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Lipid metabolism dysregulation in umbilical cord plasma of newborns from mothers with preeclampsia is associated with neonatal physical parameters at birth

Jing Ding[1†], Yihan Xiao[1†], Jie Fu[1], Qionghui Huang[1], Zijun Ma[1], Chao Zhang[2], Yan Wang[2], Guoli Liu[2], Hongkun Wu[3*] and Yifang Yuan[4*]

Abstract

Background Preeclampsia is linked to fetal growth restriction and may have long-term implications for the offspring. Despite its significance, the fundamental mechanisms remain inadequately elucidated. The objective of this investigation was to undertake an untargeted lipidomics analysis of umbilical cord plasma, with the intention of investigating lipidomic profile alterations in newborns of mothers with preeclampsia and evaluating the associations between lipidomic patterns and neonatal physical parameters at birth.

Methods 25 newborns from mothers with preeclampsia (PE group) and 25 newborns from healthy mothers (control group) were involved in the present investigation. Untargeted lipidomics was performed using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) to contrast the lipid compositions present in umbilical cord plasma. Co-expression correlation analysis was performed to explore the relationships between lipidomic patterns and neonatal weight and length percentile at birth.

Results Marked discrepancies in lipid metabolism profiles were detected in the comparison of the PE and control groups. In total, 364 separate lipids were noted, with AcylGlcADG (20:3–22:6–22:6) and GM3(d39:1) exhibiting the most significant decreases. Conversely, Cer-NS (d20:1–24:0) and DGTS (2:0–19:0) displayed the most significant increases. The primary lipid metabolic pathways altered in newborns from mothers with preeclampsia were enriched in choline and glycerophospholipid metabolic processes. Additionally, 20 distinct lipids exhibited significant associations with neonatal birth weight percentile between the two groups, while 21 distinct lipids showed significant associations with neonatal birth length percentile.

Conclusions Lipid profile disorders were identified in the umbilical cord plasma of infants born to mothers with preeclampsia, and the metabolic disturbances identified in this group correlated with neonatal physical parameters at birth. These findings suggest that lipidomic disorders in newborns from preeclamptic mothers may correlate with intrauterine growth outcomes.

Keywords Preeclampsia, Newborn, Lipidomics, Birth physical parameters

†Jing Ding and Yihan Xiao contributed equally to this work.

*Correspondence:
Hongkun Wu
wuhongkun@zju.edu.cn
Yifang Yuan
yyfjulie@163.com
Full list of author information is available at the end of the article

Introduction

Preeclampsia is a major pregnancy complication that typically arises after the 20 th week of gestation, marked by the development of hypertension and often associated with proteinuria or other signs of organ dysfunction, including kidney and liver damage, neurological injury, and thrombocytopenia [1]. This condition is a significant contributor to premature births and accounts for approximately 10–20% of perinatal mortality [2]. Furthermore, research indicates that preeclampsia is linked to fetal growth restriction (FGR) and has lasting implications for offspring, increasing their risk of developing hypertension, cardiovascular diseases, and metabolic disorders later in life [3, 4]. Preeclampsia is a multifactorial disorder with various factors influencing its development. Among these factors, few studies have assessed the role of lipids in the onset of FGR.

Lipidomics, a subfield of metabolomics, concentrates on the detailed examination of cellular lipid profiles, enhancing our understanding of the metabolic pathways involving lipids [5]. It has proven valuable as a biomarker and prognostic indicator for various diseases, including non-alcoholic fatty liver disease, neurological disorders, and cancers [6–8]. Lipids play crucial structural and metabolic roles in the body, and disturbances in lipid processing are linked to the onset of numerous diseases [9]. Notably, studies have identified specific lipid composition alterations in the bloodstream and placental tissue of expectant mothers suffering from preeclampsia. In comparison to the control group, plasma specimens from patients experiencing preeclampsia exhibited elevated levels of Glycerophosphoserines-GP03, Glycerophosphocholines-GP01, and Flavanoids-PK12. Additionally, placental analysis in patients with preeclampsia demonstrated increased concentrations of Glycerophosphoserines-GP03 and macrolides/polyketides-PK04 relative to the control group [10]. Based on these findings, we hypothesize that lipid alterations of pregnant women with preeclampsia may influence the lipid profiles of their offspring, potentially impacting their intrauterine growth and long-term health outcomes. However, investigations into the lipid profile changes in newborns of preeclamptic mothers remain limited.

Consequently, in the current study we performed untargeted lipid analysis of umbilical cord plasma from both preeclamptic and healthy pregnancies to investigate whether maternal preeclampsia impacts lipid metabolism in offspring, as well as to explore the relationship between lipidomic patterns and the physical parameters of the newborns at birth.

Materials and methods

Study design and population

This study received approval from the research ethics committee at Peking University People's Hospital. All participating women signed an informed consent form. Umbilical cord plasma specimens were obtained from expectant mothers who experienced preeclampsia as their only complication (PE group, n = 25) and from those with uncomplicated pregnancies (control group, n = 25). All participants had singleton pregnancies and given birth at Peking University People's Hospital, China, between January 2023 and September 2024. Women who had fetal anomalies, chronic renal disease, diabetes, immune disorders, or other chronic diseases were excluded to minimize confounding factors. The individuals conducting the various analyses of the lipid profiles in both study groups were "blinded" to the participants' clinical conditions.

Definition of clinical variables

Preeclampsia was diagnosed according to the criteria specified in the 2020 Practice Bulletin No. 202 by the American College of Obstetricians and Gynecologists. Pregnant women identified as having preeclampsia exhibited the subsequent attributes after 20 weeks of gestation: (1) Systolic blood pressure (SBP) of 140 mmHg or higher and/or diastolic blood pressure (DBP) of 90 mmHg or higher, recorded on at least two separate measurements, with a minimum interval of four hours; (2) proteinuria of ≥300 mg over 24 h or the presence of severe manifestations, including thrombocytopenia, dysfunctional liver function, persistent abdominal pain in the epigastric region, renal impairment, pulmonary edema, new-onset headache, or optic disruptions.

