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Association of maternal prenatal phthalate exposure and genetic polymorphisms of metabolic enzyme genes with spontaneous preterm birth: a nested case–control study in China

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Abstract

Background The relationship between prenatal phthalate exposure and preterm birth from previous studies has been inconsistent. Meanwhile, few studies have explored the relationship between spontaneous preterm birth (SPTB) and genetic polymorphisms of metabolic enzyme genes or gene-phthalate interactions. The aim of this study is to evaluate the association of maternal phthalate exposure, genetic polymorphisms, and their interactions with SPTB.

Methods A total of 182 cases with SPTB and 321 controls with full-term delivery were enrolled. Nine phthalate metabolites in maternal second trimester urine samples were measured by ultra-high performance liquid chromatography coupled with tandem mass spectrometry. Genotyping was performed on twenty-six single nucleotide polymorphisms (SNPs) of metabolic enzyme genes, including *CYP2C9*, *CYP2C19*, *UGT1A7*, *UGT2B7* and *UGT2B15* genes. The associations between maternal phthalate exposure or genetic polymorphisms and SPTB were estimated by multivariable logistic regression analysis. The impact of interactions between gene-gene and gene-phthalate exposure on SPTB were analyzed via generalized multifactor dimensionality reduction.

Results There were no significant differences in the concentrations of phthalate metabolites between the two groups. No statistically significant associations were observed between maternal phthalate exposure and SPTB. The rs4244285 polymorphism of *CYP2C19* gene was associated with decreased odds of SPTB under the log-additive (aOR = 0.73, 95% CI: 0.55–0.98) and recessive model (aOR = 0.37, 95% CI: 0.18–0.74). Two SNP loci of *UGT2B15* were associated with increased odds of SPTB under the recessive genetic model (aOR = 3.85, 95% CI: 1.31–11.35 for rs3100, and aOR = 3.85, 95% CI: 1.31–11.35 for rs4148269). However, these associations were not significant after the

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false discovery rate correction. No significant gene-gene or gene-phthalate metabolites interactions for SPTB were observed.

Conclusions Maternal phthalate exposure in the present subjects and genetic polymorphisms of metabolic enzyme genes were not associated with SPTB. Moreover, there were no significant gene-gene or gene-phthalates interactions for SPTB.

Keywords Spontaneous preterm birth, Phthalates, Metabolic enzyme gene, Genetic polymorphism, Interaction

Introduction

Preterm birth (PTB), typically defined as a delivery or birth at a gestational age less than 37 weeks, is a common adverse pregnancy outcome. New global estimates show that in 2020, approximately 9.9% of all live births worldwide were preterm birth, equivalent to 13.4 million newborn babies [1]. In China, the overall preterm birth rate has maintained an increasing trend, reaching 6.4% in 2018 compared to 5.9% in 2012 [2], and has ranked the fourth among all countries [1]. In general, approximately 70% ∼ 80% of PTBs are spontaneous preterm birth (SPTB), including spontaneous preterm labor with intact membranes and preterm prelabor rupture of membranes (PPROM) [3]. PTB complications are the leading cause of neonatal mortality and deaths in children under 5 years of age, accounting for 35% and 18% of all deaths, respectively [4, 5]. Furthermore, the treatment of premature infants not only leads to long-term economic cost of the healthcare system, but also brings a heavy psychological and economic burden to the families of premature infants [5]. Therefore, PTB has become a long-standing global public health issue, and effective preventive measures are urgently needed.

PTB is a complex outcome of pregnancy. Many maternal and fetal characteristics contribute to the pathophysiology of PTB, including some chronic conditions, pregnancy with twins, triplets or other multiples, stressful life events, polyhydramnios, certain infections, shortened cervix, problems with the uterus or placenta [6, 7]. Besides, environmental factors, such as metals and metalloids, organic pollutants, air pollutants, extreme temperatures, also can raise the risk of PTB [8–10]. In addition, genetics may also play a role in PTB. Pregnant women who are born prematurely or have siblings born preterm have an increased risk of preterm delivery in their own pregnancies [11]. Additionally, large-scale genome-wide association studies have already identified genomic loci associated with the risk of PTB [12, 13]. However, the exact cause of PTB is not yet fully understood.

Phthalates are a class of manufactured chemicals used to improve the flexibility and durability of plastics. Low-molecular-weight phthalates, such asdi-iso-butyl phthalate (DiBP), di-n-butyl phthalate (DBP), are mainly used in personal-care products (perfumes, lotions, cosmetics), sealants, solvents, lacquers, varnishes and coatings, whereas high-molecular-weight phthalates, such as di-(2-ethylhexyl)-phthalate (DEHP), butyl-benzyl-phthalate (BBP), are primarily used in construction and buildings, flooring, wall coverings, food packaging, and medical devices [14, 15].

As phthalates are not covalently bound to their plastics counterparts, they have a propensity to be easily released into environment, resulting in inevitable exposure of the general population through dietary/oral/ ingestion, dermal absorption, and inhalation [16, 17]. In China, the concentration of phthalates in indoor dust and personal care products (PCPs) is moderate, while the concentration in foods and air is the highest worldwide [18]. Phthalate metabolites (mPAEs), serving as the biomarkers to assess the short-term exposure burden to phthalates, have been consistently detected in urine from the general population including pregnant women worldwide [15, 19].

Phthalates can easily cross the placental barrier and may have a negative impact on the health of the fetus [14]. Over the past decades, numerous studies have demonstrated associations between prenatal phthalate exposure and multiple adverse pregnancy outcomes, including spontaneous pregnancy loss [20, 21], low birth weight [22], smaller head circumference [23], shorter birth length [24], fetal retarded growth [25], and congenital heart disease [26]. To date, findings from population epidemiological studies of phthalates and PTB or gestational age at delivery have not yet completely consistent. Some studies have reported that prenatal exposure to several types of phthalates is associated with an increased risk of PTB or shortened gestational age [27–38]. However, no significant associations between prenatal phthalate exposure and PTB have been observed by others [24, 39–41]. Besides, a few studies have found that increased maternal exposure to phthalates is associated with a decreased risk of PTB [42, 43]. In addition, most of previous studies have focused on overall PTB, and rarely classified PTB and analyzed SPTB separately [30, 32, 34, 36].

