Ecotoxicology and Environmental Safety 323 (2026) 120779

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv

Maternal-fetal distribution of synthetic phenolic antioxidants and their associations with gestational diabetes mellitus: A cross-sectional analysis nested within the Chongqing PREBIC cohort

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ARTICLE INFO

Keywords:
Synthetic phenolic antioxidants
Maternal–fetal distribution
BHT-quinol
Gestational diabetes mellitus
PREBIC

ABSTRACT

Synthetic phenolic antioxidants (SPAs) and their transformation products (TPs) are widespread environmental contaminants with endocrine-disrupting potential, yet their distribution across the maternal–fetal interface and relevance to maternal metabolic health remain unclear. Leveraging 222 paired maternal and umbilical cord plasma samples (51 cases of gestational diabetes mellitus [GDM] and 171 normoglycemic controls) from the Chongqing Preconception Reproductive Health and Birth Outcome Cohort (PREBIC), we quantified eight SPAs (AO246, DTBSBP, DtAP, AO2246, 4-tOP, BHA, 2,4-DtBP, and BHT) and five BHT-derived TPs (BHT-OH, BHT-CHO, BHT-COOH, BHT-quinol, and BHT-Q) using UPLC-MS/MS and performed targeted metabolomic profiling of 446 maternal plasma metabolites. In maternal plasma, 2,4-DtBP and BHT were the predominant compounds, whereas BHT-derived TPs, particularly BHT-Q and BHT-quinol, predominated in umbilical cord plasma. The transplacental transfer efficiency of BHT-quinol was significantly lower in GDM pregnancies. Maternal plasma concentrations of BHT-quinol and total TPs were higher in women with GDM. Each one-unit increase in ln-transformed BHT-quinol and total TP concentrations was associated with higher odds of GDM (adjusted odds ratio [OR], 1.83; 95% CI: 1.34–2.59; adjusted OR, 1.49; 95% CI: 1.08–2.11, respectively). Bayesian kernel machine regression identified BHT-quinol as the dominant contributor to the observed positive mixture-GDM association. Integrative metabolomic analyses identified 88 overlapping lipid metabolites showing consistent inverse associations with both maternal BHT-quinol concentrations and GDM status, with enrichment in pathways related to AGE-RAGE signaling in diabetic complications, sphingolipid signaling, and insulin resistance. These findings characterize the maternal–fetal distribution of BHT and its TPs among pregnant women in Southwest China and identify associations of maternal BHT-derived TPs with GDM and related metabolic alterations. Prospective studies are warranted to clarify the potential causal relationships between SPA exposure and maternal metabolic health.

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https://doi.org/10.1016/j.ecoenv.2026.120779
Received 23 March 2026; Received in revised form 4 September 2026; Accepted 6 September 2026

1. Introduction

Synthetic phenolic antioxidants (SPAs) are widely used to inhibit oxidation and extend shelf life. They are added to food products, food-contact materials, cosmetics, and industrial products (Wang et al., 2021a, 2021b, 2021c; Wang and Kannan, 2019). The most commonly used SPAs include 3-tert-butyl-4-hydroxyanisole (BHA), 2,6-di-tert-butyl-4-hydroxytoluene (BHT), and *tert*-butylhydroquinone (TBHQ) (Liu and Mabury, 2020). Their extensive production and use have resulted in widespread environmental contamination, with SPAs and their transformation products (TPs) frequently detected in indoor dust (Liu et al., 2017; Wang et al., 2015), surface water (Liu et al., 2015a, 2015b), biosludge (Wang et al., 2018a, 2018b), and biota (Wang et al., 2018a, 2018b). Human exposure may occur through dietary intake, dust ingestion, and dermal contact with personal care products (Du et al., 2019, 2023; Han et al., 2024; Liu and Mabury, 2019). In recent years, biomonitoring studies have increasingly detected SPAs and their TPs in maternal and umbilical cord blood (Huang et al., 2023; Tang et al., 2022; Xu et al., 2024), placenta (Tang et al., 2022), breast milk (Zhang et al., 2020a, 2020b), urine (Wang and Kannan, 2019), ovarian follicular fluid (Hao et al., 2023), and even fingernails (Li et al., 2019), indicating widespread internal exposure to these chemicals among vulnerable populations, including pregnant women and infants.

While SPAs are used as antioxidants in consumer and industrial products, increasing evidence has raised concerns about their potential health effects (Yang et al., 2017a, 2017b). Experimental studies have reported hepatotoxicity (Zhang et al., 2020a, 2020b), genotoxicity (Vandghanooni et al., 2013), endocrine disruption (Yang et al., 2017a, 2017b), and reproductive toxicity (Jeong et al., 2005; Sun et al., 2021) for selected SPAs and their metabolites. In human studies, BHT metabolites, including 3,5-di-tert-butyl-4-hydroxybenzaldehyde (BHT-CHO) and 2,6-di-tert-butyl-1,4-benzoquinone (BHT-Q), have been associated with diminished ovarian reserve (Hao et al., 2023). BHT-Q has also been associated with an increased risk of early pregnancy loss, with mitochondrial toxicity and DNA damage proposed as potential mechanisms (Xu et al., 2024). In addition, SPAs and their TPs have been detected at relatively high concentrations in the cerebrospinal fluid of children, suggesting their potential to cross the blood-cerebrospinal fluid barrier (Du et al., 2024). Nevertheless, maternal exposure levels, maternal–fetal distribution patterns, and potential maternal health implications of SPAs and their TPs remain insufficiently characterized.

Importantly, a nested case–control study in South China reported elevated concentrations of selected SPAs among women with gestational diabetes mellitus (GDM) (Huang et al., 2023). GDM is a common pregnancy-related metabolic disorder characterized by progressive insulin resistance and impaired glucose metabolism, posing significant short- and long-term health consequences for both mothers and offspring (Wicklow and Retnakaran, 2023; Ye et al., 2022). The global prevalence of GDM has steadily increased during the past two decades (Wang et al., 2022). Beyond established risk factors, growing evidence suggests that exposure to environmental endocrine-disrupting chemicals during pregnancy may contribute to GDM-related metabolic dysregulation through perturbations in hormonal signaling and glucose homeostasis (Duan et al., 2017; Liu et al., 2021; Rahman et al., 2019). In

