overweight or obese women potentially more susceptible to these metabolic disruptions.

Keywords Prenatal air pollution exposure, Fine particulate matter, Low birth weight, Metabolomics, Maternal obesity

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Background

Low birth weight is a public health concern worldwide [1]. It contributes to 34% of global mortality in children under 5 [2] and has enduring consequences for both developmental and physical health [1, 3]. Mounting evidence has identified a link between prenatal exposure to ambient air pollution, particularly fine particulate matter ($PM_{2.5}$), and low birth weight [4–6]. Recently, Niu et al. replicated previous findings using data from the Maternal and Developmental Risks from Environmental and Social Stressors (MADRES) study [7], finding that exposure to $PM_{2.5}$ and nitrogen dioxide (NO_2) during sensitive windows primarily in early to mid-pregnancy was associated with lower birth weight [8].

However, the biological mechanisms through which air pollution exposure influences birth weight remain unclear. It is hypothesized that oxidative stress, inflammation, blood coagulation, endothelial function, and hemodynamic responses are potential contributors [9], but evidence of the exact biological pathways responsible for air pollution-related adverse pregnancy outcomes is limited. Metabolism, which encompasses all the chemical reactions that occur within organisms to maintain life, plays an essential role in fetal development and can be influenced by various external factors, including air pollution [10]. Some studies have explored metabolic pathways associated with either air pollution exposure or birth weight separately [11–20]. However, few studies have examined the impact of air pollution exposure on maternal metabolism and their consequent relation to birth weight [21, 22].

Furthermore, although previous studies have shown the modifying effect of maternal body mass index (BMI) on the association between air pollution exposure and birth weight [23, 24], the metabolic basis of these associations remains underexplored. Therefore, it is crucial to further investigate how maternal BMI may affect metabolic changes in response to prenatal air pollution exposure.

This study aims to identify the metabolic pathways linking prenatal air pollution exposure to birth weight using data from the MADRES cohort study and an untargeted metabolomics approach. In addition, we explored whether the different pathways of air pollution effects on newborn birth weight among pregnant women varied by BMI level.

Methods

Study population

The MADRES study is an ongoing prospective pregnancy cohort study initiated in 2015, primarily focusing on lower-income Hispanic women in Los Angeles, California. Details of the study design and participant recruitment were previously reported [7]. Briefly, eligibility criteria included being within 30 gestational weeks, at least 18 years of age, and fluent in either English or Spanish. Women were excluded if they tested positive for HIV, had physical, mental, or cognitive disability preventing participation or consent, were currently incarcerated, or had a multifetal pregnancy. The MADRES study was approved by the Institutional Review Board of University of Southern California. Written informed consent and Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization was obtained from each participant at enrollment.

As of May 10, 2020, 424 women had reached delivery and had fasting blood samples collected in the third trimester ($\geq$26 gestational week) available for untargeted metabolomics analysis. After excluding three participants without qualified untargeted metabolomics data, 38 participants who delivered prematurely (<37 gestational week), and one participant without air pollution exposure data, there were 382 participants remaining (Figure S1).

Air pollution exposure assessment

Participants self-reported their residential address histories from one year prior to conception through the follow-up period. These along with participant contact tracking information were used to construct daily residential timelines that capture all residential moves with high spatial and temporal resolution and served as the basis for exposure linkages. Residential daily estimates of 24-h average concentrations of $PM_{2.5}$, particulate matter $\leq$10 μm in diameter (PM_{10}), and NO_2, along with 8-h maximum ozone (O_3) concentrations, were calculated using inverse-distance-squared weighted spatial interpolation based on ambient air quality data from the United Stated Environmental Protection Agency Air Quality System. Trimester-specific concentrations of ambient air pollutants for the preconception period (defined as 12 weeks prior to conception), and the first (0 < gestational week < 14) and second (14 $\leq$ gestational week < 26) trimesters were calculated based on daily estimates.

Newborn birth weight Z-score

Newborn birth weight and sex were obtained from the delivery medical records. Gestational age at delivery was estimated using a hierarchical approach, incorporating fetal crown-rump length measured by ultrasound during the first and second trimesters, the obstetrical medical record, or the self-reported date of the last menstrual period. Birth weight was then transformed into a sex- and gestational age-specific birth weight Z-score [25].