Specimen collection

The specimens of umbilical cord blood were collected from the venous side promptly following birth and subsequently transported to the core lab. The specimens of blood underwent centrifugation at 3000 rpm for 10 min at 4 ℃. The resulting supernatant plasma was collected, aliquoted into 200 µl portions, and preserved at −80 ℃ until further analysis.

Lipid extraction

First, 100 µl of the plasma specimen was combined with 480 µl of an extraction solution composed of MTBE and MeOH in a 5:1 volume ratio, which contained deuterated internal standards. This mixture was vortexed for 30 s and then sonicated for 10 min in a 4℃ water bath, followed by a one- hour incubation at −40℃ to precipitate proteins. Afterward, the specimens were centrifuged at 3000 rpm (RCF = 900 × g) for 15 min at 4℃. The supernatant was collected and evaporated to dryness using a vacuum concentrator. The dry extracts were reconstituted in 100 µl of DCM and MeOH in a 1:1 volume ratio, then vortexed for 30 s, sonicated for 10 min (50 Hz, 4℃), and

centrifuged at 12,000 rpm (RCF = 13,800 × g) for 15 min at 4℃ to remove any insoluble material. Finally, a volume of 75 µl of the supernatant was moved to glass vials for examination.

Untargeted lipidomic analysis

For lipid analysis, LC–MS/MS was conducted using an ultra-high-performance liquid chromatography (UHPLC) system, specifically the Vanquish model from Thermo Fisher Scientific. The system was equipped with a Phenomenex Kinetex C18 column, measuring 2.1 mm × 100 mm with a particle size of 2.6 µm. Additionally, an Orbitrap Exploris 120 mass spectrometer from Thermo was coupled to the setup. The mobile phase A was made up of a mixture of H2O and acetonitrile (CAN) in a 6:4 volume ratio, containing 10 mM ammonium formate. In contrast, mobile phase B consisted of isopropanol (IPA) and CAN in a 9:1 volume ratio, also with 10 mM ammonium formate. A volume of 2 µl was injected. The Orbitrap Exploris 120 mass spectrometer was utilized for its ability to obtain MS/MS spectra, with operations managed by the Xcalibur acquisition software from Thermo. In this mode, the software constantly monitors the full scan mass spectrum. The conditions for the electrospray ionization (ESI) source were established as follows: sheath gas flow rate of 30 Arb, auxiliary gas flow rate of 10 Arb, capillary temperature set to 320℃, full MS resolution at 60,000, and MS/MS resolution at 15,000. The collision energies were configured to SNCE 15/30/45, with the spray voltage set to 3.8 kV for positive mode and −3.4 kV for negative mode.

Data preprocessing and annotation

The original data files were transformed into mzXML format through the 'msconvert' program from ProteoWizard. Peak identification, extraction, alignment, and unification were performed using the CentWave algorithm in XCMS. The minimum fraction for annotation was established at 0.5, while the cutoff for annotation was set at 0.3. Lipid detection was accomplished through spectral alignment with the LipidBlast library originally developed in R and built upon XCMS.

Bioinformatics analysis

Initially, X peaks were identified and X metabolites were maintained using the interquartile range denoising technique. The absent values in the original data were imputed by filling them with fifty percent of the minimum value. Furthermore, in the course of this data analysis, total ion current normalization was implemented. The generated three-dimensional dataset included peak count, sample identifier, and standardized peak area. This dataset was processed using the SIMCA 14.1 software package (V14.1 Sartorius Stedim Data Analytics AB, Umea, Sweden) to conduct principal component analysis (PCA) and orthogonal projections to latent structures-discriminate analysis (OPLS-DA). PCA illustrated the original data distribution. Supervised OPLS-DA was employed to improve group divergence and provide a clearer insight of the factors influencing classification.

R^2Y = X and Q^2Y = X were the classification metrics obtained from the software, which indicates stable fit and statistical significance. A seven-fold cross-validation was conducted to assess the stability and prediction effectiveness of the model, complemented by a permutation test for additional validation. The R^2 and Q^2 intercept values were X and X, respectively, following 200 permutations. The low Q^2 intercept values suggest model robustness, indicating a minimal possibility of overfitting and high credibility.

A loading plot was created to demonstrate how variables contribute to the differences between the two groups according to the OPLS-DA results. The plot emphasized key variables that were situated far from the origin; however, the complexity of the loading plot arose from the presence of multiple variables. To enhance this analysis, the first principal component of variable importance in projection (VIP) was computed. The VIP values greater than 1 were identified as significantly altered metabolites. Next, Student's t-test (P-value > 0.05) was employed to evaluate the remaining variables, leading to the exclusion of those that did not show notable distinctions between the comparison groups. The databases, including KEGG http://www.genome.jp/kegg/ and MetaboAnalyst http://www. metaboanalyst.ca/, were used to explore the pathways pertaining to significantly different metabolites between the two groups.

Statistical analysis

SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) was employed for the data analysis. The $p < 0.05$ were considered statistically significant. Descriptive statistics for continuous variables exhibiting non-normal distributions are reported as medians accompanied by interquartile ranges (IQRs). Categorical variables are expressed as percentages. Between the two groups, comparisons were conducted using the Mann–Whitney U test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. The plots, including volcano, bubble, and heat maps, were generated using R software (version 4.4.1). The association between plasma lipids in newborns of mothers with preeclampsia and their physical parameters at birth was evaluated using weighted lipid co-expression network analysis (WGCNA), implemented through the R software (version 4.4.1).

Results

Characteristics of the study population

In this study, there were 25 participants in both the PE group and control group, respectively. The clinical characteristics of the mothers and their newborns are presented in Table 1.