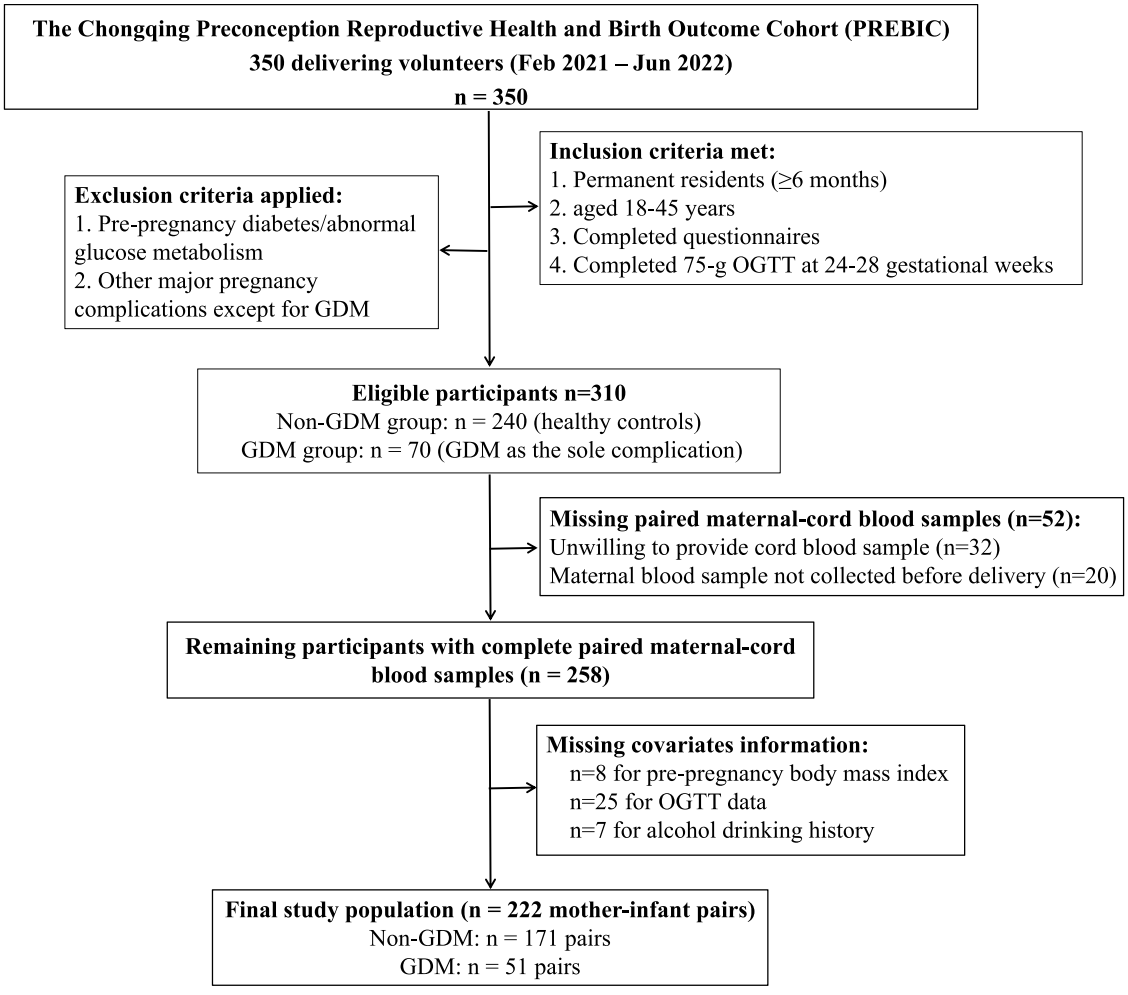

Fig. 1. Flow chart of the study design.

Southwest China, the prevalence of GDM exceeds the national average (Zeng et al., 2023), highlighting the need to investigate potentially modifiable environmental factors associated with GDM.

To address these knowledge gaps, using data from the Chongqing Preconception Reproductive Health and Birth Outcome Cohort (PREBIC), we aimed to characterize the maternal-fetal distribution of SPAs and their TPs in paired maternal and umbilical cord plasma samples and to estimate transplacental transfer efficiency at delivery. We further examined associations between maternal plasma SPA/TP concentrations and GDM status. Finally, we performed targeted metabolomic profiling to identify metabolic signatures associated separately with maternal SPA/TP concentrations and GDM status and to examine overlapping pathways to explore shared metabolic perturbations. This study may provide new insights into the maternal–fetal distribution of SPAs and their TPs during pregnancy and their potential relevance to maternal metabolic health.

2. Materials and methods

2.1. Study design and participants

This study used data from the Chongqing Preconception Reproductive Health and Birth Outcome Cohort (PREBIC), an ongoing prospective birth cohort established in October 2018 at the Chongqing Health Center for Women and Children. Details of the cohort design and recruitment procedures have been reported previously (Yang et al., 2025). Briefly, PREBIC prospectively follows couples from the preconception period through pregnancy and delivery, systematically collecting questionnaires, clinical information, and biological specimens. Offspring were subsequently followed from birth through early life. Pregnancy-related information was additionally retrieved from medical records and reviewed by trained research staff. The study protocol was approved by the Ethics Committee of the Chongqing Health Center for Women and Children (Approval No. 201802005), and written informed consent was obtained from all participants.

The present study was a cross-sectional analysis nested within PREBIC and included mother-infant pairs with paired maternal and umbilical cord plasma samples (Fig. 1). Between February 2021 and June 2022, 350 participants from the PREBIC cohort delivered at participating hospitals. Of these, 310 met the initial eligibility criteria: (a) permanent residence in Chongqing for more than 6 months; (b) age of 18–45 years; (c) completion of structured questionnaires; (d) completion of a 75-g oral glucose tolerance test (OGTT) at 24–28 gestational weeks; and (e) absence of pre-pregnancy diabetes or other pre-existing abnormal glucose metabolism and major pregnancy complications other than GDM. Participants were further excluded for unavailable paired maternal and umbilical cord blood samples, hemolyzed specimens, or insufficient plasma volume for chemical analysis ($n = 88$). The final analytical sample included 222 mother-infant pairs.

2.2. Blood collection and measurement of SPAs and transformation products

Maternal fasting venous blood samples were collected within 24 h before delivery, and corresponding umbilical cord blood samples were obtained immediately after delivery. All blood samples were collected into anticoagulant tubes, centrifuged to separate plasma, and stored at −80°C until chemical analysis.

Eight commonly used SPAs and five BHT-derived TPs were quantified in both maternal and cord plasma using ultra-high-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) with internal standard calibration. The target SPAs were 2,4,6-tri-tert-butylphenol (AO246), 2,6-di-tert-butyl-4-sec-butylphenol (DTBSBP), 2,4-di-tert-amylphenol (DtAP), 2,2′-methylenebis(6-tert-butyl-4-methylphenol) (AO2246), 4-tert-octylphenol (4-tOP), BHA, 2,4-di-tert-butylphenol (2,4-DtBP), and BHT. The BHT-derived TPs included 2,6-di-tert-butyl-4-(hydroxymethyl) phenol (BHT-OH), BHT-CHO, 3,5-di-tert-butyl-4-hydroxybenzoic acid (BHT-COOH), 6-di-tert-butyl-4-hydroxy-4-methyl-2,5-cyclohexadien-1-one (BHT-quinol), and BHT-Q. Laboratory personnel were blinded to GDM status. Detailed procedures for extraction, chromatographic separation, and mass spectrometric detection are described in **Method S1 of the** Supporting Information (Huang et al., 2023; Tang et al., 2022).

Recovery efficiencies and matrix effects were assessed using spike-recovery experiments following established quality-control protocols (Huang et al., 2023). Procedural blanks were included at a frequency of one per 10 samples. Limits of quantification (LOQs) were defined based on signal-to-noise ratios and procedural blank contamination. Detection frequency was defined as the proportion of samples with concentrations above the LOQ. Concentrations below the LOQ were imputed with $LOQ/\sqrt{2}$ for statistical analyses. CAS numbers, LOQs, and concentration ranges of the measured SPAs and TPs are presented in Tables S1 and S2.

