Exposure characteristics of phthalate metabolites among the Zunyi cohort of pregnant women in Southwest China

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Abstract

Reported evidence has increasingly indicated that exposure to phthalates can cause adverse pregnancy outcomes. However, phthalate exposure levels among pregnant women remains unclear. We aimed to evaluate the concentrations and predictors of phthalate metabolites in urine samples of the ongoing Zunyi cohort of pregnant women from Southwest China. The urine samples were collected from 1003 pregnant women during their third trimester of pregnancy. The concentrations of nine phthalate metabolites in urine samples were then determined. Data on socio-demographic profiles of the participants, lifestyle during pregnancy, parity, and sampling season were collected using questionnaires. The detectable rate of phthalate metabolites ranged from 76 to 100%. On average, mono-butyl phthalate exhibited the highest median concentration (62.45 μg/L), while mono-benzyl phthalate exhibited the lowest median concentration (0.04 μg/L). Urine concentrations of phthalate metabolites were significantly higher in older, multiparous, higher body mass index, higher income, and passive smoking during pregnancy participants. The levels of low-molecular-weight phthalate metabolites were highest during the summer. The findings indicate the health of pregnant women and fetuses in Zunyi may be generally harmed by the high exposure of phthalate metabolites, especially by mono-n-butyl phthalate. In addition, phthalate metabolites present a demographic and seasonal differential distribution among the study population. Targeted measures to reduce phthalate exposure for high-risk pregnant women and during high-exposure seasons may have potential benefits for maternal and fetal health protection.

Keywords Phthalate · Pregnancy · Urinary metabolites · Exposure levels · Sampling season · Detectable rate

Introduction

Phthalates are widely used in numerous consumer and food packaging products, resulting in the inevitable long-term exposure of the human body to phthalate metabolites (Benjamin et al. 2017; Calafat et al. 2015). These groups even include some special groups, such as preschool and elementary school students, the elderly, and pregnant women (Abdi et al. 2021; Cheng et al. 2021; Wu et al. 2020). The results of previously published studies suggest that some of these metabolites may adversely impact human health, particularly during sensitive periods of life, such as in utero (Bergman et al. 2013; Ipapo et al. 2017).

Published epidemiological data suggest that maternal prenatal exposure to phthalate metabolites endanger maternal and fetal health as well as birth outcomes. A prospective cohort study conducted in Denmark (Toft et al. 2012) found that the concentration of mono(2-ethylhexyl) phthalate
(DEHP) in pregnant women’s urine before pregnancy was correlated with the risk of spontaneous abortions. Several studies in the USA (Messerlian et al. 2016) and China (Mu et al. 2015; Gao et al. 2017a; Liao et al. 2018a) have reached the same conclusion. Additionally, maternal exposure to phthalates can increase the odds of preterm birth (Ferguson et al. 2019; Gao et al. 2019), and it is related to fetal birth size (Polariska et al. 2016; Guo et al. 2020). Moreover, maternal exposure to phthalates was observed to lead to gestational hypertension and gestational diabetes mellitus (Werner et al. 2015; James-Todd et al. 2016). Finally, in vivo (Chen et al. 2020) and in vitro experimental studies (Zong et al. 2015) have reached the same conclusions as the population studies. Chen et al. found that exposure to di-n-butyl phthalate (DBP) during pregnancy promotes the insurgence of gestational diabetes mellitus by significantly increasing the expression of protein pSTAT1 and inhibiting that of FOXM1; the authors also found that the said exposure causes a decrease in islets β cell viability (Chen et al. 2020). Zong proposed that, in mice, exposure to DEHP during pregnancy administration disrupted labyrinth vascularization of placentas, and inhibited proliferation and induced apoptosis of placenta by the activation of caspase-3 and caspase-8, up-regulation of Bax and down-regulation of Bel-2 mRNA, and protein resulting in an increase in the probability of embryonic loss and a decrease in fetal body weight (Zong et al. 2015). Recent studies have suggested that prenatal exposure to phthalates may also be associated with negative health consequences in childhood and adulthood, for example, adverse neurocognitive development (Qian et al. 2019), asthma (Adgent et al. 2020), anxious-shy behaviors (Daniel et al. 2020), and decreased skeletal muscle mass (Lee et al. 2020a) are prone to occur in childhood. Adult negative health outcomes including erectile dysfunction (Zhou et al. 2021) and disrupts testicular steroidogenesis (Barakat et al. 2019).