Maternal untargeted metabolomics

Fasting blood samples were collected at the third trimester. The mean sample collection time was 31.53 ± 1.94 gestational weeks, and the duration from sample collection to delivery was 7.82 ± 2.14 weeks. Serum was isolated and stored at −80 °C until transported to the laboratory at Emory University on dry ice. High-resolution untargeted metabolomics analysis was performed using liquid chromatography and Fourier transform high-resolution mass spectrometry (LC-HRMS, Dionex Ultimate 3000, HF Q-Exactive, Thermo Scientific) [26]. Each serum sample was analyzed in triplicate using hydrophilic interaction liquid chromatography (HILIC) coupled with an electrospray ionization (ESI) source in positive mode, and C18 hydrophobic reversed-phase chromatography followed by negative ESI mode (hereafter abbreviate as HILIC-positive mode and C18-negative mode, respectively). A detailed protocol of sample processing and detection is provided in the Supplementary Material.

Each detected chemical signal, consisting of mass-to-charge ratio (m/z), retention time, and ion abundance, was referred to as a metabolomic feature. A total of 10800 and 10578 metabolomic features were identified using HILIC-positive mode and C18-negative mode, respectively. Metabolomic features detected in ≤ 50% of all samples, as well as samples in which ≤ 50% of metabolomic features were detected, were excluded from the final analysis. Missingness in intensity data was imputed by assigning half of the minimum intensity of a specific metabolomic feature. Quantile normalization [27] and log2 transformation were performed to normalize the intensity data. Additionally, metabolomic features with coefficients of variation (CVs) ≥ 30% across Qstd3 samples were further excluded [26, 28–31]. Qstd3 is pooled EDTA plasma obtained from 50 healthy donors purchased from Equitech-Bio (SHP45) without information on drug use or fasting status [26]. It was analyzed in duplicate at the beginning, middle, and end of each of the 18 batches. Detailed quality control and data transformation procedures are shown in Figure S1, and the distribution of CVs for untargeted metabolomics data is presented in Figure S2. 7393 metabolomic features in 377 serum samples detected with HILIC-positive mode and 8928 metabolomic features in 382 serum samples analyzed with C18-negative mode were included in the statistical analysis.

Covariates

Maternal race/ethnicity, education, household income, marital status, and smoking history, as well as newborn race/ethnicity were obtained using interviewer-administrated questionnaires. Pre-pregnancy BMI was calculated as the ratio of self-reported pre-pregnancy weight (kg) to the square of standing height (m^2), measured with a stadiometer at onsite study visits. Participants were divided into two BMI categories, namely "Underweight or normal" versus "Overweight or obese", using a cutoff of pre-pregnancy BMI = 25 kg/m^2. Maternal age at delivery was calculated as the difference between the delivery date and mother's birth date. Conception date was estimated with the same hierarchical information used for gestational age estimation and was further categorized into warm (April-September) and cold (October–March) conception seasons. The enrollment time point indicated in which gestational period the participants were enrolled (regular entry: < 20 gestational weeks versus late entry: 20–30 gestational weeks). Missingness of categorical variables was categorized as "Unknown".

Statistical analysis

Descriptive data are reported as mean ± standard deviation (SD) or number (%), as appropriate. The associations between covariates and birth weight Z-score were examined using linear regression. Students' t-test and chi-square test were used to compare continuous and categorial covariates between pre-pregnancy BMI subgroups, respectively.

A previous study of 628 MADRES participants found that $PM_{2.5}$ exposure during 14–22 gestational weeks and NO_2 exposure during 9–14 gestational weeks were significantly associated with lower birth weight [8]. To validate these findings, we used linear regression models to examine the associations of trimester-specific concentrations of $PM_{2.5}$, PM_{10}, NO_2, and O_3, as well as $PM_{2.5}$ exposure during 14–22 gestational weeks and NO_2 exposure during 9–14 gestational weeks, with birth weight Z-score in a subset of 382 MADRES participants with metabolomics data. The models were adjusted for maternal age at delivery, pre-pregnancy BMI, smoking history, education, household income, marital status, newborn ethnicity, conception season, and enrollment time point. We selected the air pollution exposure that was significantly associated with birth weight in subsequent analyses. To investigate the modifying effect of pre-pregnancy BMI on the association between prenatal air pollution exposure and birth weight, an interaction term between pre-pregnancy BMI categories and air pollution exposure levels was added to the linear regression models.