2.3. Assessment of gestational diabetes mellitus

GDM was diagnosed using a 75-g OGTT performed at 24–28 weeks of gestation according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (Basri et al., 2018). GDM was defined as meeting or exceeding at least one of the following plasma glucose thresholds: fasting glucose $\geq$ 5.1 mmol/L, 1-hour glucose $\geq$ 10.0 mmol/L, or 2-hour glucose $\geq$ 8.5 mmol/L.

2.4. Targeted plasma metabolomics profiling

Targeted metabolomic profiling of maternal plasma was performed using a validated targeted metabolomics platform that quantified 446 metabolites (Li et al., 2024). These metabolites included 34 fatty acids, 20 amino acids, 55 acylcarnitines, 34 organic acids, and 303 lipid metabolites spanning 19 lipid classes and subclasses.

Metabolite extraction, chromatographic separation, and quantification procedures followed previously established protocols (Li et al., 2024). Detailed metabolite identification procedures are provided in **Method S2 and** Tables S3–S4 **of the** Supporting Information. Quality control measures included pooled plasma samples analyzed in each batch, and metabolites with relative standard deviations (RSDs) > 20% were excluded from subsequent analyses.

2.5. Covariates

Information on maternal sociodemographic and clinical characteristics was collected by trained nurses through face-to-face interviews before delivery. Variables included maternal age, pre-pregnancy height (cm), weight (kg), smoking status during pregnancy (never or current), and alcohol consumption during pregnancy (never or current). Pre-pregnancy body mass index (BMI; kg/m^2) was calculated from pre-pregnancy weight and height.

Information on gravidity (0, 1–2, or ≥3), parity (primiparous or multiparous), family history of chronic diseases (yes or no), history of allergy (yes or no), gestational age at OGTT, gestational age at delivery (weeks), delivery mode (vaginal delivery or caesarean section), newborn sex (male or female), and newborn birthweight (g) was retrieved from medical records. Family history of chronic diseases was defined as a reported family history of diabetes mellitus, hypertension, or hyperlipidemia.

2.6. Statistical analysis

Participant characteristics were summarized using medians and interquartile ranges (25th–75th percentiles) for continuous variables and frequencies and percentages for categorical variables. Group differences between GDM cases and non-GDM controls were evaluated using the Mann–Whitney *U* test for continuous variables and Pearson's

Table 1
Distributions of the study participant characteristics.

Characteristics	All subjects (N = 222)	Non-GDM (N = 171)	GDM (N = 51)	*P-values*
Maternal age (years)	30.0 (27.0–33.0)	29.5 (26.0–32.3)	31.5 (29.0–33.9)	< 0.001
Pre-pregnancy BMI (kg/m^2)	21.2 (19.5–23.4)	20.9 (19.5–23.0)	22.3 (20.8–24.0)	0.010
Gestational age (weeks)	39.0 (38.4–39.7)	39.0 (38.4–39.8)	39.0 (38.2–39.6)	0.538
Newborn birthweight (g)	3240.0 (3002.5–3537.5)	3240.0 (3010.0–3565.0)	3270.0 (3000.0–3445.0)	0.990
Maternal smoking status during pregnancy				
Never	219 (98.6)	168 (98.2)	51 (100.0)	1.000
Current	3 (1.4)	3 (1.8)	0 (0.0)	
Maternal alcohol consumption during pregnancy				
Never	187 (84.2)	141 (82.5)	46 (90.2)	0.266
Current	35 (15.8)	30 (17.5)	5 (9.8)	
Number of pregnancies				
0	9 (4.1)	9 (5.3)	0 (0.0)	0.487
1–2	131 (59.0)	96 (56.1)	35 (68.6)	
3 +	82 (36.9)	66 (38.6)	16 (31.4)	
Parity				
Primiparous	138 (62.2)	105 (61.4)	33 (64.7)	0.875
Multiparous	84 (37.8)	66 (38.6)	18 (35.3)	
Family history of chronic diseases				
No	143 (64.4)	112 (65.5)	31 (60.8)	0.652
Yes	79 (35.6)	59 (34.5)	20 (39.2)	
History of allergic				
No	208 (93.7)	159 (93.0)	49 (96.1)	0.531
Yes	14 (6.3)	12 (7.0)	2 (3.9)	
History of abnormal reproduction				
No	137 (61.7)	104 (60.8)	33 (64.7)	0.736
Yes	85 (38.3)	67 (39.2)	18 (35.3)	
Delivery way				
Vaginal delivery	89 (40.1)	67 (39.2)	22 (43.1)	0.731
Caesarean section	133 (59.9)	104 (60.8)	29 (56.9)	
Newborn sex				
Male	111 (50.0)	84 (49.1)	27 (52.9)	0.750
Female	111 (50.0)	87 (50.9)	24 (47.1)	

Represented as "median (25th to 75th percentile)" or n (percentage). The Mann-Whitney U-test and Chi-squared test were used to compare the demographic characteristics of the non-GDM and GDM groups. Abbreviations: GDM, gestational diabetes mellitus; BMI, body mass index.

Chi–squared test or Fisher's exact test for categorical variables, as appropriate. Concentrations of SPAs and TPs underwent natural log (ln)-transformation to address right-skewed distributions.

Maternal-fetal distribution of SPAs and TPs was characterized using detection frequencies and concentration distributions in paired maternal and cord plasma samples. Spearman rank correlation analysis was used to assess correlations among measured SPA and TP concentrations. Transplacental transfer efficiency (TTE) was calculated as the cord-to-maternal concentration ratio. Associations between paired maternal and cord plasma concentrations were further assessed using linear regression analysis.

We used logistic regression models to estimate the associations between maternal plasma concentrations of SPAs and their TPs and GDM status in the full analytical sample. Analytes with detection frequencies greater than 60% in maternal plasma were included. Each ln-transformed analyte concentration was modeled as a continuous predictor in crude and multivariable-adjusted logistic regression models. Covariates were selected a priori based on biological plausibility and previous literature (Sun et al., 2023; Yu et al., 2021), and included maternal age, pre-pregnancy BMI, parity, alcohol consumption during pregnancy, family history of chronic diseases, and gestational age at delivery. Effect estimates were expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs) per one-unit increase in ln-transformed exposure concentration. Equivalent models were constructed for maternal plasma concentrations of total TPs ($\sum$TPs; the sum of BHT-OH, BHT-CHO, BHT-COOH, and BHT-quinol) and total SPAs ($\sum$SPAs; the sum of 2,4-DtBP, BHT, and BHT-derived TPs).

To evaluate the joint effect of the chemical mixture, Bayesian kernel machine regression (BKMR) was performed in a matched subset of 44 GDM cases and 88 controls. Cases were matched to controls by maternal age (±2 years), pre-pregnancy BMI (±2 kg/m^2), and gestational age at OGTT (±1 week). BKMR models used a probit link and Gaussian kernel, with adjustment for parity, family history of chronic diseases, alcohol consumption during pregnancy, and gestational age at delivery. Posterior inference was based on 10,000 Markov Chain Monte Carlo iterations, including a 5,000-iteration burn-in period.