Separation of plasma lipid composition profiles between the newborns of PE and control group

Untargeted lipidomics using UHPLC-QE-MS was employed to analyze alterations in plasma lipid composition profiles between the PE and control groups. To ensure data integrity, quality control (QC) samples were utilized to monitor instrument variability during the analysis. In both positive and negative ion modes, the total ion chromatogram (TIC) of the QC samples demonstrated excellent overlap, which indicates robust stability and reproducibility of the system (Figure S1). A total of 10,190 peaks in positive ion mode and 9436 peaks in negative ion mode were preserved subsequent to normalization with QC data and processing of original data (Table S1). Identification of lipids was performed using the LipidBlast database, resulting in the characterization of 1395 lipids based on their MS2 fragmentation patterns. An Orthogonal Partial Least Squares Discriminant Analysis (OPLS-DA) model was implemented to differentiate lipid composition patterns between the PE and control groups. The resulting scatter plot indicated a notable separation between the two groups (Fig. 1A). The permutation test conducted on the model showed that R^2Y (R-squared for Y) was 0.79 and Q^2 (predictive ability) was −0.89 (Fig. 1B), further supporting robustness of the findings. These results indicate that the OPLS-DA models were not prone to overfitting and are reliable for deeper exploration of lipid profile alterations.

Distinct of the umbilical cord plasma lipid profiles that exhibited notable differences between PE and control group

The OPLS-DA model revealed that 364 lipids ($p < 0.05$ and VIP > 1) were distinctly different between the preeclampsia (PE) and control groups. This encompassed 19 lipids that were increased in abundance and 345 that were decreased in the PE group. Volcano plots were utilized to visually represent the significant differences in lipid profiles. In these plots, the dimension of the dots corresponds to VIP values. The gray dots reflect insubstantial changes, the blue dots represent downregulated lipids, and the red dots indicate upregulated lipids (Fig. 2A). Notably, the levels of specific lipids, such as AcylGlcADG (20:3–22:6–22:6) and GM3(d39:1), were markedly decreased in the PE group in comparison to the control. Conversely, the levels of Cer-NS (d20:1/24:0) and DGTS (2:0–19:0) were notably elevated in the PE group. The distribution of the identified complicated lipid subclasses and the comparative differences in the notably altered lipids were presented in Figs. 2B and 2C. The top 10 lipids that significantly increased and decreased in the PE group are displayed in Fig. 3.

Pathway analysis of the lipid profiles in newborns of mothers with preeclampsia

The KEGG (http://www.genome.jp/kegg) and MetaboAnalyst (http://www.metaboanalyst.ca) platforms were utilized to identify the significantly perturbed metabolic pathways based on the differential lipids identified. The

Table 1 Demographic and clinical characteristics of the mother and neonates of PE and control groups

Parameters	PE group ($n = 25$)	Control group ($n = 25$)	*P* value
Age at delivery, year	31.0 (28.5,35.0)	31.0 (28.0, 32.5)	0.470
Gravidity	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.138
Parity	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.760
Firstborn, n (%)	17 (68%)	18 (72%)	0.758
Assisted reproductive pregnancy, n (%)	7 (28%)	1 (4%)	**0.049**
BMI, kg/m^2	25.0 (23.1, 26.4)	21.5 (19.4, 23.0)	**0.000**
Cesarean section rate, n(%)	20 (80%)	15 (60%)	0.217
GA at birth, weeks	37.7 (36.0, 39.1)	39.6 (39.1, 40.6)	**0.000**
Female, n (%)	12 (48%)	13 (52%)	0.777
Birth weight, g	2900 (2445, 3320)	3350 (3140, 3600)	**0.001**
Birth length, cm	49(47, 50)	50(49, 51)	**0.002**
SGA, n(%)	2 (8%)	2 (8%)	1.000
Apgar/1 min	10 (10, 10)	10 (10, 10)	0.332

BMI: Body mass index of the women before pregnancy

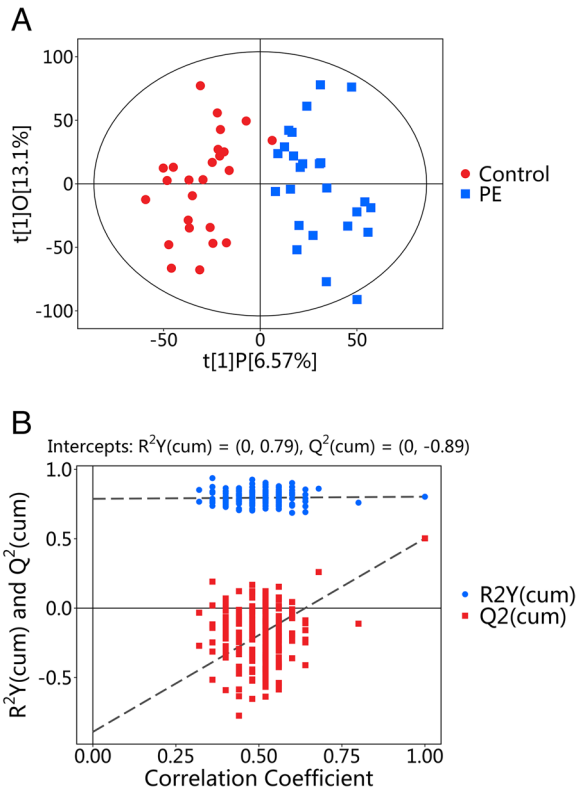

Fig. 1 Score scatter plot and permutation test of the OPLS-DA model. **A** Score plots were generated from the LC–MS/MS data of umbilical cord blood plasma lipidomic profiles for both the PE and control groups. The x-axis and y-axis represent the first and second principal components, respectively, with red and blue colors indicating the respective groups. **B** Permutation tests were conducted using the LC–MS/MS data. In the permutation test, the x-axis represents the correlation coefficient, while the y-axis displays the values of R^2Y and Q^2. OPLS-DA refers to orthogonal partial least squares discriminant analysis; PE, preeclampsia

altered lipids were particularly enriched in choline and glycerophospholipid metabolism, as illustrated in Fig. 4.