We used a meet-in-the-middle strategy in metabolome-wide association study (MWAS). MWAS analyses were performed using linear regression models to identify third-trimester metabolomic features in significant association with either air pollution exposure or birth weight Z-score. All models were adjusted for maternal age at delivery, smoking, education, income, marital status,

ethnicity (maternal ethnicity in air pollution model and newborn ethnicity in birth weight model, respectively), conception season (air pollution model only), and enrollment time point. Stratified MWAS analyses were further conducted to examine the associations between metabolomic features and air pollution exposure among different BMI subgroups. Results with p-value < 0.05 were considered statistically significant. False discovery rate (FDR) calculated using Benjamini–Hochberg method [32] was applied to address multiple testing. Statistical analysis was conducted using R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

Mummichog pathway enrichment analysis [33] was conducted to identify metabolic pathways associated with air pollution exposure and birth weight, respectively. Metabolomic features detected with HILIC-positive mode and C18-negative mode were analyzed separately using Mummichog version 2.6.1 and metabolic model MFN_1.10.4, with a mass tolerance of 5 ppm and a p-value threshold of 0.05. Pathways with p-value < 0.05 based on Fisher's exact test was considered significantly enriched. Only pathways containing at least three metabolites were interpreted. Mummichog annotated metabolomic features were further compared with a laboratory-developed reference of 467 chemical compounds using MS2 spectra [26] based on the criteria of mass difference ≤ 5 ppm, retention time difference ≤ 30 s, and having the same adduct. Metabolomic features matched to the compound reference were considered as metabolites with confirmed identity, following the Metabolomics Standard Initiative level 1 criteria [34].

Mediation analyses were conducted using R package "mediation" [35] to examine whether selected metabolomic features mediated the associations between air pollution exposure and birth weight. Two types of metabolomic features were included in the analyses: 1) A single metabolomic feature with a Mummichog annotation which was significantly associated with both air pollution exposure and birth weight Z-score. 2) Multiple metabolomic features sharing the same Mummichog annotation, where some features were significantly associated with air pollution exposure, while others were linked to birth weight Z-score. Maternal age at delivery, smoking, education, income, marital status, maternal ethnicity, conception season, and enrollment time point were adjusted for as covariates in the models.

Results

The characteristics of 382 MADRES participants are summarized in Table 1. The mean maternal age at delivery was 29.4 ± 5.9 years. Participants predominantly self-identified as Hispanic (80% newborns and 78% mothers) and the majority of women were overweight or obese (68%). 267 (70%) women never smoked and 109 (29%) smoked before pregnancy but stopped smoking during pregnancy. Among the 382 women, 24% completed less than 12th grade of education, 45% had household income < $30,000 per year, and 23% were single or divorced. Additionally, overweight or obesity was significantly associated with higher birth weight Z-score, while reporting unknown income and living together were each associated with lower birth weight Z-score. Table S1 shows the characteristics of participants stratified by pre-pregnancy BMI. Overweight or obese women were older, more likely to be Hispanic, and had lower education levels compared to those who were underweight or of normal BMI.

Table S2 presents the levels of $PM_{2.5}$, PM_{10}, NO_2, and O_3 in the preconception period, the first and second trimesters, and the time window during which air pollution exposure was significantly associated with birth weight in previous MADRES analysis [8]. Among all the air pollutants we investigated, only $PM_{2.5}$ exposure in the second trimester was significantly associated with lower birth weight Z-score [−0.18 (95% confidence interval (CI): −0.33, −0.03)]. There were no significant associations observed for PM_{10}, NO_2, or O_3 (Table S3). Additionally, among women who were underweight or had normal BMI, an interquartile range increase in second-trimester $PM_{2.5}$ exposure was associated with a −0.24 (95% CI: −0.43, −0.04) change in birth weight Z-score. In contrast, this association was not significant among overweight or obese women [−0.12 (95% CI: −0.32, 0.08)], with a p-value for the interaction term of 0.37.