In humans, phthalates are rapidly metabolized to their respective primary monoesters followed by oxidation of the monoester side chain by the cytochrome P450 enzymes (CYPs) resulting into secondary metabolites–mainly with hydroxy, oxo, and carboxy functional groups. Then, most metabolites further undergo conjugation,

which is catalyzed mainly by uridine diphosphate (UDP)-glucuronyl transferases (UGTs), forming hydrophilic conjugates that are easily excreted [44]. Nucleotide polymorphisms (SNPs) in *CYP2C9*, *CYP2C19*, *UGT1A7*, *UGT2B7* and *UGT2B15* may lead to differences in metabolic enzyme activity and further affect the adverse effects of phthalate exposure. For instance, rs7439366 of *UGT2B7* and rs1902023 of *UGT2B15* have been reported to be associated with the concentrations of bisphenol A (BPA) and phthalates in patients with polycystic ovary syndrome (PCOS) [45]. In addition, the SNPs of CYPs, such as rs1799853 and rs1057910 of *CYP2C9* can reduce DEHP biotransformation, and rs1799853 and rs1057910 of *CYP2C9*, rs12248560 of *CYP2C19*, and rs11692021 of *UGT1A7* might represent biomarkers of susceptibility or resilience to phthalate exposure [46]. Our previous study found that SNP locus rs4124874 of *UGT1A7* was associated with an increased risk of congenital heart disease [47]. However, few studies have investigated the impact of maternal genetic susceptibility on the association of PTB with phthalates. In addition, there are few studies exploring possible gene-environment interactions. Therefore, it is necessary to conduct research on genetic susceptibility and the impact of interaction between phthalate exposure and genetic polymorphisms of metabolic enzyme genes on PTB. This will provide new evidence for the cause and prevention of PTB.

In this study, we first investigated the association between maternal exposure to phthalates and SPTB by measuring the levels of phthalate metabolites in the urine of pregnant women during the second trimester. Then, we evaluated the association between maternal genetic polymorphisms and SPTB. Finally, we explored the impact of potential interaction between maternal genetic variants and phthalate exposure on SPTB.

Materials and methods

Study population, epidemiological data and samples collection

This nested case-control study was a part of the maternal drug exposure birth cohort that recruited pregnant women between August 2018 and December 2021 [48].

Pregnant women in this study were recruited from Fujian Provincial Maternal and Child Healthcare Hospital, and Maternal and Child Healthcare Hospital of Guangxi, Zhuang Autonomous Region. The recruitment criteria included: (1) attending their first antenatal appointment between 6 and 14 gestational weeks; (2) planning to establish their health record and deliver in the same hospitals. The exclusion criteria were as follows: (1) having mental health diseases and could not cooperate with questionnaire investigation; (2) having multiple pregnancies, including twins and triplets.

Each participant was asked to complete the self-administered questionnaire under the guidance of the investigators in the first, the second, and the third trimester, respectively. In order to avoid sample contamination, we followed the standard operating procedures (SOP) and carried out strict quality control [48]. Twenty milliliters (mL) maternal first morning urine specimens were collected using polypropylene urine cups in the first and the second trimester, and promptly stored at– 80℃until analysis. Moreover, to correct for potential background interference, ultra-pure water was collected as an experimental blank for quality control. Four mL of EDTA-anticoagulated maternal blood samples were collected in the first and the second trimester, respectively. After standing of blood samples for 30 min, blood cells were obtained by centrifuging and stored at– 80 °C until genotyping.

Gestational weeks were calculated according to each woman's last menstrual period (LMP) or determined by ultrasound if menstruation was irregular. SPTB was defined as delivery before 37 gestational weeks without iatrogenic causes, including spontaneous preterm labor with intact membranes and preterm premature rupture of membranes (PPROM) referring the previous study [6]. Two hundred and twelve SPTB cases were identified. Among them, 30 SPTB cases without maternal urine or blood samples of second trimester were excluded. Three hundred and twenty-one women with full-term delivery (≥ 37 weeks) and having both maternal blood and urine specimens of second trimester were randomly selected as the control group. Ultimately, a total of 182 cases with SPTB and 321 controls with a full-term delivery were included in our nested case–control study.

Phthalate metabolites measurements

Among SPTB cases, the number of pregnant women with second trimester urine samples accounted for the largest proportion. Moreover, considering that the second trimester is closer to the time that preterm birth occurs, the urine samples in the second trimester were analyzed by ultra-high performance liquid chromatography coupled with tandem mass spectrometry (UHPLC-MS/ MS) at the West China School of Public Health, Sichuan University. The analysis was performed using an ultra-high performance liquid chromatography ACQUITY UPLC I-Class coupled to an Xevo TQ-XS triple stage quadrupole mass spectrometer (Waters, USA). The experimental procedures have been described in detail in our previous study [47].

By referring to the previous relevant studies on phthalate exposure and adverse pregnancy outcomes [28, 31], and combining with the existing technologies of the testing laboratory [49], nine phthalate metabolites from five parent compounds were quantified, including mono-n-butyl phthalate (MnBP, metabolite of di-n-butyl phthalate

(DnBP)); mono-isobutyl phthalate (MiBP, metabolite of diisobutyl phthalate (DiBP)); mono-benzyl phthalate (MBzP, metabolite of butylbenzyl phthalate (BBzP)); monoethyl phthalate (MEP, metabolite of diethyl phthalate (DEP)); and five metabolites of di-(2-ethylhexyl) phthalate (DEHP): mono-(2-ethyl-hexyl) phthalate (MEHP), (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECCP), and mono-2-carboxymethyl hexyl phthalate (MCMHP).

Due to the dilution of urine, creatinine-adjusted concentrations of urinary phthalate metabolites were calculated. The concentrations of urinary creatinine is shown in Table S1. The concentrations below the limit of detection (LOD) were replaced by LOD/ $\sqrt{2}$ [50].

DNA extraction and genotyping

Maternal genomic DNA was extracted from peripheral blood leukocytes with magnetic bead method (BioTeke, Wuxi, China) according to the recommended protocol.

SNPs in the *CYP2C19*, *CYP2C9*, *UGT1A7*, *UGT2B7* and *UGT2B15* genes were selected based on the following principal criteria: (1) an association with diseases in previous studies or the metabolic levels of phthalates, and (2) a minor allele frequency > 0.05 in Han Chinese. In total, twenty-six SNPs were selected. These SNP loci were genotyped via multiple-polymerase chain reaction amplification (iGeneTech Bioscience Co., Ltd, Beijing, China). More detailed information about the studied genetic variants and genotyping is presented in Supplementary Appendix, Table S2.

For quality-control assessment, 10% of the samples were randomly selected for repeated genotyping, and the consistency was 100%.

Statistical analyses

The comparison of baseline characteristics between case and control groups was conducted by χ^2 test. These characteristics included maternal age at the time of the last menstrual period (years), maternal ethnicity (Han, others), maternal education level (primary or lower, junior high, high school, college or higher), parental smoking or environmental tobacco smoke (ETS) exposure (whether either/both of the parents smoked or was exposed to environmental tobacco smoke during the time from 3 months before pregnancy to the first trimester, yes or no), maternal alcohol consumption (whether drunk during the time from 3 months before pregnancy to the first trimester, yes or no), maternal gravidity (none, once or more), maternal pre-pregnancy body mass index (ppBMI, kg/m^2), maternal medication use (whether took the medication after pregnancy, yes or no), maternal folic acid supplement (whether supplemented with folic acid after pregnancy, yes or no), infant gender (male or female).