However, the presence of phthalate pollution at a high level is a prerequisite for phthalate hazard to maternal and fetal harm. Because phthalate pollution is related to the degree of social and economic development, the exposure rate and degree vary across countries, regions, and human populations (Wenzel et al. 2018). Therefore, pollution levels in some underdeveloped areas with good ecology and a low degree of industrialization and socialization may be low, and the aforementioned hazards may not exist. Until now, only a few related investigations have been undertaken in China. To our knowledge, only three studies have reported phthalate metabolite concentrations and predictors in Chinese pregnant women (Gao et al. 2017a; He et al. 2019; Li et al. 2019a, b). These three studies showed that MBP had the highest concentration, providing a preliminary profile of phthalate exposure in Chinese pregnant women. However, the generalizability of these results to Chinese pregnant women may be limited because they were more developed cities in China. Therefore, more studies on persons in economically underdeveloped areas are needed to better understand the phthalate exposure patterns and levels in Chinese pregnant women.

Therefore, the goal of the present investigation was to conduct a population-based study aimed at determining the level of phthalate metabolites in pregnant women from undeveloped Southwest China as well as the correlation of this parameter with demographic characteristics, lifestyle, parity, and seasonal variations. Such knowledge is vital to our understanding of the global trends and exposure patterns and can offer suggestions on suitable specific interventions to reduce the risk of high phthalate exposure during pregnancy.

### Methods

#### Study population

Pregnant women hospitalized for childbirth in the third trimester were recruited from August 2020 to July 2021 at Xishui and Meitan County People’s Hospital, which are located in Zunyi city, Southwest China. After informed consent, study participants signed the informed consent form and filled in the electronic questionnaire during face-to-face interviews. Study eligibility criteria included natural conception, singleton pregnancy, and live fetus. Patients were excluded if they were suffering from serious chronic diseases and infectious diseases, such as cancer, chronic cardiovascular and cerebrovascular diseases, chronic renal failure, and HIV infection. This study was ethically reviewed by the Affiliated Hospital of Zunyi Medical University (batch No.: KLL-2019-006).

#### Survey questionnaire

The questions to include in the questionnaire were discussed and decided by several epidemiological experts over many meetings. Demographic information was obtained through a questionnaire administered to women upon enrollment in the study; the questionnaire included queries on the demographic data of pregnant women: age, weight, height, education, annual household income, lifestyle during pregnancy (smoking, drinking, passive smoking, and drinking bottled water), parity, and sampling season. The participants’ BMI (weight (kg)/height (m)²) was calculated based on physician-recorded height and weight at the time of enrollment. Based on maternal age, participants were divided into the following three groups: < 25 years, 25–29 years, and ≥ 30 years of age. Based on BMI, participants were divided into the following three groups: underweight (<18.5 kg/m²), normal (18.5–23.9 kg/m²), and overweight (≥ 24 kg/m²).
Participants were divided into four groups based on annual household income: low income (<¥100,000), middle income (¥100,000–¥150,000), high income (≥ ¥150,000), and do not know. Based on maximum education level reached, participants were divided into three ordinal groups: nulliparous (0) and multiparous (≥ 1). Passive smoking is defined as exposure to cigarette smoke for at least half an hour a day. The sampling seasons were defined as follows: spring (March–May), summer (June–August), fall (September–November), and winter (December–February). Maternal age and BMI were treated as continuous variables, and annual household income, maternal education, passive smoking, parity, drinking bottled water, and sample collection season were treated as categorical variables.