Association of lipid profiles with neonatal physical parameters at birth

To determine whether changes in fetal lipid profiles could influence physical parameters, we conducted co-expression correlation analysis on the lipid metabolites which demonstrated differences between the PE and control groups, examining their relationships with neonatal birth weight and length percentiles. This analysis identified a statistically significant correlation between 20 lipids and newborn birth weight percentile, including TAG (16:1–20:4–20:4), TAG (18:1–18:2–18:2), PC (20:4e-27:0), TAG (17:1–17:1–21:0), TAG (13:0–22:2–22:2), TAG (18:1–18:1–22:6), TAG (19:1–19:1–19:1), TAG (18:1–18:2–22:4), SM (d14:3–36:2), TAG (16:1–18:1–18:2), TAG (19:0–19:1–19:1), TAG (18:1–18:1–20:2), TAG (13:1–22:0–22:0), TAG (16:1–18:2–22:5), TAG (16:1–18:1–21:1), SM (d14:0–32:0), TAG (16:0–18:1–20:3), TAG (16:0–16:0–20:5), TAG (16:0–18:2–20:3) and TAG(16:1–16:1–18:2). Notably, all these lipids exhibited negative correlations with neonatal birth weight percentile (Figs. 5A and 5B).

Additionally, the analysis demonstrated a statistically significant correlation between 21 lipids and newborn birth length percentile, which included OxPC (18:1–18:1 + 3O), TAG (16:1–20:4–20:4), TAG (18:1–18:2–18:2), PC (20:4e-27:0), TAG (17:1–17:1–21:0), TAG (13:0–22:2–22:2), TAG (18:1–18:1–22:6), TAG (19:1–19:1–19:1), TAG (18:1–18:2–22:4), SM (d14:3–36:2), TAG (16:0–16:1–22:6), TAG (16:1–18:1–18:2), TAG (19:0–19:1–19:1), TAG (18:1–18:1–20:2), TAG (13:1–22:0–22:0), TAG (16:1–18:2–22:5), TAG (16:1–18:1–21:1), TAG (18:0–18:1–20:3), TAG (16:1–18:2–18:3), PC (16:0–22:6) and PC (19:0–20:4). Similarly, all these lipids demonstrated negative correlations with neonatal birth length percentile (Figs. 5A and 5B).

Discussion

In our study, we observed lipid profile disturbances in the umbilical cord plasma of newborns born to mothers with preeclampsia. The metabolic alterations identified in this group were found to correlate with neonatal birth weight and length percentiles. These findings indicate that metabolic disorders in newborns born to preeclamptic mothers may be linked to intrauterine growth outcomes, potentially impacting their long-term health.

Preeclampsia is a severe pregnancy complication which negatively impacts both maternal and fetal health. Neonates delivered by mothers with preeclampsia generally demonstrate a birth weight that is, on average, 5% lower than that of infants delivered following uncomplicated pregnancies [11]. Additionally, preeclampsia is a key risk contributor to premature birth [12]. In terms of short-term outcomes, infants affected by preeclampsia are susceptible to several complications, including respiratory distress syndrome, bronchopulmonary dysplasia and neurodevelopmental disabilities in childhood [13–15]. Long-term consequences also include an elevated cardiovascular risk in offspring exposed to preeclampsia in utero [16]. However, the underlying mechanisms that contribute to these adverse outcomes remain inadequately understood.

Lipids are essential fatty compounds that perform various functions within the body, including energy storage and transport, vitamin absorption, and hormone synthesis. The metabolism and transport of lipids and lipoproteins are crucial in the development of cardiovascular disease [17, 18]. Zhang et al. reported notable alterations in glycerophospholipid levels between patients with