Creatinine-adjusted phthalate metabolites urine concentrations were described as median (25%, 75%) and compared with Mann–Whitney U test due to skewed distributions. Odds ratios (OR) and 95% Confidence Intervals (CI) were calculated by multivariable logistic regression analysis to evaluate the association between the levels of phthalate metabolites and SPTB. Phthalate metabolites levels were analyzed as continuous values or categorical variables which were classified as the first tertile, the second tertile, and the third tertile. The covariates, including maternal age, ethnicity, education level, parental smoking or ETS exposure, alcohol consumption, gravidity, ppBMI, medication use, folic acid supplement, infant gender, which are associated with PTB and frequently included for adjustment based on evidence from previous studies, were included in the adjusted models regardless of statistical significance. All the above analyses were conducted using SPSS version 16.0 software (SPSS Inc., IBM, Chicago, USA).

Restricted cubic spline models were developed to examine the dose-effect relationship between the phthalate metabolites levels and SPTB. The adjustment variables of the spline curve model were consistent with those of the fully adjusted model in logistic regression. The Wald chi-square test was performed to examine the overall and nonlinear relationship between phthalate metabolites levels and SPTB. Analyses were done using R version 4.4.2 (R Development Core Team) for the figures.

Hardy–Weinberg equilibrium was assessed in the controls using Plink software (http://zzz.bwh.harvard.edu/plink/ld.shtml). Unconditional logistic regression analysis was performed to investigate the association between individual genetic polymorphism and SPTB using Plink software.

Generalized multifactor dimensionality reduction (GMDR, version 0.7, University of Virginia, Charlottesville, VA) was used to analyze the impact of high-dimensional interaction among *CYP2C19*, *CYP2C9*, *UGT1A7*, *UGT2B7*, *UGT2B15* genes and phthalate metabolites on SPTB [51].

All analyses were adjusted for covariates. False discovery rate (FDR) correction of multiple-hypothesis testing was performed. Two-sided $P < 0.05$ was considered statistically significant.

Results

Descriptive characteristics of the study population

The baseline characteristics of all 503 study subjects are presented in Table 1. There were significant differences in maternal age, parental smoking or environmental tobacco smoke (ETS) exposure, and maternal alcohol consumption between the two groups. The other variables, including maternal ethnicity, maternal education level, maternal gravidity, maternal ppBMI,

Table 1 Descriptive characteristics of the participants

Variable/Characteristic	Controls ($n=321$)	SPTB Cases ($n=182$)	F/χ^2	*P*-value
	No. (%)	No. (%)		
Maternal age (years) [a]			0.02	0.048
	30.20 ± 4.43	31.02 ± 4.41		
Pre-pregnancy BMI (kg/m^2) [a]			3.71	0.138
	20.73 ± 2.83	21.14 ± 3.20		
Maternal ethnicity[b]			2.17	0.338
Han	212 (66.04)	125 (68.68)		
Others	109 (33.96)	57 (31.32)		
Maternal education level [b]			8.13	0.087
Primary or lower	2 (0.62)	1 (0.55)		
Junior high	21 (6.54)	10 (5.49)		
High school	54 (16.82)	27 (14.84)		
College or higher	244 (76.02)	144 (79.12)		
Parental smoking or ETS exposure [b]			20.03	< 0·001
Yes	102 (31.78)	25 (13.74)		
No	219 (68.22)	157 (86.26)		
Maternal alcohol consumption [b]			6.98	0.008
Yes	84 (26.17)	29 (15.93)		
No	237 (73.83)	153 (84.07)		
Maternal gravidity [b]			0.98	0.322
None	183 (57.01)	112 (61.54)		
Once or more	138 (42.99)	70 (38.46)		
Maternal medication use [b]			1.73	0.189
Yes	93 (28.97)	63 (34.62)		
No	228 (71.03)	119 (65.38)		
Folic acid supplements [b]			0.59	0.442
Yes	237 (73.83)	140 (76.92)		
No	84 (26.17)	42 (23.08)		
Infant gender [b]			3.21	0.073
Male	155 (48.29)	103 (56.59)		
Female	166 (51.71)	79 (43.41)		

[a]Using the two independent samples Student's t-test

[b]Using the Chi-square test

maternal medication use, maternal folic acid supplement, and infant gender, did not show statistical differences between the two groups.

Levels of phthalate metabolites in maternal urine

The LODs, detection rates, and distributions of phthalate metabolites are summarized in Table 2. The LOD for MEP, MiBP, MnBP, MBzP, MEHP, MEHHP, MEOHP, MECPP and MCMHP was 0.50 ng/mL, 0.50 ng/mL, 0.50 ng/mL, 0.05 ng/mL, 0.50 ng/mL, 0.05 ng/mL, 0.05 ng/mL, 0.10 ng/mL, and 0.20 ng/mL, respectively. Overall, the detection rates were nearly 100% for most phthalate metabolites, except for MBzP, of which the detection rate was only 63.62%, and was excluded in the subsequent analysis.

The median concentrations of MiBP, MBzP, and MECPP were higher in SPTB compared to controls (13.2 vs. 13.05, 2.94 vs. 2.81, 3.57 vs. 3.45 μg/g creatinine, respectively), whereas the median concentrations of MEP, MnBP, MEHP, MEHHP, MEOHP, and MCMHP were lower in SPTB than in controls (8.96 vs. 11.7, 95.97 vs. 103.46, 3.79 vs. 4.34, 1.72 vs. 1.91, 8.17 vs. 9.01, 8.96 vs. 11.7 μg/g creatinine, respectively). However, no significant differences between the two groups were observed for these phthalate metabolites ($P_{all} > 0.05$).