In the overall population, 691 and 755 metabolomic features detected in HILIC-positive and C18-negative mode were significantly associated with second-trimester $PM_{2.5}$ exposure, respectively ($p < 0.05$). After FDR-adjustment, the MWAS associations remained significant for three C18-negative metabolomic features (FDR < 0.05) (Figure S3). Metabolic pathways in significant association with second-trimester $PM_{2.5}$ exposure are shown in Fig. 1 and Table S4. Fourteen metabolic pathways were significantly associated with second-trimester $PM_{2.5}$ exposure and C21-steroid hormone biosynthesis and metabolism was the top significantly enriched pathway ($p = 0.001$). 324 HILIC-positive and 513 C18-negative metabolomic features were found to be significantly associated with birth weight Z-score ($p < 0.05$), and the MWAS association was significant at FDR < 0.05 for one C18-negative metabolomic feature (Figure S3). These metabolomic features were significantly enriched in sixteen metabolic pathways (Fig. 1 and Table S4). Among them, vitamin A (retinol) metabolism showed the most significant association, as indicated by the smallest p-value from Fisher's exact test ($p = 0.004$). There were seven common

Table 1 Characteristics of 382 MADRES participants

Variable	Category	Mean ± SD / N (%)	Estimate[a]	*P*-value[a]
Number of participants		382 (100)	-	-
Maternal age at delivery (year)		29.4 ± 5.9	0.01	0.38
Newborn ethnicity	Non-Hispanic	73 (19)	Ref	Ref
	Hispanic	306 (80)	0.21	0.12
	Unknown	3 (1)	−0.66	0.27
Maternal ethnicity	Non-Hispanic	82 (21)	Ref	Ref
	Hispanic	297 (78)	0.18	0.15
	Unknown	3 (1)	−0.68	0.25
Maternal pre-pregnancy BMI	Underweight or normal	122 (32)	Ref	Ref
	Overweight or obese[b]	**260 (68)**	**0.31**	**0.01**
Maternal smoking	Never smoked	267 (70)	Ref	Ref
	Smoked before pregnancy but stopped during pregnancy	109 (29)	−0.09	0.41
	Smoked before and during pregnancy	6 (2)	−0.27	0.51
Maternal education	Less than 12th grade	90 (24)	Ref	Ref
	High school or some college or technical school	213 (56)	−0.17	0.19
	Completed 4 years of college or above	76 (20)	−0.16	0.31
	Unknown	3 (1)	−0.95	0.11
Household income	< $30,000	170 (45)	Ref	Ref
	≥ $30,000 or more	99 (26)	0.01	0.97
	Unknown	**113 (30)**	**−0.28**	**0.02**
Maternal marital status	Married	116 (30)	Ref	Ref
	Living together	**150 (39)**	**−0.26**	**0.04**
	Single or divorced	88 (23)	−0.19	0.17
	Unknown	28 (7)	−0.17	0.42
Conception season	Cold	203 (53)	Ref	Ref
	Warm	179 (47)	0.05	0.63
Enrollment time point	Regular entry (< 20 week)	283 (74)	Ref	Ref
	Late entry (20–30 week)	99 (26)	−0.21	0.08

[a] The associations between covariates and birth weight Z-score were examined using linear regression

[b] Bold characters denote significant associations between covariates and birth weight Z-score

metabolic pathways associated with both $PM_{2.5}$ exposure and birth weight, including C21-steroid hormone biosynthesis and metabolism, bile acid biosynthesis, tyrosine metabolism, ascorbate (vitamin C) and aldarate metabolism, vitamin D3 (cholecalciferol) metabolism, vitamin A (retinol) metabolism, and pyrimidine metabolism. Pathways related to amino acid, carbohydrate, and nucleotide metabolism were predominantly identified in the C18-negative mode, while pathways associated with lipid and vitamin metabolism were primarily identified in the HILIC-positive mode.

241 HILIC-positive and 687 C18-negative metabolomic features were significantly associated with second-trimester $PM_{2.5}$ exposure among underweight or normal-weight participants ($p < 0.05$), and one C18-negative metabolomic feature was significant at FDR < 0.05; among overweight or obese participants, the number of metabolomic features associated with $PM_{2.5}$ exposure was 772 for HILIC-positive mode and 742 for C18-negative mode ($p < 0.05$), and the associations remained significant at FDR < 0.05 for 24 HILIC-positive metabolomic features (Figure S4). Notably, metabolic pathways associated with second-trimester $PM_{2.5}$ exposure differed by BMI status. As shown in Fig. 1 and Table S4, among women who were underweight or of normal BMI, four lipid metabolism pathways and one glycan biosynthesis and metabolism pathway were significantly associated with $PM_{2.5}$ exposure, while more metabolic pathways were changed among overweight or obese women, including ten lipid metabolism pathways, one amino acid metabolism pathway, one carbohydrate metabolism pathway, two glycan metabolism pathways, three vitamin metabolism pathways, two nucleotide metabolism pathways, and one hyaluronan metabolism pathway. C21-steroid hormone biosynthesis and metabolism, bile acid biosynthesis, and fatty acid activation were common