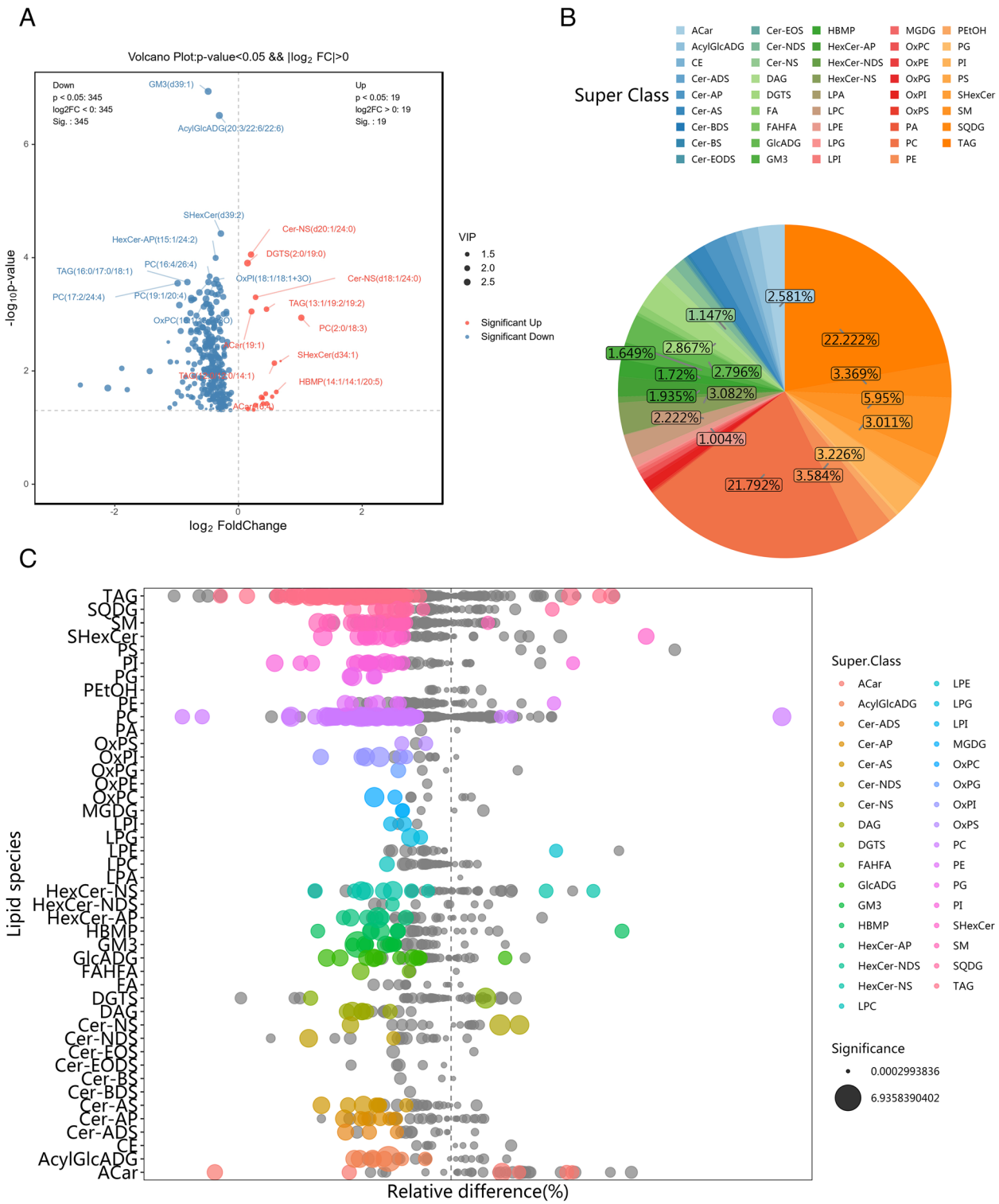

Fig. 2 Umbilical cord plasma lipid species exhibited notable differences between the PE and control groups. **A** The volcano plot was utilized to assess significantly different lipids. Blue dots represent downregulated lipids in the PE group, while red dots indicate significantly upregulated lipids. Grey dots denote lipids that did not show significant changes in the PE group. The size of the dots corresponds to the VIP values. **B** Pie charts illustrate the composition of differential lipid species. **C** The bubble plot displays the relative differences in the detected significantly different lipids. Each bubble represents a specific lipid, with the y-axis indicating the lipid subclass and the x-axis representing the relative difference of various lipids. A positive relative difference indicates that the concentration of that lipid was higher in the PE group, whereas a negative relative difference signifies that the concentration was lower in the PE group

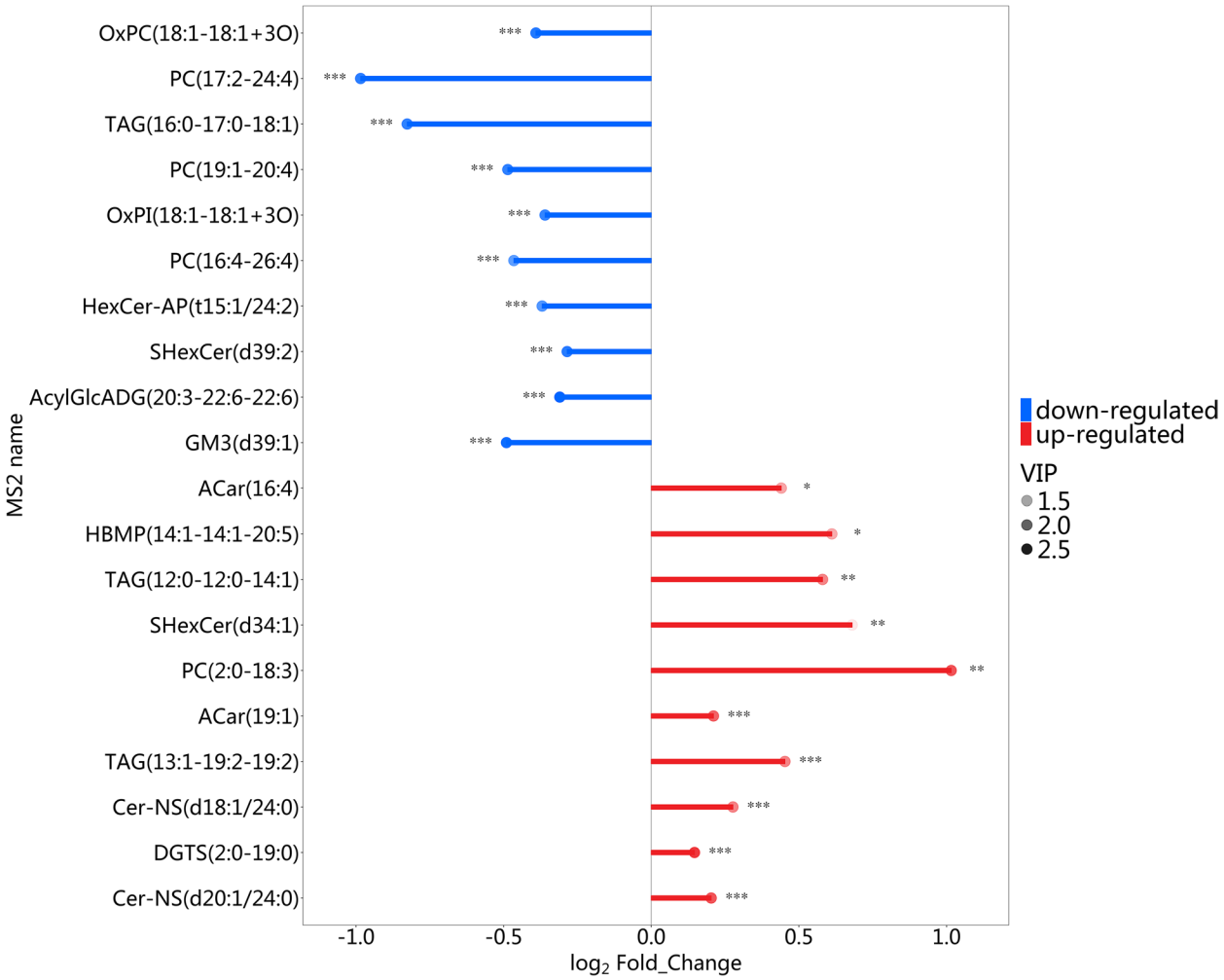

Fig. 3 The matchstick plot illustrates the top 10 lipids that are significantly upregulated and downregulated between the PE and control groups. VIP, variable importance in projection