Association between maternal phthalate exposure and SPTB

Adjusted dose–response relationships between phthalate metabolites levels and SPTB by restricted cubic spline model is shown in Figure S1. Among the eight metabolites (MEP, MiBP, MnBP, MEHP, MEHHP, MEOHP, MECPP, MCMHP), only MEHP categorical levels exhibited an inverted U-shaped association with SPTB (*P* for overall = 0.028, *P* for nonlinearity = 0.011). However, no relationship between continuous phthalate metabolites concentrations and SPTB was observed. Moreover, compared with the first-tertile concentration of each

Table 2 Urinary concentrations of phthalate metabolites in maternal urinary samples

Diether phthalate	Phthalate metabolites (μg/g creatinine)	LOD (ng/mL)	Concentration ≥ LOD, No. (%)	Median (25%, 75%)			*P*-Value[a]
				Total participants (*n* = 503)	Controls (*n* = 321)	SPTB Cases (*n* = 182)	
DEP	MEP	0.50	502(99.8%)	10.61(5.18,26.54)	11.7(5.06,28.58)	8.96(5.28,22.92)	0.164
DiBP	MiBP	0.50	502(99.8%)	13.13(7.67,20.18)	13.05(7.73,20.71)	13.2(7.56,18.62)	0.430
DnBP	MnBP	0.50	503(100%)	100.44(45.99,189.69)	103.46(50.58,187.97)	95.97(35.82,190.75)	0.203
BBzP	MBzP	0.05	320(63.62%)	2.88(1.57,5.72)	2.81(1.49,6.03)	2.94(1.72,5.38)	0.858
DEHP	MEHP	0.50	476(94.63%)	4.04(2.69,6.92)	4.34(2.76,7.01)	3.79(2.59,6.29)	0.330
	MEHHP	0.05	503(100%)	1.79(1.15,2.86)	1.91(1.22,3.16)	1.72(1.1,2.72)	0.189
	MEOHP	0.05	503(100%)	8.72(5.58,14.04)	9.01(5.68,14.38)	8.17(5.41,13.28)	0.540
	MECPP	0.10	503(100%)	3.48(2.4,5.37)	3.45(2.29,5.53)	3.57(2.49,5.15)	0.393
	MCMHP	0.20	499(99.2%)	10.61(5.18,26.54)	11.7(5.06,28.58)	8.96(5.28,22.92)	0.164

[a] *P* values for the Mann–Whitney U test between case and control group

phthalate metabolite, the second- and third-tertile concentrations were not associated with SPTB, as shown in Table 3 which presents the results on the association between maternal phthalates exposure and SPTB.

Association between maternal genetic polymorphisms and SPTB

The genotype distributions for polymorphisms of *CYP2C19*, *CYP2C9*, *UGT1A7*, *UGT2B7*, and *UGT2B15* are shown in Table S3. Except for three loci rs6742078, rs7439366, and rs6837575, the distributions of the remaining SNPs in the control group were consistent with Hardy-Weinberg equilibrium, and therefore were included in the subsequent analysis.

The association between single gene loci polymorphism and SPTB under different genetic models is presented in Table 4. In the *CYP2C19* gene, the SNP rs4244285 was associated with decreased odds of SPTB (under the log-additive model: aOR = 0.73, 95% CI: 0.55–0.98; under the recessive model: aOR = 0.37, 95% CI: 0.18–0.74). Under the recessive genetic model, two SNPs loci of *UGT2B15* were associated with increased odds of SPTB (aOR = 3.85, 95% CI: 1.31–11.35 for rs3100, and aOR = 3.85, 95% CI: 1.31–11.35 for rs4148269). However, the above associations were not statistically significant after the false discovery rate (FDR) correction. No significant association was found between any of the remaining nineteen selected loci and SPTB.

GMDR analyses for gene–gene and gene–environment interactions for SPTB

The gene-gene and gene-environment interaction model by GMDR is presented in Table 5. The *P* value was determined using the permutation test with 1000 replications. For gene-gene interaction, three-locus to seven-locus interaction models were observed, yet no any statistical significance was detected. In addition, for gene-phthalate metabolites interaction, three interaction combinations were observed, but there were no statistical differences.

Discussion

In this nested case-control study, no statistically significant associations were observed between the concentrations of maternal phthalate metabolites in the second trimester and SPTB. Furthermore, there was no statistically significant associations between three SNPs, including rs4244285 of *CYP2C19* gene, rs3100 and rs4148269 of *UGT2B15*, and SPTB after FDR correction. Moreover, no significant effect of gene-gene or gene-phthalate metabolites interactions on SPTB was found.

We did not find any significant association of the eight phthalate metabolites (MnBP, MiBP, MEP, MEHP, MEHHP, MEOHP, MECCP, and MCMHP) with SPTB, which was similar to the results of four previous studies [24, 39–41]. A prospective cohort study in Anhui, China, observed no link between prenatal phthalate exposure and preterm birth or gestational age [24]. A study in Taiwan found no correlation between amniotic fluid phthalate levels and gestational age [39]. Moreover, a study in Japan also observed no association between maternal urinary phthalates and preterm birth [40]. In addition, a study in Netherlands reported no significant association between maternal occupational exposure to phthalates and PTB using job-exposure matrix-based assessments [41]. However, our results were inconsistent with multiple previous studies indicated that prenatal phthalate exposure increased the odds of SPTB or overall preterm birth [27–38]. Regarding SPTB, a nested case-control study in USA observed that MEHP, MEOHP, MECPP, ΣDEHP, MBzP, MBP, and mono-(3-carboxypropyl) phthalate (MCPP) metabolite levels were all associated with significantly elevated odds of SPTB [34]. Later, a cohort in Puerto Rico observed that DiBP metabolites were associated with increased odds of SPTB (OR = 1.46, 95% CI: 1.07–1.99) [30]. Moreover, a prospective birth cohort in the Infant Development and the Environment Study (TIDES) population from the same group found that MBP levels in the first trimester were associated with increased odds of SPTB (OR = 1.45 [95% CI:

Table 3 Logistic regression analyses of the association between phthalate metabolites and SPTB