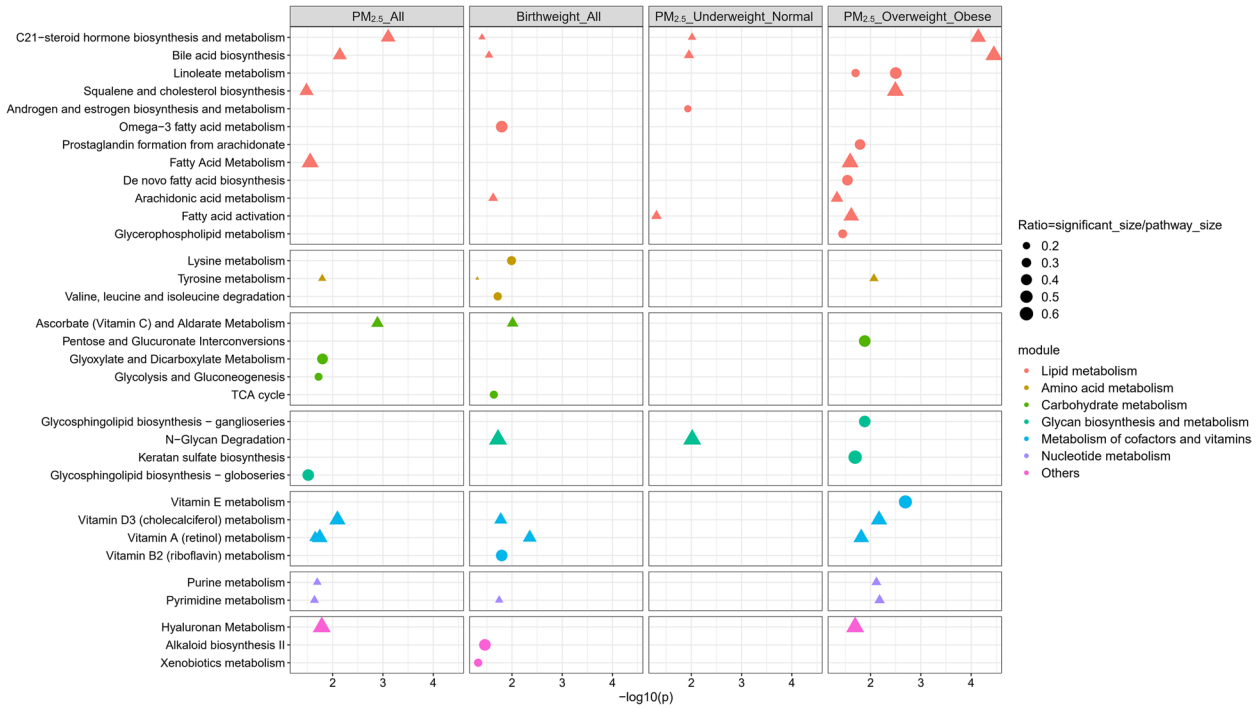

Fig. 1 Metabolic pathways significantly associated with second-trimester $PM_{2.5}$ exposure and birth weight Z-score. Triangles denote common pathways in at least two columns

metabolic pathways in significant association with $PM_{2.5}$ exposure in both BMI groups. Moreover, out of the seven common metabolic pathways associated with both $PM_{2.5}$ exposure and birth weight among the overall population, two pathways showed significant association with $PM_{2.5}$ exposure among underweight or normal-weight women and six showed significant association with $PM_{2.5}$ exposure among overweight or obese women.