preeclampsia and normal blood pressure [19]. Furthermore, Brown et al. observed a marked elevation in the placental concentrations of neutral storage lipids, such as triglycerides and cholesterol esters, in preeclamptic placentas compared to healthy controls [20]. Consequently, we hypothesize that dyslipidemia may be present in the newborns of mothers with preeclampsia, and this dysfunction in lipid metabolism could contribute to inhibited intrauterine growth and an elevated risk of cardiovascular disorders in these offspring.

Lipidomics involves the comprehensive analysis of lipid pathways and networks within biological systems, providing advanced insights into the functional roles of lipids in cellular processes [5]. Decreased or elevated levels of specific lipids may correlate with increased risks of developmental issues, metabolic disorders, and inflammatory conditions. For instance, altered fatty acid profiles can affect brain development and immune function, potentially leading to cognitive deficits or increased susceptibility to infections [21, 22].

In our study, we focused on lipid alterations in umbilical cord plasma from neonates delivered by mothers with preeclampsia. We observed that specific lipids, including AcylGlcADG (20:3–22:6–22:6) and GM3(d39:1), were significantly decreased in newborns from mothers affected by preeclampsia. AcylGlcADG is a distinct acylated diacylglycerol. Alterations in diacylglycerol levels are related to a variety of health issues, including metabolic and cardiovascular disorders [23, 24]. The reduced levels of AcylGlcADG (20:3–22:6–22:6) in newborns from preeclamptic mothers may be linked to an elevated risk of future cardiovascular disorders. GM3 (d39:1) is a specific ganglioside belonging to the glycosphingolipid family. GM3 engages in numerous physiological activities, including cell signaling, neurodevelopment, immunological adjustment, and protection against pathogens

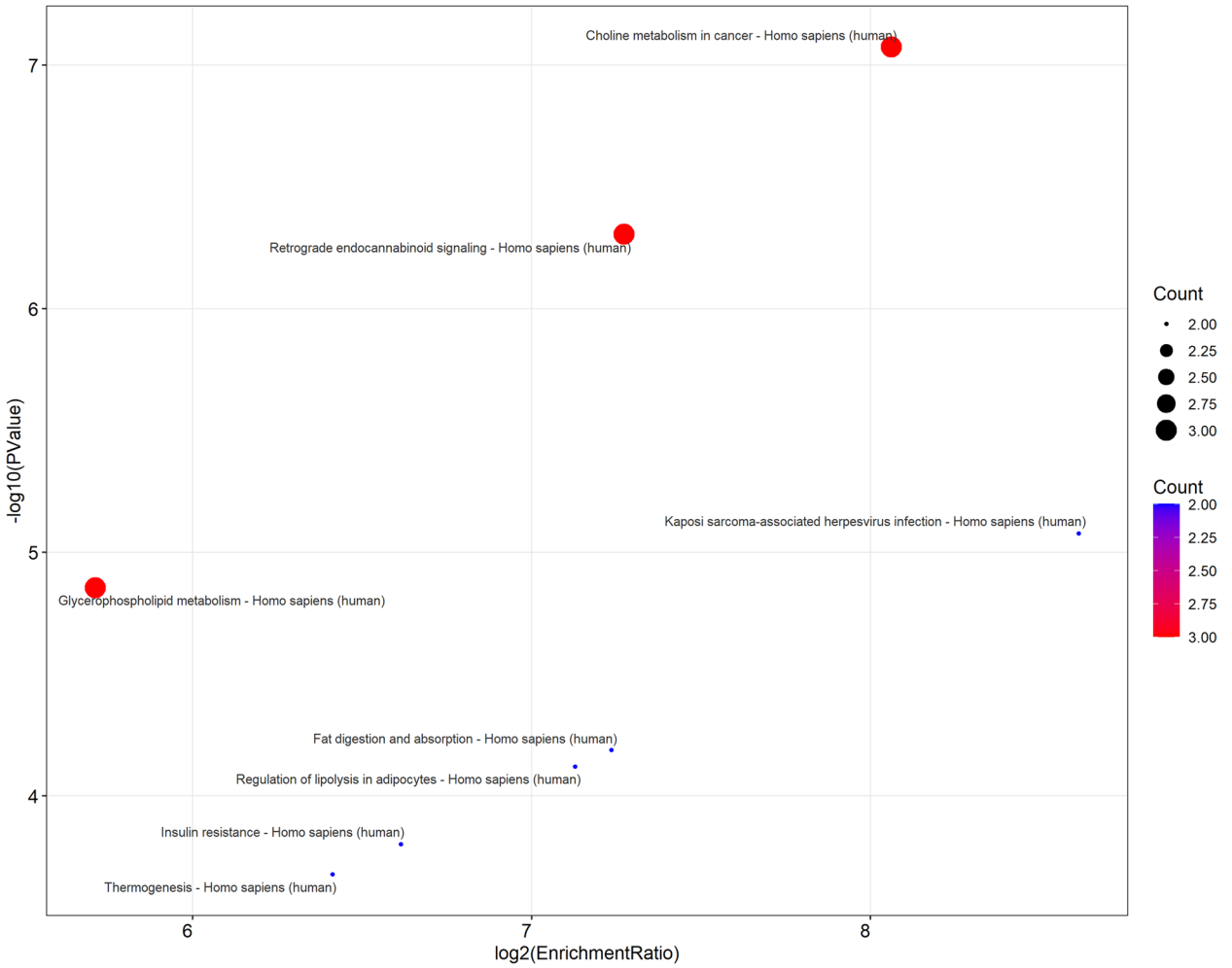

Fig. 4 The metabolomic pathway analysis of significantly different lipids. The y-axis represents the transformation of the original p-value derived from the enrichment analysis. The x-axis reflects the values obtained from the pathway topology analysis

[25, 26]. Previous studies showed the GM3 could attenuate insulin signaling pathway [27]. The decreased level of GM3 (d39:1) may also contribute to the elevated risk of metabolic disorders observed in some of the offspring of mothers with preeclampsia. Even though the fold changes of AcylGlcADG (20:3–22:6–22:6) and GM3(d39:1) are not substantial, their significant roles in metabolic pathways and processes that influence health outcomes suggest that these changes are biologically meaningful.