Phthalate metabolites	Concentration levels	Controls	SPTB Cases	cOR (95% CI)	aOR (95% CI)[a]
		No.(%)	No.(%)		
MEP	Per unit	-	-	1.00 (1.00–1.00)	1.00 (1.00–1.00)
	First-tertile	105(32.71)	62(34.07)	Reference	Reference
	Second-tertile	99(30.84)	69(37.91)	1.18(0.76–1.83)	1.19(0.75–1.89)
	Third-tertile	117(36.45)	51(28.02)	0.74(0.47–1.16)	0.73(0.45–1.18)
MiBP	Per unit	-	-	0.99 (0.98-1.00)	0.99 (0.98-1.00)
	First-tertile	106(33.02)	61(33.52)	Reference	Reference
	Second-tertile	104(32.4)	64(35.16)	1.07(0.69–1.67)	1.08(0.67–1.74)
	Third-tertile	111(34.58)	57(31.32)	0.89(0.57–1.40)	1.01(0.63–1.64)
MnBP	Per unit	-	-	1.00 (1.00–1.00)	1.00 (1.00–1.00)
	First-tertile	99(30.84)	68(37.36)	Reference	Reference
	Second-tertile	112(34.89)	56(30.77)	0.73(0.47–1.14)	0.70(0.44–1.13)
	Third-tertile	110(34.27)	58(31.87)	0.77(0.49–1.20)	0.67(0.41–1.08)
MEHP	Per unit	-	-	1.00 (1.00-1.01)	1.00 (0.99–1.01)
	First-tertile	110(34.27)	57(31.32)	Reference	Reference
	Second-tertile	101(31.46)	67(36.81)	1.28(0.82-2.00)	1.40(0.87–2.24)
	Third-tertile	110(34.27)	58(31.87)	1.02(0.65–1.60)	0.94(0.58–1.52)
MEHHP	Per unit	-	-	1.00 (1.00–1.00)	1.00(0.99-1.00)
	First-tertile	102(31.78)	65(35.71)	Reference	Reference
	Second-tertile	104(32.4)	64(35.16)	0.97(0.62–1.50)	0.91(0.57–1.46)
	Third-tertile	115(35.83)	53(29.12)	0.72(0.46–1.13)	0.67(0.41–1.07)
MEOHP	Per unit	-	-	1.00 (0.99–1.01)	1.00(0.99–1.01)
	First-tertile	99(30.84)	68(37.36)	Reference	Reference
	Second-tertile	110(34.27)	58(31.87)	0.77(0.49–1.20)	0.78(0.49–1.26)
	Third-tertile	112(34.89)	56(30.77)	0.73(0.47–1.14)	0.69(0.43–1.11)
MECPP	Per unit	-	-	1.00(1.00–1.00)	1.00(1.00–1.00)
	First-tertile	106(33.02)	61(33.52)	Reference	Reference
	Second-tertile	103(32.09)	65(35.71)	1.10(0.70–1.71)	1.01(0.63–1.61)
	Third-tertile	112(34.89)	56(30.77)	0.87(0.55–1.36)	0.8(0.50–1.29)
MCMHP	Per unit	-	-	1.00(0.99–1.01)	1.00(0.98–1.01)
	First-tertile	113(35.2)	54(29.67)	Reference	Reference
	Second-tertile	104(32.4)	64(35.16)	1.29(0.82–2.02)	1.29(0.80–2.09)
	Third-tertile	104(32.4)	64(35.16)	1.29(0.82–2.02)	1.20(0.74–1.95)

[a]aOR, adjusted odds ratio. Logistic regression was used to calculate odds ratios and 95% CIs. All models were adjusted for maternal age (continuous), maternal ethnicity, maternal education level, gravidity, pre-pregnancy BMI (continuous), maternal medication use, parental smoking or ETS exposure, maternal alcohol consumption, folic acid supplements and infant gender

1.01–2.10]) and MCOP was also associated with elevated odds (OR = 1.48, [95% CI: 1.09–2.01]) [36]. Furthermore, a cohort study in USA suggested that exposure to MBP in the second trimester increased odds of spontaneous late preterm birth (LPTB) by 54% for every 2-fold increase of MBP [32]. Notably, our analysis revealed initial spikes in ORs for several phthalate metabolites at lower exposure ranges, a pattern that categorical analyses might fail to capture. These nonlinear dose-response relationships suggest potential threshold effects or biological mechanisms that warrant further investigation. Future studies should prioritize continuous exposure assessments and explore molecular pathways underlying these dynamics.

To date, findings from population epidemiological studies on the association between prenatal phthalate exposure and preterm birth were not completely consistent. This inconsistency may be explained from three aspects. First, differences in study designs (cohort studies, nested case-control studies, and cross-sectional study), population characteristics (e.g., age, ethnicity, education, and quality of care), exclusion criteria, and/or exposure levels or sources, may affect study findings. For instance, a study detected interactions for PTB in which African Americans were at higher risk than whites for greater MiBP ($P = 0.08$) and MEP ($P = 0.02$) although lower risk for greater MEHP ($P = 0.09$) [52]. Second, differences in sample collection time points may also affect study results. For instance, a study found that the associations between MBP and preterm birth were greater in magnitude for concentrations measured at 24 weeks of gestation (OR = 1.38, 95% CI: 1.05–1.81) compared to 20 weeks (OR = 1.11, 95% CI: 0.82–1.49) or 28

Table 4 Association between maternal genetic polymorphisms and SPTB

Gene	dbSNP_ID	Model	Genotype	Controls	SPTB cases	aOR[a](95% CI)	*P*-Value	FDR-BH *P*-Value
				No. (%)	No. (%)			
CYP2C19	rs12248560	Log-additive	-	-	-	1.8(0.41–7.91)	0.44	0.92
		Dominant	C/C	317(98.75)	178(97.8)	1	0.44	0.82
			C/T-T/T	4(1.25)	4(2.2)	1.8(0.41–7.91)		
		Recessive	C/C-C/T	321(100)	182(100)	1	NA	NA
			T/T	0(0)	0(0)	NA		
CYP2C19	rs4244285	Log-additive	-	-	-	0.73(0.55–0.98)	0.04	0.45
		Dominant	G/G	136(42.37)	89(48.9)	1	0.31	0.82
			G/A-A/A	185(57.63)	93(51.1)	0.82(0.56–1.2)		
		Recessive	G/G-G/A	273(85.05)	171(93.96)	1	0.01	0.11
			A/A	48(14.95)	11(6.04)	0.37(0.18–0.74)		
CYP2C9	rs1057910	Log-additive	-	-	-	1.4(0.59–3.35)	0.45	0.92
		Dominant	A/A	309(96.26)	171(93.96)	1	0.45	0.82
			A/C-C/C	12(3.74)	11(6.04)	1.4(0.59–3.35)		
		Recessive	A/A-A/C	321(100)	182(100)	1	NA	NA
			C/C	0(0)	0(0)	NA		
UGT1A7	rs11692021	Log-additive	-	-	-	1.2(0.83–1.72)	0.33	0.92
		Dominant	T/T	215(66.98)	117(64.29)	1	0.57	0.82
			T/C-C/C	106(33.02)	65(35.71)	1.12(0.75–1.68)		
		Recessive	T/T-T/C	316(98.44)	175(96.15)	1	0.12	0.51
			C/C	5(1.56)	7(3.85)	2.66(0.79–9.03)		
UGT1A7	rs2018985	Log-additive	-	-	-	0.88(0.57–1.36)	0.58	0.92
		Dominant	A/A	244(76.01)	144(79.12)	1	0.37	0.82
			A/G-G/G	77(23.99)	38(20.88)	0.81(0.51–1.29)		
		Recessive	A/A-A/G	319(99.38)	179(98.35)	1	0.2	0.51
			G/G	2(0.62)	3(1.65)	3.54(0.51–24.35)		
UGT1A7	rs4124874	Log-additive	-	-	-	0.98(0.73–1.3)	0.88	0.92
		Dominant	T/T	128(39.88)	78(42.86)	1	0.61	0.82
			T/G-G/G	193(60.12)	104(57.14)	0.9(0.61–1.33)		
		Recessive	T/T-T/G	287(89.41)	159(87.36)	1	0.65	0.99
			G/G	34(10.59)	23(12.64)	1.15(0.64–2.07)		
UGT1A7	rs10929302	Log-additive	-	-	-	0.87(0.56–1.34)	0.52	0.92
		Dominant	G/G	243(75.7)	144(79.12)	1	0.32	0.82
			G/A-A/A	78(24.3)	38(20.88)	0.79(0.5–1.26)		
		Recessive	G/G-G/A	319(99.38)	179(98.35)	1	0.2	0.51
			A/A	2(0.62)	3(1.65)	3.54(0.51–24.35)		
UGT1A7	rs3755319	Log-additive	-	-	-	0.96(0.72–1.28)	0.78	0.92
		Dominant	A/A	128(39.88)	79(43.41)	1	0.51	0.82
			A/C-C/C	193(60.12)	103(56.59)	0.88(0.6–1.29)		
		Recessive	A/A-A/C	287(89.41)	159(87.36)	1	0.65	0.99
			C/C	34(10.59)	23(12.64)	1.15(0.64–2.07)		
UGT1A7	rs887829	Log-additive	-	-	-	0.93(0.6–1.42)	0.72	0.92
		Dominant	C/C	243(75.7)	142(78.02)	1	0.49	0.82
			C/T-T/T	78(24.3)	40(21.98)	0.85(0.54–1.35)		
		Recessive	C/C-C/T	319(99.38)	179(98.35)	1	0.2	0.51
			T/T	2(0.62)	3(1.65)	3.54(0.51–24.35)		
UGT1A7	rs4148323	Log-additive	-	-	-	1.35(0.91–2.01)	0.13	0.77
		Dominant	G/G	242(75.39)	126(69.23)	1	0.15	0.82
			G/A-A/A	79(24.61)	56(30.77)	1.37(0.89–2.09)		
		Recessive	G/G-G/A	317(98.75)	179(98.35)	1	0.48	0.87
			A/A	4(1.25)	3(1.65)	1.79(0.35–8.99)		
UGT1A7	rs6717546	Log-additive	-	-	-	1.01(0.76–1.33)	0.96	0.96
		Dominant	G/G	138(42.99)	74(40.66)	1	0.74	0.82