To identify metabolites associated separately with maternal SPA/TP concentrations and GDM status, standardized metabolite concentrations were regressed separately on each ln-transformed maternal SPA/TP concentration and on GDM status. Models included the same covariates as the logistic regression models. The Benjamini–Hochberg false discovery rate (FDR) correction was applied across the 446 metabolites, with q-values < 0.05 considered statistically significant.

For the integrative analysis, we focused on the metabolomic profile associated with the key SPA/TP analyte identified in the preceding exposure-GDM analyses. Metabolites significantly associated with both the key analyte and GDM status (FDR-adjusted q-values < 0.05) were identified as overlapping and visualized in a Venn diagram. Pathway enrichment analysis was subsequently performed for these overlapping metabolites using MetaboAnalyst 6.0 (https://www.metaboanalyst.ca) and Lipid Pathway Enrichment Analysis (LIPEA, https://hyperlipea.org/home) to characterize biological pathways represented by the shared metabolomic signature (Misra and Mohapatra, 2019; Pang et al., 2024). *P* values from the pathway enrichment analyses were adjusted using the Benjamini–Hochberg procedure, with adjusted *P* values < 0.05 considered statistically significant.

All statistical analyses were conducted using R software (version 4.2.1). Two-tailed *P* values < 0.05 were considered statistically significant, with the FDR correction applied for multiple comparisons when specified.

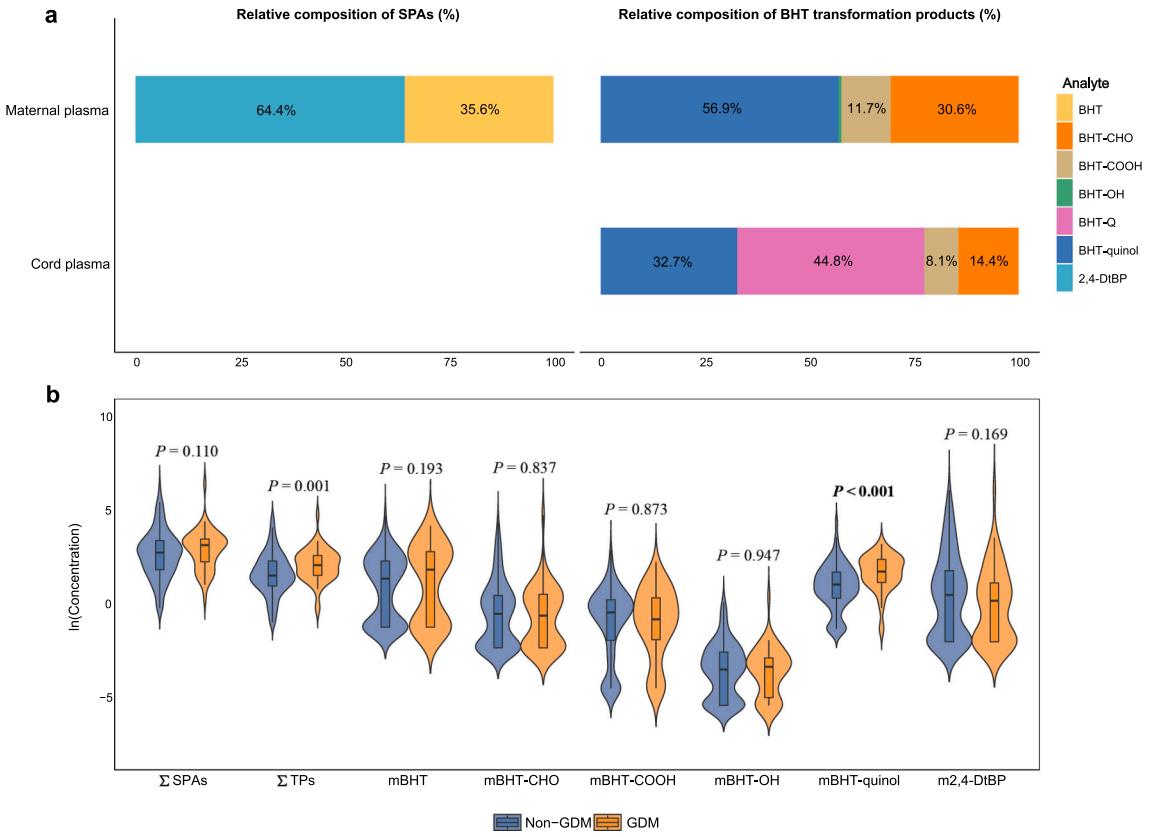

Fig. 2. Relative composition of SPAs and their TPs in maternal and cord plasma and maternal plasma concentrations according to GDM status. Relative composition of parent SPAs and BHT-derived TPs in paired maternal and cord plasma samples (n = 222 mother–infant pairs). Percentages represent the contribution of each compound to the total concentration of the corresponding compound group (SPAs or TPs) within each plasma type. (b) Violin plots showing the distributions of natural log (ln)-transformed maternal plasma concentrations of SPAs/TPs and their summed concentrations (∑SPAs and ∑TPs) in non-GDM (blue) and GDM (orange) groups. Box plots indicate the median and interquartile range. *P*-values were derived from the Mann–Whitney *U* test. Abbreviations: 2,4-DtBP, 2,4-di-tert-butylphenol; BHT, 2,6-di-tert-butyl-4-hydroxytoluene; BHT-CHO, 3,5-di-tert-butyl-4-hydroxybenzaldehyde; BHT-COOH, 3,5-di-tert-butyl-4-hydroxybenzoic acid; BHT-OH, 2,6-di-tert-butyl-4-(hydroxymethyl) phenol; BHT-quinol, 2,6-di-tert-butyl-4-hydroxy-4-methyl-2,5-cyclohexadien-1-one; BHT-Q, 2,6-di-tert-butyl-1,4-benzoquinone; GDM, gestational diabetes mellitus; SPAs, synthetic phenolic antioxidants; TPs, transformation products; ∑SPAs, summed concentrations of 2,4-DtBP, BHT, and BHT metabolites; ∑TPs, summed concentrations of four BHT metabolites, including BHT-OH, BHT-CHO, BHT-COOH, and BHT-quinol.

3. Results

3.1. Characteristics of the study population

This study included 222 mother-infant pairs, of which 51 mothers had a diagnosis of GDM and 171 served as non-GDM controls. Baseline demographic characteristics are summarized in Table 1. The median maternal age was 30.0 years, and the median pre-pregnancy BMI was 21.2 kg/m^2. Most women reported never smoking (98.6%), did not consume alcohol during pregnancy (84.2%), and 62.2% were primiparous. Compared with non-GDM controls, women with GDM were older (median: 31.5 vs. 29.5 years, $P < 0.001$) and had a higher pre-pregnancy BMI (22.3 vs. 20.9 kg/m^2, $P = 0.01$). No significant differences were observed between the two groups for the other characteristics examined (all $P > 0.05$).