Metabolomic features having common Mummichog annotations that were associated with second-trimester $PM_{2.5}$ exposure or birth weight Z-score are summarized in Table S5. These common annotations were involved in C21-steroid hormone biosynthesis and metabolism, ascorbate (vitamin C) and aldarate metabolism, glycolysis and gluconeogenesis, glycosphingolipid biosynthesis – globoseries, N-glycan degradation, and biosynthesis of unsaturated fatty acids. A metabolomic feature was matched to confirmed identity, that is FA 20:5 (eicosapentaenoic acid) involved in biosynthesis of unsaturated fatty acids. A metabolomic feature without confirmed identity (m/z = 177.0413, retention time = 227, mode = C18-negative) and FA 20:5 (eicosapentaenoic acid) were both significantly associated with both $PM_{2.5}$ exposure and birth weight Z-score among the overall population. They also mediated the association between second-trimester $PM_{2.5}$ exposure and birth weight Z-score [$\beta_{indirect} = 0.01$ (95% CI: 0, 0.02), $p = 0.02$ and $\beta_{indirect} = -0.01$ (95% CI: −0.02, 0), $p = 0.07$, respectively]. Additionally, a significant mediating effect was observed for the same metabolomic feature m/z = 177.0413 (retention time = 227, mode = C18-negative) among overweight and obese women [$\beta_{indirect} = 0.01$ (95% CI: 0, 0.03), $p = 0.04$].

Discussion

In the MADRES pregnancy cohort study, only second-trimester $PM_{2.5}$ exposure was significantly associated with lower birth weight, while no significant associations were observed for the other ambient air pollutants, including PM_{10}, NO_2, and O_3. Through high-resolution untargeted metabolomics analysis, we identified metabolic pathways potentially underlying the associations between prenatal exposure to $PM_{2.5}$ and lower birth weight, including maternal metabolism of C21-steroid hormones, bile acids, tyrosine, ascorbate and aldarate, vitamin D3, vitamin A, and pyrimidine during late pregnancy. Additionally, women who were overweight or obese exhibited more pronounced metabolic perturbations by prenatal $PM_{2.5}$ exposure.

Our study highlighted the important role of steroid metabolism, including C21-steroid hormone, bile acid, and vitamin D3, in linking prenatal $PM_{2.5}$ exposure to lower birth weight. We observed that disturbance in C21-steroid hormone biosynthesis and metabolism was associated with altered birth weight, which is consistent

with previous studies profiling metabolomics in maternal or newborn blood samples [11, 12, 18]. C21-steroid hormones, systematically known as pregnanes and including progesterone and corticosteroids, play pivotal roles in all stages of pregnancy [36, 37]. Progesterone is implicated profoundly in initiation and maintenance of pregnancy, fetal growth and development, as well as parturition, through immune modulation [38–40]. Progesterone has also been associated with alternation in brown adipose tissue that can affect gestational metabolism and fetal growth [41] and a lower level of maternal progesterone is a predictor of low birth weight [42–44]. Additionally, prenatal $PM_{2.5}$ exposure has been associated with lower steroid hormones in pregnant women and newborns [45, 46], potentially by affecting related enzymes [47]. A metabolomic study also demonstrated that air pollution exposure interfered with C21-steroid hormone metabolism in follicular fluid of women undergoing in vitro fertilization [14]. In summary, by employing a meet-in-the-middle strategy, our study bridges previous findings, providing evidence on the potential role of C21-steroid hormone metabolism in linking prenatal $PM_{2.5}$ exposure to lower birth weight.

Bile acids are steroid acids involved in intestinal fat absorption and triglyceride, cholesterol, glucose, and energy homeostasis regulation, which have critical roles in pregnancy [48]. Dysregulated bile acid metabolism is linked to gestational diseases such as intrahepatic cholestasis of pregnancy, gestational diabetes mellitus, and asymptomatic hypercholanemia, and can detrimentally impact the mother, the placenta, and the developing fetus [49]. Previous studies have shown the associations between excessive bile acids and lower birth weight as well as an increased risk of small for gestational age [50–53]. Consistent with our finding, a study among 214 mothers living in California's Central Valley found that traffic-related air pollution exposure during pregnancy was associated with perturbations in bile acid metabolism [54]. $PM_{2.5}$ exposure may detrimentally affect bile acid synthesis through downregulated expression of farnesoid X receptor [55], which is a nuclear receptor repressing bile acid synthesis through a feedback regulatory pathway [56].