Table 4 (continued)

Gene	dbSNP_ID	Model	Genotype	Controls	SPTB cases	aOR[a](95% CI)	*P*-Value	FDR-BH *P*-Value
				No. (%)	No. (%)			
			G/A-A/A	183(57.01)	108(59.34)	1.07(0.73–1.57)		
		Recessive	G/G-G/A	278(86.6)	160(87.91)	1	0.7	0.99
			A/A	43(13.4)	22(12.09)	0.89(0.5–1.59)		
UGT2B7	rs4587017	Log-additive	-	-	-	0.95(0.69–1.3)	0.73	0.92
		Dominant	G/G	180(56.07)	98(53.85)	1	0.87	0.88
			G/T-T/T	141(43.93)	84(46.15)	1.03(0.7–1.52)		
		Recessive	G/G-G/T	300(93.46)	174(95.6)	1	0.22	0.51
			T/T	21(6.54)	8(4.4)	0.58(0.25–1.38)		
UGT2B7	rs7662029	Log-additive	-	-	-	0.88(0.64–1.22)	0.45	0.92
		Dominant	G/G	172(53.58)	98(53.85)	1	0.75	0.82
			G/A-A/A	149(46.42)	84(46.15)	0.94(0.64–1.38)		
		Recessive	G/G-G/A	300(93.46)	174(95.6)	1	0.22	0.51
			A/A	21(6.54)	8(4.4)	0.58(0.25–1.38)		
UGT2B7	rs12233719	Log-additive	-	-	-	1.1(0.76–1.61)	0.6	0.92
		Dominant	G/G	226(70.4)	128(70.33)	1	0.72	0.82
			G/T-T/T	95(29.6)	54(29.67)	1.08(0.71–1.64)		
		Recessive	G/G-G/T	316(98.44)	177(97.25)	1	0.49	0.87
			T/T	5(1.56)	5(2.75)	1.6(0.42–6.07)		
UGT2B7	rs10028494	Log-additive	-	-	-	0.8(0.56–1.14)	0.21	0.92
		Dominant	A/A	196(61.06)	117(64.29)	1	0.24	0.82
			A/C-C/C	125(38.94)	65(35.71)	0.79(0.53–1.18)		
		Recessive	A/A-A/C	308(95.95)	177(97.25)	1	0.49	0.87
			C/C	13(4.05)	5(2.75)	0.68(0.23–2.01)		
UGT2B15	rs3100	Log-additive	-	-	-	1.39(0.99–1.96)	0.06	0.45
		Dominant	G/G	221(68.85)	113(62.09)	1	0.24	0.82
			G/A-A/A	100(31.15)	69(37.91)	1.27(0.85–1.9)		
		Recessive	G/G-G/A	316(98.44)	170(93.41)	1	0.01	0.11
			A/A	5(1.56)	12(6.59)	3.85(1.31–11.35)		
UGT2B15	rs4148269	Log-additive	-	-	-	1.39(0.99–1.96)	0.06	0.45
		Dominant	T/T	221(68.85)	113(62.09)	1	0.24	0.82
			T/G-G/G	100(31.15)	69(37.91)	1.27(0.85–1.9)		
		Recessive	T/T-T/G	316(98.44)	170(93.41)	1	0.01	0.11
			G/G	5(1.56)	12(6.59)	3.85(1.31–11.35)		
UGT2B15	rs2045100	Log-additive	-	-	-	0.89(0.66–1.2)	0.44	0.92
		Dominant	T/T	155(48.29)	91(50)	1	0.88	0.88
			T/A-A/A	166(51.71)	91(50)	0.97(0.66–1.43)		
		Recessive	T/T-T/A	288(89.72)	170(93.41)	1	0.14	0.51
			A/A	33(10.28)	12(6.59)	0.58(0.28–1.19)		
UGT2B15	rs1902023	Log-additive	-	-	-	1.03(0.78–1.34)	0.85	0.92
		Dominant	C/C	109(33.96)	60(32.97)	1	0.7	0.82
			C/A-A/A	212(66.04)	122(67.03)	1.08(0.72–1.62)		
		Recessive	C/C-C/A	260(81)	148(81.32)	1	0.91	0.99
			A/A	61(19)	34(18.68)	0.97(0.6–1.58)		
UGT2B15	rs9994887	Log-additive	-	-	-	1.03(0.79–1.35)	0.81	0.92
		Dominant	G/G	110(34.27)	60(32.97)	1	0.64	0.82
			G/A-A/A	211(65.73)	122(67.03)	1.1(0.73–1.65)		
		Recessive	G/G-G/A	260(81)	148(81.32)	1	0.9	0.99
			A/A	61(19)	34(18.68)	0.97(0.6–1.58)		
UGT2B15	rs13112099	Log-additive	-	-	-	1.03(0.79–1.35)	0.81	0.92
		Dominant	G/G	110(34.27)	60(32.97)	1	0.64	0.82
			G/T-T/T	211(65.73)	122(67.03)	1.1(0.73–1.65)		
		Recessive	G/G-G/T	260(81)	148(81.32)	1	0.9	0.99