3.2. Maternal–fetal distribution and transplacental transfer efficiencies of SPAs and TPs

Distinct distribution profiles of SPAs and their TPs were observed between maternal and cord plasma (Fig. 2**a**). Among the eight parent SPAs measured, 2,4-DtBP and BHT were the predominant compounds in maternal plasma, with median concentrations of 1.29 and 3.92 ng/mL, respectively, whereas parent SPAs were nearly undetectable in cord plasma. Four BHT-derived TPs were detected in maternal plasma, with BHT-quinol accounting for 56.9% of the total TP burden (median: 3.00 ng/mL), followed by BHT-CHO (30.6%) and BHT-COOH (11.7%). In contrast, BHT-Q accounted for the largest proportion of TPs in cord plasma (median: 6.03 ng/mL; 44.8% of the total TP burden), followed by BHT-quinol (32.7%). Correlations among detected SPAs/TPs were largely positive within maternal and cord plasma, while maternal-cord correlations were mostly negative (Fig. S1).

For compounds measured in paired maternal and cord plasma, the mean TTEs were 1.59 for BHT-COOH, 1.41 for BHT-quinol, and 1.09 for BHT-CHO. Maternal and cord plasma concentrations showed weak correlations, with R^2 values below 0.02 and $P > 0.05$ for all compounds (Fig. S2a**)**.

3.3. Associations of maternal plasma SPA/TP concentrations with GDM status

Maternal plasma concentrations of BHT-quinol and ∑TPs were significantly higher in GDM cases than in non-GDM controls (BHT-quinol: 5.37 vs. 2.69 ng/mL, $P < 0.001$; ∑TPs: 7.55 vs. 4.33 ng/mL, $P = 0.001$), whereas concentrations of other measured SPAs/TPs and ∑SPAs did not differ significantly between groups (Fig. 2**b,** Table S5). The TTE of BHT-quinol was also lower in GDM pregnancies ($P = 0.027$), while TTEs for BHT-COOH and BHT-CHO were comparable between groups (Fig. S2b**)**.

Moreover, higher maternal plasma concentrations of BHT-quinol and ∑TPs were significantly associated with increased odds of GDM in both crude and adjusted models (Table 2). For BHT-quinol, the crude OR for

Table 2
Associations of maternal concentrations of SPAs and their TPs with GDM status estimated using logistic regression models (n = 222).

Analyte	crude model[a] OR (95% *CI*)	P-values	adjusted model[b] OR (95% *CI*)	P-values
2,4-DtBP	0.90 (0.77–1.04)	0.176	0.89 (0.75–1.04)	0.157
BHT	1.08 (0.91–1.30)	0.366	1.09 (0.90–1.31)	0.393
BHT-OH	0.98 (0.78–1.22)	0.852	0.96 (0.75–1.22)	0.742
BHT-CHO	0.96 (0.79–1.15)	0.645	0.92 (0.75–1.13)	0.437
BHT-COOH	1.00 (0.85–1.19)	0.965	0.98 (0.82–1.17)	0.805
BHT-quinol	**1.83 (1.36–2.55)**	**< 0.001**	**1.83 (1.34–2.59)**	**< 0.001**
∑SPAs	1.02 (0.85–1.23)	0.801	1.02 (0.84–1.23)	0.868
∑TPs	**1.53 (1.14–2.10)**	**0.006**	**1.49 (1.08–2.11)**	**0.019**

Note: [a] Crude model: unadjusted. [b] Adjusted model: adjusted for maternal age, pre-pregnancy BMI, parity, alcohol consumption during pregnancy, family history of chronic diseases, and gestational age at delivery. Logistic regression was used to estimate the associations. For each analyte, natural log-transformed maternal plasma concentration was modeled as a continuous variable in separate logistic regression models. Effect estimates are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Abbreviations: SPAs, synthetic phenolic antioxidants; TPs, transformation products; GDM, gestational diabetes mellitus; 2,4-DtBP, 2,4-di-tert-butylphenol; BHT, 2,6-di-tert-butyl-4-hydroxytoluene; BHT-OH, 2,6-di-tert-butyl-4-(hydroxymethyl)phenol; BHT-CHO, 3,5-di-tert-butyl-4-hydroxybenzaldehyde; BHT-COOH, 3,5-di-tert-butyl-4-hydroxybenzoic acid; BHT-quinol, 2,6-di-tert-butyl-4-hydroxy-4-methyl-2,5-cyclohexadien-1-one; ∑SPAs represents the sum of 2,4-DtBP, BHT, and BHT metabolites; ∑TPs represents the sum of four BHT metabolites, including BHT-OH, BHT-CHO, BHT-COOH, and BHT-quinol.

GDM per one-unit increase in the ln-transformed concentration was 1.83 (95% CI: 1.36, 2.55), with a similar association after covariate adjustment [OR = 1.83 (95% CI: 1.34, 2.59), $P < 0.001$]. Higher maternal plasma concentrations of ∑TPs were also associated with higher odds of GDM [adjusted OR = 1.49 (95% CI: 1.08, 2.11), $P = 0.019$]. No significant associations were observed for 2,4-DtBP, BHT, ∑SPAs, BHT-OH, BHT-CHO, or BHT-COOH (all $P > 0.05$).

In the exploratory BKMR analysis of the matched subset (Fig. S3), the estimated overall mixture-GDM association showed an increasing pattern at mixture quantiles above the 50th percentile. Among the individual components, BHT-quinol exhibited the most pronounced positive exposure-response pattern and the largest component-specific effect estimates, whereas estimates for most other compounds were close to the null, with their 95% credible intervals including zero.

3.4. Associations of maternal SPA/TP concentrations and GDM status with maternal plasma metabolomic profiles

After covariate adjustment and FDR correction, maternal plasma concentrations of BHT, BHT-OH, BHT-quinol, 2,4-DtBP, and BHT-COOH were significantly associated with changes of 241, 183, 141, 2, and 1 metabolites, respectively, whereas no metabolite was associated with BHT-CHO (Fig. 3). Specifically, higher concentrations of BHT and BHT-OH were mainly linked to higher levels of lipid metabolites, such as phosphatidylcholines (PCs), phosphatidylethanolamines (PEs), triglycerides (TGs), sphingomyelins (SMs), phosphatidylinositols (PIs), and cholesteryl esters (CEs). Conversely, higher BHT-quinol concentrations were significantly associated with lower levels of 34 PEs, 23 TGs, 18 PCs, 16 SMs, 10 PIs, and 34 other metabolites (Table S6).

Compared with non-GDM controls, GDM cases showed an overall pattern of lower lipid metabolite levels (Fig. S4 **and** Table S7). In multivariable linear regression analyses, 100 metabolites remained significantly associated with GDM status after FDR correction, including 33 PEs, 19 PCs, 11 PIs, 10 SMs, 9 TGs, and 18 metabolites from other classes ($q < 0.05$; Table S8**)**. Of these, 98 were inversely associated with GDM status, whereas two were positively associated.