Measurement of phthalate metabolites

Urine samples from 1003 women were analyzed to determine the concentration of nine phthalate metabolites by high-performance gas chromatography mass spectrometry (GC-MS/MS, Agilent 7010b, Santa Clara, CA, USA); these metabolites are mono-methyl phthalate (MMP), mono-ethyl phthalate (MEP), mono-isobutyl phthalate (MiBP), mono-butyl phthalate (MBP), mono-octyl phthalate (MOP), mono-benzyl phthalate (MBZP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP). Spot urine specimens were collected in polypropylene tubes in the obstetrical clinics and transferred to the Zunyi Medical University Laboratory (Zunyi, Southwest China) for analysis; urine samples were divided into 1-mL aliquots and stored at −80°C until analysis. Urinary creatinine concentration was determined by the laboratory of the Affiliated Hospital of Zunyi Medical University using an automatic urine analyzer (Beckman, AU5800, Kraemer Boulevard Brea, CA, USA). Details of the method for detecting the concentration of metabolites in urine can be found in the Supplementary information. Briefly, 1.5 mL of urine were added into a 10-mL centrifuge tube, add 1 mL of sodium acetate solution buffer to urine sample and standard sample, 10 μL 5μg/ml internal standard solution, and 10 μL β-glucuronidase/sulphatase enzyme to fully hydrolyze the sample; excess MgSO4·7H2O was then added to reach supersaturation. Add to each tube 1 mL of a mixed solvent comprising n-hexane and diethyl ether (4:1); place the tubes on the multi-tube vortex mixer, and shake them evenly for 5 min at 2500 R/min, until no additional precipitation is noticed; centrifuge then the tubes for 10 min at 3500 rpm, and transfer the supernatant to a new 5-mL centrifuge tube, this step was repeated twice; store the organic phases in 5-mL centrifuge tubes were concentrated to about 150 μL with nitrogen gas, do not blow-dry completely; then move to the internal intubation and flush to a 5-mL centrifuge tube with 100 μL n-hexane + diethyl ether, move it into the inner cannula again and blow-dry with nitrogen; the silylation reagent [N. O-bis (trimethylsilyl) trifluoroacetamide: trimethylchlorosilane=99:1] was then added to 5-mL centrifuge tubes containing the supernatants; after the complete derivatization 45 min and analyze them after allowing the bottle to cool to 37°C.

Temperature analysis of extracted phthalates using gas-mass chromatography

Chromatographic conditions were as follows: the injection port is set to non shunt mode, 99.999% helium is the carrier gas, the flow rate is 1.2 mL/min, automatic sample injection is performed, the volume of sample taken each time is 1 μL, the temperature of the injection port is set to 250°C, and the temperature of the transmission line is set to 280°C. Temperature rise procedure: the initial temperature is set at 60°C for 3 min; the temperature is made to rise evenly to 150°C for 3 min and 210°C for 5 min (at a heating rate of 10°C/min); Finally, the temperature is made to rise evenly to 280°C at the same rate; the whole process lasts 33 min.