Table 4 (continued)

Gene	dbSNP_ID	Model	Genotype	Controls	SPTB cases	aOR[a](95% CI)	*P*-Value	FDR-BH *P*-Value
				No. (%)	No. (%)			
			T/T	61(19)	34(18.68)	0.97(0.6–1.58)		
UGT2B15	rs7686914	Log-additive	-	-	-	1.03(0.79–1.35)	0.81	0.92
		Dominant	C/C	110(34.27)	60(32.97)	1	0.64	0.82
			C/T-T/T	211(65.73)	122(67.03)	1.1(0.73–1.65)		
		Recessive	C/C-C/T	260(81)	148(81.32)	1	0.9	0.99
			T/T	61(19)	34(18.68)	0.97(0.6–1.58)		
UGT2B15	rs7696472	Log-additive	-	-	-	1.03(0.79–1.35)	0.81	0.92
		Dominant	A/A	110(34.27)	60(32.97)	1	0.64	0.82
			A/G-G/G	211(65.73)	122(67.03)	1.1(0.73–1.65)		
		Recessive	A/A-A/G	260(81)	148(81.32)	1	0.9	0.99
			G/G	61(19)	34(18.68)	0.97(0.6–1.58)		

[b]aOR, adjusted odds ratio. Logistic regression was used to calculate odds ratios and 95% CIs. All models were adjusted for maternal age (continuous), maternal ethnicity, maternal education level, gravidity, pre-pregnancy BMI (continuous), maternal medication use, parental smoking or ETS exposure, maternal alcohol consumption, folic acid supplements and infant gender

Table 5 GMDR analysis for gene–gene and gene–phthalate exposure interaction models in SPTB

Model[a]	Training Bal. Acc	Testing Bal. Acc	Sign Test (*P*-Value)	CV Consistency
Gene-gene interactions				
rs4244285×rs6717546×rs2045100	0.6200	0.5111	6(0.3770)	4/10
rs4244285×rs6717546×rs3100×rs2045100	0.6652	0.4730	3(0.9453)	3/10
rs4244285×rs4124874×rs6717546×rs3100×rs2045100	0.7252	0.4910	5(0.6230)	5/10
rs4244285×rs4124874×rs6717546×rs3100×rs2045100×rs1902023	0.7949	0.4573	3(0.9453)	3/10
rs4244285×rs11692021×rs4124874×rs6717546×rs3100×rs2045100×rs1902023	0.8620	0.4525	3(0.9453)	1/10
Gene-phthalate metabolites interaction				
rs4148323×MEP	0.5869	0.5294	7(0.1719)	8/10
rs4244285×rs4124874×rs6717546×rs10028494×rs2045100×rs9994887×MEP×MiBP	0.9194	0.4736	5(0.6230)	2/10
rs4244285×rs11692021×rs4124874×rs6717546×rs10028494×rs3100×rs1902023×MEP×MEHP	0.9579	0.4887	7(0.1719)	2/10

Notes: Training Bal. Acc: training balanced accuracy; Testing Bal. Acc: testing balanced accuracy; CV Consistency: cross validation consistency

[a] All models were adjusted for maternal age (continuous), maternal ethnicity, maternal education level, gravidity, pre-pregnancy BMI (continuous), maternal medication use, parental smoking or ETS exposure, maternal alcohol consumption, folic acid supplements and infant gender

weeks (OR = 1.15, 95% CI: 0.84–1.59) [30]. Another study observed that summed di-2-ethylhexyl phthalate (ΣDEHP) metabolites measured in urine samples from the third trimester, but not the first trimester, were associated with increased odds of PTB (OR = 1.44, 95% CI: 1.06–1.95) [36]. In our study, maternal urine samples were collected at second trimester. Third, the types of biological specimen used may influence the study results. Most studies measured urine specimens from different pregnancy periods. A study in China found that cord blood levels of phthalates (DMP, DEP, DEEP, DPP, BMPP, DNHP, BBP, DNOP, DMEP, DBP, DIBP, DBEP, DEHP and DNP) were significantly associated with increased risk of PTB [27]. Another study found no significant correlation between either phthalate monoester (MBP or MEHP) in amniotic fluid and gestational age [39].

Accumulating evidence has shown that the differences in metabolic ability among individuals can influence the effects of environmental exposure on adverse pregnancy outcomes [53–56]. *CYP2C19* and *CYP2C9*, two members of the CYP family, are known to participate in phthalate metabolism [46]. The polymorphisms in *CYP2C9* (rs1057910) and *CYP2C19* (rs12248560 and rs4244285) were related to multiple diseases, such as association between A/C or C/C genotype at rs1057910 (A > C) and an increased risk for adenoma recurrence (aRR = 1.47, 95% CI: 1.19–1.83) [57], CT + TT genotype at rs12248560 (C > T) and a decreased risk of breast cancer (aOR = 0.77, 95% CI: 0.65–0.93) [58], G/A or A/A genotype at rs4244285 (G > A) and a higher risk of long-term ischemic stroke events (hazard ratio: 1.64, 95% CI: 1.06–2.53) [59]. In our previous research, we observed no significant association between any of these three polymorphic loci and the risk of congenital heart diseases [47]. To our knowledge, there have been no studies on the relationship between *CYP2C9* or *CYP2C19* polymorphisms and PTB susceptibility. In our study, among the examined polymorphisms (rs1057910 in *CYP2C9*, rs12248560 and

rs4244285 in *CYP2C19*), only rs4244285 polymorphism was associated with decreased SPTB under the log-additive and recessive model; however, this association was not observed after the FDR correction.