In addition to the observed decreases in AcylGlcADG(20:3–22:6–22:6) and GM3(d39:1), we also noted elevated levels of Cer-NS (d20:1–24:0) and DGTS(2:0–19:0) in the newborns of mothers with preeclampsia. Ceramides is recognized as a bioactive lipid that can activate the NLRP3 inflammasome in both macrophages and adipocytes to increase cytokine secretion [28, 29]. Elevated levels of ceramides, including Cer-NS, have been shown to be connected to disorders of metabolism, like circulatory diseases, diabetes mellitus and obesity [30]. DGTS (2:0–19:0), or diacylglycerol trimethylhomoserine is betaine lipid. Previous studies suggest that betaine may possess antioxidant properties, aiding in the scavenging of oxygen radicals and mitigating oxidation-related damage within cells [31]. Oxidative stress is implicated in the pathophysiological mechanisms underlying preeclampsia, contributing to endothelial dysfunction and placental insufficiency [32]. Furthermore, it is demonstrated that oxidative stress is elevated in neonates born to mothers with preeclampsia [33]. Thus, the increased levels of DGTS may reflect a complementary antioxidant response within the body.

The interplay of lipids with other metabolic factors can influence growth patterns, raising concerns about long-term health outcomes for infants. Understanding these impacts is crucial for early interventions and better health strategies. The WGCNA analysis indicated that

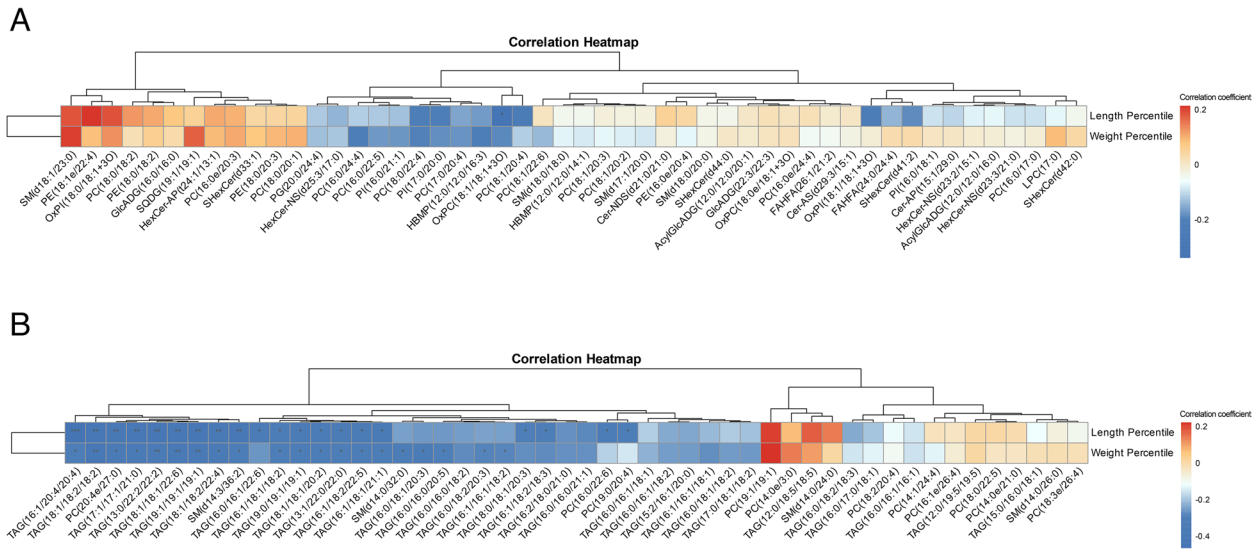

Fig. 5 Correlations between specific differential umbilical cord plasma lipids and neonatal birth physical parameters percentile in the PE and control groups. **A** Heatmap illustrates the correlation between negative ion lipids and neonatal birth weight and length percentile. **B** Heatmap depicts the correlation between positive ion lipids and neonatal birth weight and length percentile. Red is a positive correlation, blue is a negative correlation. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

the metabolic pathways exhibiting the most notable differences between newborns in two groups were primarily enriched in choline and glycerophospholipid metabolism pathway. Choline metabolism is vital for numerous physiological processes, including cell membrane formation, neurotransmitter synthesis, lipid metabolism and methylation reactions [34]. Abnormalities in choline metabolism have been linked to several health issues, including liver disease, cardiovascular disease, and neurological disorders. The choline metabolism disorders of offspring of mothers with preeclampsia maybe involved in their long-term risk of heart disease. In addition, glycerophospholipid metabolism is crucial for maintaining cell structure, facilitating signaling processes, regulating immune responses, and supporting energy metabolism [35]. Glycerophospholipid metabolism is intricately linked to the pathophysiology of preeclampsia through its effects on endothelial function, inflammation, oxidative stress, and fetal development. Previous studies show there are glycerophospholipid metabolism disorders in the pregnant women with preeclampsia [19]. These findings suggest that maternal dyslipidemia may influence fetal lipid metabolism.