3.5. Integrated metabolite prioritization and pathway enrichment analysis

We identified 88 overlapping metabolites whose lower levels were significantly associated with higher maternal BHT-quinol concentrations and the presence of GDM **(**Fig. 4**a and** Table S9**)**. These overlapping metabolites consisted entirely of lipids, including 59 glycerophospholipids, 17 sphingolipids, 11 glycerolipids, and one cholesteryl ester.

Pathway enrichment analysis of the 88 overlapping metabolites identified several metabolic and signaling pathways that remained significant after Benjamini–Hochberg correction, including AGE-RAGE signaling in diabetic complications, sphingolipid signaling, and insulin resistance, together with glycosylphosphatidylinositol (GPI)–anchor biosynthesis and autophagy–other **(**Fig. 4**b)**.

4. Discussion

To the best of our knowledge, this is the first study to characterize the maternal-fetal distribution of SPAs and their TPs in a cohort of pregnant women from Southwest China, and to investigate their associations with GDM via integrative metabolomic profiles. We observed distinct distribution patterns between maternal and cord plasma: parent SPAs were predominantly detected in maternal plasma, whereas BHT-derived TPs were enriched in cord plasma. Maternal plasma concentrations of BHT-quinol and ∑TPs were higher in women with GDM, and both were associated with GDM status. Furthermore, integrative metabolomic analyses revealed that BHT-quinol concentrations and GDM status shared a substantial lipidomic signature, yielding 88 overlapping lipid metabolites with concordant inverse associations. These shared metabolites were enriched in pathways related to AGE–RAGE signaling in diabetic complications, sphingolipid signaling, and insulin resistance.

Consistent with previous biomonitoring studies (Du et al., 2019; Tang et al., 2022), the detection of multiple SPAs and their TPs in maternal and cord plasma in our study supports widespread prenatal exposure and extends current knowledge on their maternal-fetal distribution patterns. Notably, BHT-derived TPs (particularly BHT-quinol, BHT-CHO, and BHT-COOH) were detected substantially more frequently in cord plasma than most parent SPAs (Hao et al., 2023; Tang et al., 2022). This differential partitioning likely reflects multiple determinants. Previous studies have suggested that humans may be more frequently exposed to BHT metabolites than to the parent compound (Li et al., 2019; Liu et al., 2015a, 2015b). Additionally, metabolic conversion of BHT may alter its lipophilicity and molecular polarity, thereby facilitating placental transfer (Gao et al., 2019; Li et al., 2020). Differential protein binding between the maternal and fetal circulations may also contribute to the compound-specific distribution patterns (Baillie, 2020). Although maternal–fetal partitioning of BHT metabolites has been reported previously (Du et al., 2019; Tang et al., 2022), our findings further highlight the predominance of BHT-Q and BHT-quinol in cord plasma. In the present study, BHT-Q concentrations were below the LOQ in all maternal plasma samples but quantifiable in all cord plasma samples. Although the underlying mechanism remains unclear, previous evidence suggests that maternal–fetal concentration differences may be influenced by compound-specific placental transfer, metabolism, protein binding, and fetal clearance (Aylward et al., 2014). Given the immaturity of fetal CYP enzymes and conjugation pathways, which limit detoxification capacity (Xu et al., 2021), greater fetal exposure to these reactive TPs may warrant particular attention because of their potential to perturb fetal metabolic processes.

Maternal plasma concentrations of BHT (median: 3.92 ng/mL) and BHT-quinol (median: 3.0 ng/mL) in our cohort were substantially higher than the median concentrations reported in Maoming (BHT 0.36 ng/mL; BHT-quinol 0.42 ng/mL) and Guangzhou (BHT-quinol 0.29 ng/g ww) (Du et al., 2019; Tang et al., 2022), suggesting potential regional differences. Such differences may reflect variation in exposure sources, dietary habits, product use, or other population characteristics.