Additionally, we found that vitamin D3 metabolism, which is a secosteroid hormone originating from cholesterol, might serve as an underlying mechanism linking prenatal $PM_{2.5}$ exposure to low birth weight. Vitamin D3 metabolism is essential in fetal skeletal growth, particularly during the third trimester when the fetus undergoes accelerated skeleton accumulation [57]. Deficiency of vitamin D3 has long been linked to an increased risk of low birth weight [58–60]. A study enrolling 125 women undergoing in vitro fertilization reported that exposure to NO_2 and $PM_{2.5}$ could disrupt vitamin D3 metabolism in follicular fluid, implying a link between vitamin D3 metabolism and reproductive impacts of air pollution exposure [14]. Notably, a complex interplay exists between bile acid and vitamin D3 metabolism. Vitamin D regulates bile acid production and transport, and conversely bile acids act as ligands for vitamin D receptors [61, 62]. Circulating levels of vitamin D metabolites have been inversely associated with fecal bile acid concentrations [63]. Our finding, which aligns with prior research and exhibits biological plausibility, supports the notion that bile acid biosynthesis and vitamin D3 metabolism may serve as pathways through which prenatal $PM_{2.5}$ exposure contributes to reduced birth weight.

Pathway enrichment results suggest that oxidative stress and inflammation may be underlying mechanisms contributing to abnormal birth weight related to $PM_{2.5}$ exposure. Tyrosine, an aromatic amino acid, has been closely linked to oxidative stress and inflammation [64, 65], and is a well-established risk factor for obesity, insulin resistance, type 2 diabetes, and gestational diabetes mellitus [66–68]. Our study and prior research demonstrated that exposure to ambient and traffic-related air pollution could disrupt tyrosine metabolism [13, 15, 16, 19], which may partly attribute to oxidative stress [65]. The disruption may further lead to lower birth weight, owing to the multifaceted role of tyrosine in oxidative stress, inflammatory responses, and glucose metabolism. Furthermore, ascorbate (vitamin C) is a potent antioxidant with significant implications in oxidative stress and inflammation [69, 70]. Studies have consistently shown the relationship between vitamin C deficiency and an elevated risk of low birth weight [71–73], while separate findings have linked alterations in ascorbate and aldarate metabolism to particulate air pollution exposure [14, 16, 17, 20]. Our research not only corroborates prior observations but also provides a clear and direct insight into the potential role of ascorbate and aldarate metabolism in linking prenatal $PM_{2.5}$ exposure and low birth weight. Additionally, we identified a metabolite, FA 20:5 (eicosapentaenoic acid), that was associated with both prenatal $PM_{2.5}$ exposure and birth weight. Notably, FA 20:5 (eicosapentaenoic acid) exhibited a mediating role in a mediation testing framework. FA 20:5 (eicosapentaenoic acid), part of the α-linolenic acid (n-3 fatty acid) family, is known as an anti-inflammatory agent and a cardiovascular protective compound [74–76]. These observations further underscore the critical role of inflammation.

Vitamin A is an essential micronutrient for fetal growth and development. It is required for normal visual functioning, immune responses, gene expression, embryogenesis, and hematopoiesis, as well as lung growth and maintenance of the integrity of respiratory tract epithelial

cells [77, 78]. Previous metabolomic studies have independently illustrated the associations between vitamin A metabolism and two distinct factors: birth weight [18], and air pollution exposure [14, 15], while our meet-in-the-middle analysis further indicates that vitamin A metabolism may serve as a pathway linking these two factors. Additionally, pyrimidine metabolism was associated with both prenatal $PM_{2.5}$ exposure and birth weight, suggesting that prenatal $PM_{2.5}$ exposure may adversely affect birth weight by inducing DNA damage [15, 16].

Overweight or obese women may experience more pronounced metabolic disruptions in response to prenatal $PM_{2.5}$ exposure, as demonstrated by our findings. Similarly, a study reported near-roadway air pollution exposure had a stronger association with non-esterified fatty acids and branched-chain amino acids among adolescents and young adults who were overweight or obese than normal-weight participants [79]. Previous studies have shown that pregnant women who were overweight and obese demonstrated metabolic alterations, characterized by dysregulation in pathways related to the antioxidant defense system, nucleotide production, lipid metabolism, and energy production [80, 81], while $PM_{2.5}$ exposure has been linked to metabolic perturbations in similar pathways [15–17]. Consequently, it is plausible that overweight or obese women may exacerbate the metabolic disruptions of $PM_{2.5}$ exposure.