Furthermore, neonatal birth weight and length percentiles were significantly associated with several lipid species. Negative correlations were observed between both neonatal weight and length percentiles at birth and the following lipids: TAG (16:1–20:4–20:4), TAG (18:1–18:2–18:2), PC (20:4e-27:0), TAG (17:1–17:1–21:0), TAG (13:0–22:2–22:2), TAG (18:1–18:1–22:6), TAG (19:1–19:1–19:1), TAG (18:1–18:2–22:4), TAG (18:1–18:1–20:2), TAG (13:1–22:0–22:0), TAG (16:1–18:2–22:5) and TAG (16:1–18:1–21:1). While previous studies suggest that preeclampsia in pregnant women may influence fetal birth weight, the underlying mechanisms remain unclear [36]. Our research indicates that lipid profile disturbances in the offspring of mothers with preeclampsia may constitute the underlying mechanisms affecting their size and weight. However, the specific effects of individual lipids on fetal growth remain ambiguous. We believe it may be important to conduct animal experiments in the future to further elucidate the mechanisms underlying this phenomenon.

Lipidomics of plasma from cord blood in newborns born to preeclamptic mothers provides critical insights into the underlying mechanisms affecting neonatal health. Key lipids, including AcylGlcADG (20:3–22:6–22:6), GM3 (d39:1), Cer-NS (d20:1–24:0) and DGTS(2:0–19:0), exhibit dysregulation. This dysregulation may result in altered energy metabolism and inflammation status in the newborn, ultimately impacting growth and development outcomes. Moreover, the metabolic disturbances identified in the PE group could have lasting implications for health into adulthood. Understanding these lipid alterations may elucidate the effects of maternal preeclampsia on infant health and facilitate the design of targeted approaches.

Strengths and limitations

This study represents the first investigation into untargeted lipidomic changes in umbilical cord plasma of newborns delivered by mothers with preeclampsia compared to those from healthy mothers. However, this is a pilot study and has certain limitations. The primary limitation is the small sample size. Additionally, due to the underlying pathological mechanisms of preeclampsia, there was a lack of complete alignment in maternity-related BMI and neonatal gestational age between the two groups, which may introduce bias. Therefore, future prospective cohort studies are necessary to expand the sample size and adequately address confounding factors for instance maternal BMI and neonatal gestational age when the specimen was collected. This will facilitate a deeper insight into the effects of maternal preeclampsia on neonatal lipid metabolism.

Conclusions

Our study identified significant variations in lipid metabolism profiles between newborns of mothers with preeclampsia and those of healthy mothers. Notably, choline and glycerophospholipid metabolism emerged as the primary disrupted pathway in umbilical cord plasma lipid metabolism. Furthermore, the metabolic disturbances observed in the newborns of the preeclampsia group were found to correlate with their growth parameters at birth. This finding suggests that lipid metabolism may serve not only as a target for enhancing the intrauterine growth in neonates delivered by mothers with preeclampsia but also for reducing the risk of metabolic disorders in adulthood.

Abbreviations

PE	Preeclampsia
UPLC-MS/MS	Ultra-performance liquid chromatography-tandem mass spectrometry
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
RCF	Relative centrifugal force
PCA	Principal component analysis
OPLS-DA	Orthogonal projections to latent structures-discriminate analysis
VIP	Variable importance in the projection
MTBE	Methyltert-butylether
MeOH	Methyl alcohol
UHPLC	Ultra high performance liquid chromatography
CAN	Cerium ammonium nitrate
ESI	Electron spray ionization
SNCE	Stepped normalized collision energy
IQRs	Interquartile ranges
WGCNA	Weighted lipid co-expression network analysis
NLRP3	Nlr family pyrin domain containing 3
AcylGlcADG	Acylglucuronosyldiacylglycerol
GM3	Ganglioside
SQDG	Sulfoquinovosyl diacylglycerol
PC	Phosphatidylcholine
SHexCer	SulfurHexosylceramide hydroxyfatty acid
OxPI	Oxidized phosphatidylinositol
LPC	Lysophophatidylcholine
SHexCer	SulfurHexosylceramide hydroxyfatty acid
PE	Phosphatidylethanolamine
TAG	Triacylglycerol
SM	Sphingomyelin
PG	Phosphatidylglycerol
PI	Phosphatidylinositol
GlcADG	Glucuronosyldiacylglycerol
HexCer-AP	Hexosylceramide alpha-hydroxy fatty acid-phytospingosine

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Authors' contributions

Dr. Ding and Xiao: protocol/project design, data gathering, data evaluation, manuscript preparation. Drs. Yuan, Fu, Huang, Ma, Zhang, Liu and Wang: data gathering, data evaluation. Dr. Wu and Yuan: project design, manuscript revision. All authors collaborated on the conception and design of the study. The manuscript's first draft was prepared by Jing Ding and YiHan Xiao. All authors provided feedback on earlier versions of the manuscript. All authors reviewed and endorsed the final manuscript.

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Data availability

The study's original contributions are detailed in the article and supplementary materials; for additional inquiries, please contact the corresponding author.

Declarations

Ethics approval and consent to participate

All procedures conducted in studies involving human participants adhered to the ethical standards set forth by the institutional and/or national research committee, as well as the 1964 Helsinki Declaration and its subsequent amendments, or comparable ethical guidelines. This study received approval from the Ethics Committee (EC) of Peking University People's Hospital (2024PHB497-001). Written informed consent was obtained from all individual participants involved in the study.

Consent for publication

Written informed consent was secured from every participant included in the study.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Pediatrics, Peking University People's Hospital, Beijing 100044, People's Republic of China. [2]Department of Gynecology and Obstetrics, Peking University People's Hospital, Beijing 100044, People's Republic of China. [3]Department of Hepatobiliary and Pancreatic Surgery, the First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou 310058, Zhejiang, People's Republic of China. [4]Clinical Research Institute, Institute of Advanced Clinical Medicine, Peking University, Beijing 100191, People's Republic of China.

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