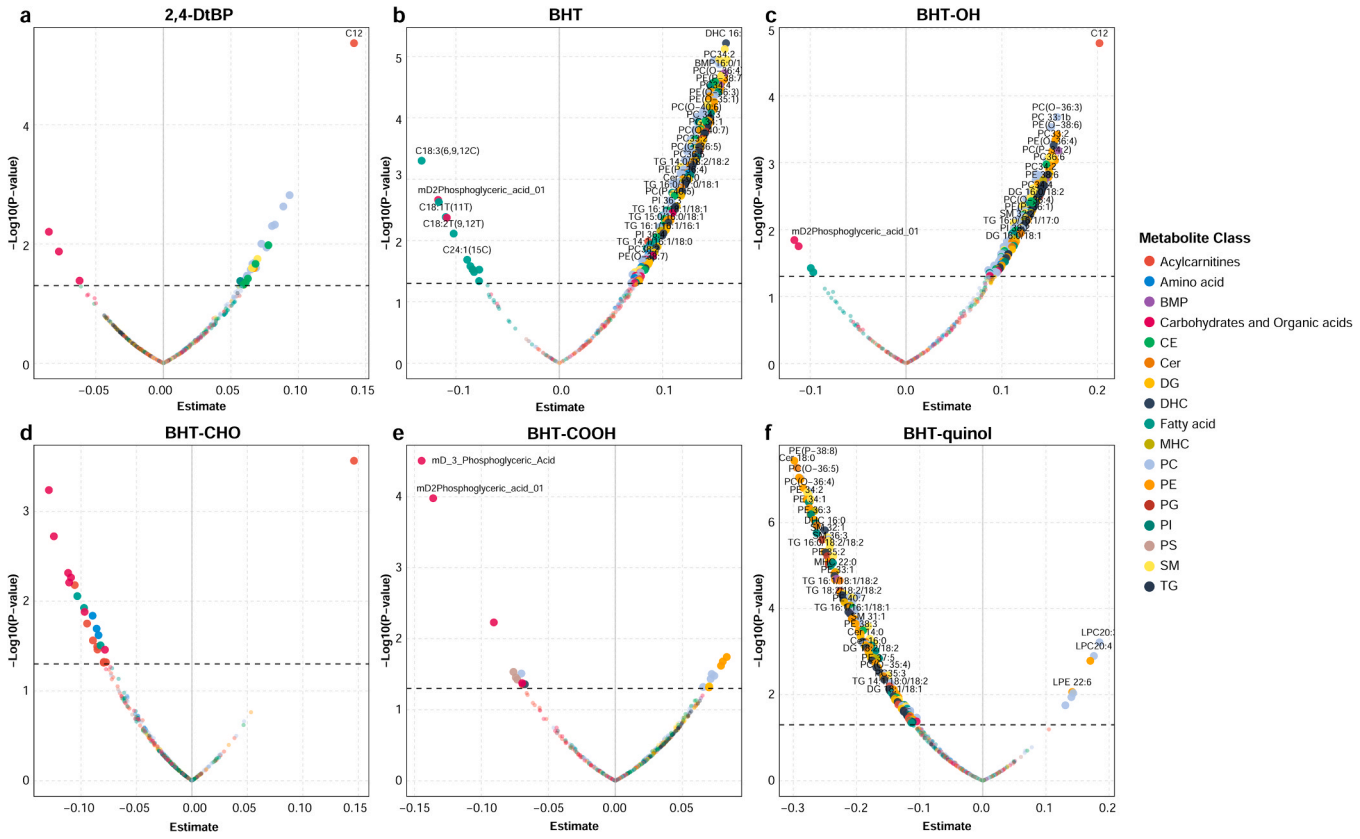

Fig. 3. Associations between maternal plasma SPA/TP concentrations and metabolomic profiles. Multivariable linear regression models were used to evaluate the associations between maternal plasma SPA/TP concentrations and 446 plasma metabolites. Metabolite concentrations were standardized, and SPA/TP concentrations were natural log-transformed. Models were adjusted for maternal age, pre-pregnancy BMI, parity, alcohol consumption during pregnancy, family history of chronic diseases, and gestational age at delivery. Panels show associations for **(a)** 2,4-DtBP, **(b)** BHT, **(c)** BHT-OH, **(d)** BHT-COOH, and **(e)** BHT-quinol. The x-axis represents the regression coefficient (β), and the y-axis shows -$\log_{10}$(*P*-value). Points are colored by metabolite class. Horizontal dashed lines indicate the $P = 0.05$ threshold. Abbreviations: 2,4-DtBP, 2,4-di-tert-butylphenol; BMI, body mass index; BHT, 2,6-di-tert-butyl-4-hydroxytoluene; BHT-CHO, 3,5-di-tert-butyl-4-hydroxybenzaldehyde; BHT-COOH, 3,5-di-tert-butyl-4-hydroxybenzoic acid; BHT-OH, 2,6-di-tert-butyl-4-(hydroxymethyl)phenol; BHT-quinol, 2,6-di-tert-butyl-4-hydroxy-4-methyl-2,5-cyclohexadien-1-one; BMP, bis(monoacylglycero) phosphate; CE, cholesteryl ester; Cer, ceramide; DG, diacylglycerol; DHC, dihydroceramide; MHC, monohexosylceramide; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PI, phosphatidylinositol; PS, phosphatidylserine; SM, sphingomyelin; SPAs, synthetic phenolic antioxidants; TG, triglyceride; TPs, transformation products.

Comparisons with early-pregnancy cohorts also revealed distinct exposure profiles. Studies in Beijing and the Tongji-Shuangliu cohort reported broader chemical spectra (including AO2246 and 4-tOP) and significantly higher parent BHT levels (Huang et al., 2023; Xu et al., 2024). For example, Xu et al. reported a median BHT concentration of 21.0 ng/mL in early pregnancy, more than five times the level observed in our pre-delivery cohort (Xu et al., 2024). These discrepancies may reflect differences in exposure patterns, physiological conditions, and metabolic processes across gestation, as well as population-specific differences in exposure characteristics.

We observed higher maternal plasma concentrations of BHT-quinol and ∑TPs among participants with GDM, and both measures were positively associated with GDM status. Experimental studies suggest that some SPAs and their TPs may affect lipid metabolism and glucose homeostasis by inducing oxidative stress and inflammatory responses, disrupting endocrine signaling, and impairing pancreatic β-cell function, processes that are closely implicated in insulin resistance and glucose dysregulation during pregnancy (De Abrew et al., 2022; Yang et al., 2018; Ye et al., 2022). In addition, BHT can be biotransformed into derivatives such as BHT-Q and BHT-quinol, some of which exhibit relatively high chemical reactivity and pro-oxidative potential (Guo et al., 2014; Hao et al., 2023; Yang et al., 2017a, 2017b). These experimental findings provide biological plausibility for the associations observed in our study. A previous prospective study reported that higher first-trimester 2,4-di-tert-butylphenol concentrations were associated with an increased risk of GDM, further supporting the potential relevance of SPA exposure to GDM development (Huang et al., 2023). Given the extensive use of SPAs in food packaging and personal care products and the consequent potential for widespread human exposure, large-scale prospective cohort studies are warranted to investigate the associations of SPAs, particularly their TPs, with maternal metabolic health and explore the underlying biological mechanisms.

Notably, the 88 overlapping lipid metabolites were inversely associated with maternal BHT-quinol concentrations and were present at lower levels in women with GDM, with glycerophospholipids and sphingolipids predominating. Previous GDM lipidomics studies have reported mixed findings. An early-pregnancy study in Chinese women similarly identified inverse associations of MHC 18:0, SM 34:1, DHC 24:0, DHC 24:1, and PC 40:7 with subsequent GDM, although several other species, including PI 40:6, PE(P-38:6), and DG 18:0/18:1, showed positive associations (Wang et al., 2021a, 2021b, 2021c). Likewise, a prospective multiracial study linked lower levels of PCs, SMs, and cholesteryl esters to higher risk of GDM, consistent with our findings, but also reported higher DGs and selected TGs, contrasting with the lower glycerolipid levels observed in our study (Rahman et al., 2021). Compared with women without GDM, women who subsequently developed GDM had higher early-pregnancy concentrations of several ceramide species (Mustaniemi et al., 2023), whereas women with GDM in our study had lower pre-delivery levels of Cer 12:0, Cer 18:0, and Cer 20:0. These differences suggest that GDM-associated lipid signatures