We applied a meet-in-the-middle strategy in MWAS analysis to investigate the maternal metabolic pathways linking prenatal $PM_{2.5}$ exposure to lower birth weight. The novel insight on biological pathways may illuminate promising intervention and prevention targets to mitigate the detrimental effects of prenatal $PM_{2.5}$ exposure. The study had some limitations. First, air pollution exposure was estimated using inverse-distance-squared weighted spatial interpolation, which may not fully capture the fine spatial variability of air pollution. However, Southern California has the densest ambient air pollution monitoring network in the United States, providing excellent data for capturing spatial variability. In addition, we developed detailed daily level residential timelines that accounted for all residential mobility with high spatial and temporal resolution, allowing for more accurate estimates of daily residential exposure to ambient air pollution. Second, the sample size may have limited statistical power due to the large number of metabolomic features analyzed, and chemical annotation remains a great challenge in untargeted metabolomics research. However, in our main results, we focused primarily on presenting air pollution-related metabolic pathways that convened information from multiple metabolites within a pathway. The pathway findings provide more robust evidence than individual metabolites. Third, while our study adds knowledge on the metabolic pathways through which prenatal $PM_{2.5}$ exposure adversely affect fetal growth in an underrepresented population [82], more studies in diverse populations remain imperative. Fourth, the presence of uncontrolled confounding factors in this observational study limits the establishment of causality, which highlights the need for evidence from interventional or experimental studies.

Conclusions

In the MADRES pregnancy cohort, we applied a meet-in-the-middle strategy in an untargeted metabolomics study to investigate the metabolic mechanisms linking prenatal $PM_{2.5}$ exposure to lower birth weight. We found that metabolic pathways in relation to steroid metabolism including C21-steroid hormone biosynthesis and metabolism, bile acid biosynthesis, and vitamin D3 (cholecalciferol) metabolism; oxidative stress and inflammation including tyrosine metabolism and ascorbate (vitamin C) and aldarate metabolism; vitamin metabolism including vitamin A (retinol) metabolism; and DNA damage including pyrimidine metabolism, may serve as underlying mechanisms. Additionally, overweight or obese women may have enhanced susceptibility to metabolic disturbances of prenatal $PM_{2.5}$ exposure. Further studies are essential to explore the potential of these biological pathways as intervention targets for mitigating the detrimental impacts of $PM_{2.5}$ exposure and unravel the intricate interplay of various risk factors in influencing adverse birth outcomes.

Abbreviations

BMI	Body mass index
CV	Coefficient of variation
ESI	Electrospray ionization
FDR	False discovery rate
HILIC	Hydrophilic interaction liquid chromatography
LC-HRMS	Liquid chromatography coupled with Fourier transform high-resolution mass spectrometry
MADRES	Maternal and Developmental Risks from Environmental and Social Stressors
MWAS	Metabolome-wide association study
m/z	Mass-to-charge ratio
NO_2	Nitrogen dioxide
O_3	Ozone
$PM_{2.5}$	Fine particulate matter
PM_{10}	Particulate matter ≤ 10 μm in diameter
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-025-01162-x.

Supplementary Material 1.

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Authors' contributions
WC: Methodology, Software, Formal Analysis, Writing-Original Draft, Writing—Review & Editing, Visualization; CQ: Methodology, Software, Formal Analysis, Data Curation, Writing—Review & Editing; JH: Writing—Original Draft, Writing—Review & Editing; JL: Software, Writing—Review & Editing; FL: Investigation, Writing—Review & Editing; NP: Investigation, Writing—Review & Editing; RH: Investigation, Writing—Review & Editing; DJ: Investigation, Resources, Writing—Review & Editing; TB: Investigation, Resources, Project administration, Writing—Review & Editing, Funding acquisition; CB: Investigation, Resources, Project administration, Writing—Review & Editing, Funding acquisition; and ZC: Conceptualization, Methodology, Project administration, Writing—Review & Editing, Supervision, Funding acquisition.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Written informed consent and HIPAA authorization to obtain medical records from each participant is obtained at study entry for herself and her child. The University of Southern California's Institutional Review Board approved the protocol (Protocol #HS-15–00498). The study was conducted in accordance with the Declaration of Helsinki.

Clinical trial number
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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