UGT1A7, UGT2B7 and UGT2B15 are the main Phase II metabolizing enzymes and catalyze the glucuronidation of multiple substrates including phthalates. The genetic polymorphisms of these three genes have been reported to be correlated with the risks of multiple diseases. Regarding *UGT1A7* gene, T/C or C/C genotype at rs11692021 (T > C) was associated with an increased risk of chronic pancreatitis (aOR = 1.76, 95% CI: 1.26–2.46) [60]. Besides, T/G or G/G genotype at rs4124874 (T > G) and G/A or A/A genotype at rs4148323 (G > A) were related to a higher risk of hyperbilirubinemia [61, 62]. Moreover, our previous study found that rs4124874 polymorphisms and T/T genotype at rs887829 (C > T) of *UGT1A7* gene were significantly associated with an increased risk of congenital heart diseases [47]. As for *UGT2B7* gene, G/G genotype at rs7662029 (A > G), T/G or G/G genotype at rs4587017 (T > G), and G/T or T/T genotype at rs12233719 (G > T) were associated with the severity of withdrawal symptoms in methadone maintenance patients [63], the analgesic effects of fentanyl in the cold pressor-induced pain test [64], never-smoking female lung cancer risk [65], respectively. In the present study, among 20 SNPs in *UGT1A7*, *UGT2B7* and *UGT2B15* gene, only the polymorphisms of maternal *UGT2B15* gene at rs4124874 and rs887829 loci were associated with increased SPTB. However, these associations were not statistically significant after FDR correction. Due to the current lack of research on the genetic polymorphisms of the three genes and PTB, it is impossible to compare our results with those of similar studies.

It is now widely believed that gene-environment interaction is a major contributor to PTB. More and more studies have reported significant gene-environment interactions for the development of preterm birth. For instance, a study found that exposure to high levels of PM10 during the third trimester in the presence of the *GSTM1* null genotype was significantly associated with an increased risk of preterm delivery [66]. A study demonstrated that the risk of preterm delivery that was associated with tag SNPs in genes regulating the inflammatory response was modified by an environmental exposure such as bacterial vaginosis [67]. A study showed that maternal *COL24A1* variants had a significant impact of genome-wide interaction with maternal pre-pregnancy overweight/obesity on PTB risk [68]. A study suggested that the effect of *NODAL* polymorphisms (rs1904589 and rs10999338) on preterm birth depended on maternal infection/inflammation status [69]. A study observed that certain maternal and fetal genes linked to infectious/inflammatory and hormonal regulation processes increased PTB risk according to clinical subtype when mothers are exposed to urinary tract infections or vaginal infections [70]. However, in the present study, we observed no significant interaction of gene-gene or gene-phthalate metabolites for SPTB, and more large-scale studies are needed to explore the interactions in the future.

This study has several strengths. First, to our knowledge, this is the first study to investigate the effect of the interaction between maternal exposure to phthalates during pregnancy and maternal genetic polymorphisms on odds of SPTB. Second, this study was nested in a prospective cohort, which allowed us to record exposure and outcome data prospectively, and to minimize the potential of selection and recall bias. Third, the subjects were non-occupational, low-dose phthalate-exposed pregnant women, therefore, the results are considered generalizable and can be applied to all women because the environmental factors can be assessed at the individual level. Nevertheless, our study has some limitations. First, the sample size was relatively small which might limit the statistical power and weaken potential associations. Second, we only measured phthalate metabolites from a single urine sample collected at the second trimester which would not reflect overall picture of exposure throughout pregnancy. Given the crucial role of the first trimester in fetal development, future research should conduct a similar analysis using the first trimester urine samples. Third, we only considered the effects of maternal phthalate exposure and genetic polymorphisms. Future studies are needed to estimate the effects of fetal exposure, fetal genetic polymorphisms, and the impact of their interactions on SPTB.

Conclusions

Our findings indicated that maternal phthalate exposure in the second trimester at the exposure levels of the present subjects was not associated with SPTB. A total of twenty-three polymorphisms of maternal *CYP2C19*, *CYP2C9*, *UGT1A7*, *UGT2B7*, and *UGT2B15* genes were not significantly associated with SPTB. No significant gene-gene or gene-phthalate metabolites interactions for SPTB was observed. Additional more large-scale human studies are warranted to confirm or refute our findings in the future.

Abbreviations

PTB	Preterm birth
SPTB	Spontaneous preterm birth
PPROM	Preterm prelabor rupture of membranes
SNPs	Single nucleotide polymorphisms
CYP2C9	Cytochrome P450 family 2 subfamily C member 9
CYP2C19	Cytochrome P450 family 2 subfamily C member 19
UGT1A7	Uridine diphosphate (UDP) glucuronosyl transferase family 1 member A7
UGT2B7	Uridine diphosphate (UDP) glucuronosyl transferase family 2 member B7

UGT2B15	Uridine diphosphate (UDP) glucuronosyl transferase family 2 member B15
UHPLC-MS/MS	Ultra-high performance liquid chromatography coupled with tandem mass spectrometry
MnBP	Mono-n-butyl phthalate
DnBP	Di-n-butyl phthalate
MiBP	Mono-isobutyl phthalate
DiBP	Diisobutyl phthalate
MBzP	Mono-benzyl phthalate
BBzP	Butylbenzyl phthalate
MEP	Monoethyl phthalate
DEP	Metabolite of diethyl phthalate
DEHP	Di (2-ethylhexyl) phthalate
MEHP	Mono(2-ethyl-hexyl) phthalate
MEHHP	Mono(2-ethyl-5-hydroxyhexyl) phthalate
MEOHP	Mono(2-ethyl-5-oxohexyl) phthalate
MECCP	Mono (2-ethyl-5-carboxypentyl)phthalate
MCMHP	Mono-2- carboxymethyl hexyl phthalate
LOD	Limit of detection
ETS	Environmental tobacco smoke
aOR	Adjusted odds ratio
95% CI	95% confidence interval
GMDR	Generalized multifactor dimensionality reduction
FDR	False discovery rate

Supplementary Information

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Supplementary Material 1

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Author contributions

Ping Yu and Jun Zhu developed the study design. Nana Li and Ping Yu conducted the experiments and drafted the manuscript. Lu li, Zhen Liu, Ying Deng, Meixian Wang, Yuting Li and Hong Kang assisted in organizing and collecting the samples. Yanping Wang participated in reviewing, editing, and revising the manuscript. All authors have read and approved the final manuscript.

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Data availability

The variant data for this study have been deposited in the European Variation Archive (EVA) at EMBL-EBI under accession number PRJEB79929.

Declarations

Ethics approval and consent to participate

An informed consent was obtained from each participant. This research was approved by the Ethics Committee of Sichuan University (No. K2017045), Fujian Provincial Maternal and Child Healthcare Hospital (No. 2017KR-030), and Maternal and Child Healthcare Hospital of Guangxi, Zhuang Autonomous Region (No. 20174-2), and followed the tenets of the Declaration of Helsinki.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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