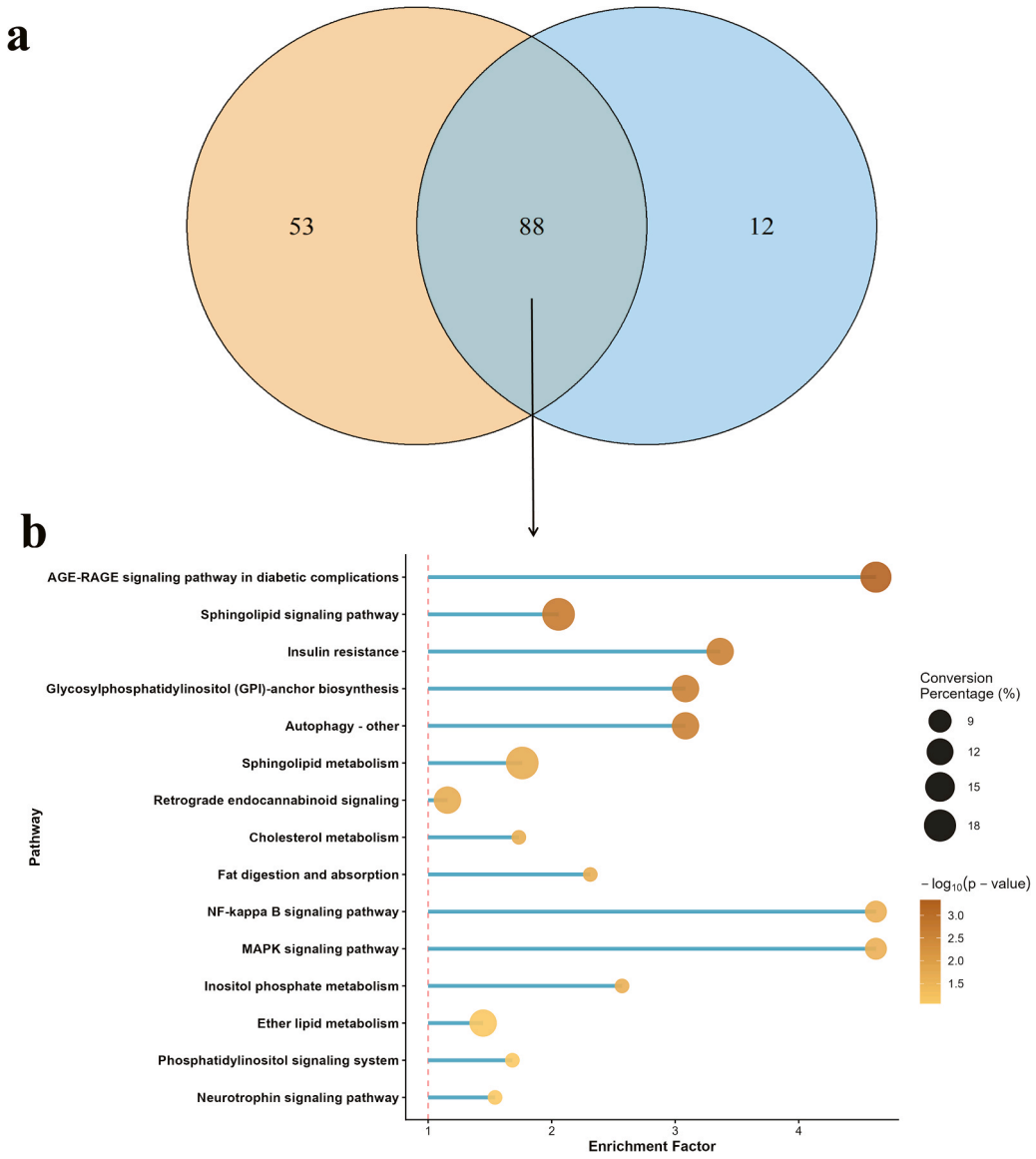

Fig. 4. Overlap and pathway enrichment of metabolites associated with maternal BHT-quinol concentrations and GDM status. (a) Venn diagram showing the overlap between two metabolite sets: metabolites significantly associated with maternal plasma BHT-quinol concentrations ($q < 0.05$, Table S6) and those significantly associated with GDM status ($q < 0.05$, Table S8). The overlapping region represents metabolites jointly associated with both exposures ($n = 88$). **(b)** Pathway enrichment analysis of the 88 overlapping lipid metabolites using Lipid Pathway Enrichment Analysis (LIPEA). The lollipop plot displays the top 15 enriched pathways ranked by *P* value. The vertical dashed line at enrichment factor = 1 indicates no enrichment relative to background. Abbreviations: AGE-RAGE, advanced glycation end products-receptor for advanced glycation end products; FDR, false discovery rate; GDM, gestational diabetes mellitus; GPI, glycosylphosphatidylinositol; LIPEA, Lipid Pathway Enrichment Analysis; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B.

may vary across individual molecular species, study populations, and gestational stages.

The pathway enrichment results reinforce a potential link between the shared lipidomic alterations and metabolic processes relevant to GDM, particularly disturbances in insulin signaling, sphingolipid homeostasis, and oxidative and inflammatory stress. These findings are consistent with previous omics evidence indicating that lipid remodeling, particularly involving phospholipids and sphingolipids, is an important metabolic feature of GDM and gestational insulin resistance (Alesi et al., 2021; Wang et al., 2021a, 2021b, 2021c). In addition, sphingolipid signaling is critically involved in insulin action, and the AGE-RAGE signaling pathway has been linked to oxidative stress, inflammation, and metabolic dysfunction in diabetes (Rameh and Deeney, 2016; Saucedo et al., 2023). These pathways are interconnected, with extensive cross-talk between oxidative stress, inflammation, AGE-RAGE signaling, and lipid signaling networks (Chiefari et al., 2017; Johns et al., 2018). Collectively, these processes may provide a biologically plausible context for the overlapping lipidomic patterns observed in the present study. Nevertheless, these shared pathway enrichments should not be interpreted as evidence of a direct causal relationship between maternal BHT-quinol exposure and GDM.

However, several limitations should be acknowledged. First, because maternal SPAs/TPs and metabolomic profiles were measured using pre-delivery blood samples collected after the routine diagnosis of GDM in the second trimester, the temporal sequence required for causal inference could not be established. Although maternal blood samples were collected under fasting conditions, SPA/TP concentrations measured shortly before delivery may reflect recent dietary exposure, peripartum physiological changes, or delivery-related fluctuations rather than long-term prenatal exposure. Similarly, metabolomic profiles measured near delivery may partly reflect physiological and endocrine adaptations during late pregnancy. Without repeated measurements across

gestation, we could not distinguish whether the observed metabolic differences preceded GDM or emerged after its development. Second, information on several potentially relevant factors, including diet, physical activity, socioeconomic characteristics, gestational weight gain, late-pregnancy clinical factors, and co-exposure to other environmental chemicals, was unavailable, and residual confounding cannot be completely excluded. Finally, the relatively small analytical sample size, together with the high dimensionality of the mixture and metabolomic analyses, may have limited statistical power and the precision of some estimates. Therefore, our findings should be interpreted as exploratory and require validation in larger prospective cohorts with repeated biospecimen collection before and after GDM diagnosis.

5. Conclusions

In summary, this study characterized the maternal–fetal distribution of SPAs and BHT-derived TPs at delivery among pregnant women in Southwest China and found that higher maternal plasma concentrations of BHT-quinol were associated with increased odds of GDM. Integrative metabolomic analyses further identified shared lipidomic signatures associated with both maternal BHT-quinol concentrations and GDM status. These findings highlight the importance of including transformation products in maternal–fetal biomonitoring and provide an exploratory foundation for future longitudinal studies examining the associations of BHT/TPs with maternal metabolic health.

CRediT authorship contribution statement

Da Chen: Data curation. **Liwen Zhang:** Investigation. **Xue Li:** Investigation. **Yangyang Pi:** Data curation. **Huan Yang:** Data curation, Conceptualization. **Xi Ling:** Data curation, Conceptualization. **Niya Zhou:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Jing Li:** Supervision, Investigation, Data curation, Conceptualization. **Shengzhi Sun:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis. **Yutao Li:** Writing – original draft, Methodology, Investigation, Formal analysis. **Qing Chen:** Writing – review & editing, Supervision, Project administration, Investigation, Data curation. **Furong Wang:** Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Jia Cao:** Supervision, Funding acquisition. **Gongli Chen:** Data curation.

Declaration of Competing Interest

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

Acknowledgment

This study was supported by the Key Program of the National Natural Science Foundation of China (grant number 82130097), the National Natural Science Foundation of China (grant numbers 82373535 and 42577490), Chongqing Science and Health Joint Medical Research Project (2026KFXM005), and Guizhou Province Graduate Education Innovation Program (2025YJSKYJJ255). We thank all participants who provided data or biological samples for PREBIC, and all staff in or ever in our team for assistance with data collection, sampling, participant communications, and coordination.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2026.120779.

Data availability

Data will be made available on request.

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