Statistical analyses

The limit of detection (LOD) of phthalate metabolites were assumed to correspond numerically to three times the signal-to-noise ratio; therefore, the LOD values for MMP, MEP, MiBP, MBP, MOP, MBZP, MEOHP, MEHHP, and MEHP were determined to be 0.038, 0.029, 0.002, 0.002, 0.063, 0.041, 1.071, 0.010, and 0.033 μg/L, respectively; notably, in our analyses, we replaced the phthalate metabolite concentrations that were below the LOD with the relevant LOD value divided by the square root of 2. The total concentration of low-molecular-weight (LMW) phthalates (ΣLMW) was calculated as the total sum of the molar concentrations of the three metabolites (MMP, MEP, and MBP), because MBP concentration includes MiBP, MiBP is not calculated here, and the formula is ΣLMW (nmol/L) = [MMP (μg/L)/180 + MEP (μg/L)/194 + MBP(μg/L)/222] × 1000. The total concentration of DEHP (ΣDEHP) was calculated as the total sum of the molar concentrations of the three metabolites (MEHP, MEOHP, and MEHHP), and the formula is ΣDEHP (nmol/L) = [MEHP (μg/L)/278+ MEOHP (μg/L)/294 + MEHHP(μg/L)/292] × 1000. Urine creatinine concentration was used to correct for urine dilution employing the following formula: urine creatinine–corrected phthalate metabolite concentration (μg/g crea) = phthalate metabolite concentration (μg/L) / [urine creatinine concentration (μg/L) × 113 (g/mol) × 10−6]. Notably, we calculated both the unadjusted and creatinine-adjusted urine phthalate concentration...
metabolite concentration distributions (geometric mean and percentile values). The distributions of nine phthalate metabolites as well as ΣLMW and ΣDEHP were skewed; thus, we performed the natural logarithm transformation (ln) of creatinine-adjusted phthalate metabolite concentrations to produce more normal distributions for statistical analyses. Multivariable linear regression was employed to determine the relationship among demographic variable category, lifestyle, parity and season and metabolite concentrations corrected for urinary creatinine. Finally, Spearman’s rank correlation coefficient was used to test the correlation between different phthalate metabolite concentrations. All analyses were performed with SPSS version 25.0 (IBM Corp. Armonk, NY, USA); the applied threshold for statistical significance was \( p < 0.05 \) (two-tailed).

**Results**

**Basic demographic characteristics**

The basic demographic characteristics of the overall population are presented in Table 1. The average age was 26.7 ± 5.0 years old, and the age group comprising the largest proportion of participants (40.4%) was the 25–29 years old category. The average BMI value was 22.4 ± 3.5 kg/m², and the BMI category comprising the largest proportion of participants (61.3%) was the normal weight group. Moreover, 59.4% of participants had an education level of middle school or below, 58% came from households in the annual middle-income bracket, and multiparous participants accounted for 60.4% of the cohort. In this study, none of the participants smoked or drank alcohol during pregnancy, but 11.7% were categorized as passive smokers. Approximately 92.4% of participants drank bottled water during pregnancy. The highest proportion of participants was enrolled in the study during the winter (44%), while the lowest proportion was enrolled during the summer (7.5%).

**Phthalate metabolite distribution**

The values for the detectable rate, geometric mean, and the quartile of both unadjusted and creatinine-adjusted concentrations of phthalate metabolites are listed in Table 2. The detectable rates of the phthalate metabolites MMP, MEP, MiBP, MBP, MOP, MB₂P, MEHP, MEHHP, and MEHPP in participants’ urine samples were 76%, 97.8%, 99.6%, 100%, 87.1%, 77.5%, 93.7%, 87.4%, and 93.7%, respectively. On average, MBP exhibited the highest concentration in urine samples, and the median concentration value for this metabolite was 62.45 μg/L. By contrast, MB₂P exhibited on average the lowest concentration in urine samples, and the median concentration for this metabolite was 0.04 μg/L.

**Socio-demographic variable, lifestyle, parity, and sampling season analyses**

In Tables 3 and 4 are listed data reflecting the effects that different demographic variables, lifestyle, parity, and sampling seasons have on the concentrations of LMW metabolites and high-molecular-weight (HMW) metabolites in participants’ urine. Data reflecting the correlation between sampling season and phthalate metabolite concentration is reported in Fig. 1. The correlations between other demographic variables, lifestyle, and parity (maternal age, BMI, annual household income, education, parity, passive smoking, and drinking bottled water) and phthalate metabolite concentrations are reflected by data reported in Figures S1-7. The results of multivariable linear regression analyses indicated that the exposure level to phthalate metabolites during pregnancy...
was mainly related to maternal age, BMI, annual household income, passive smoking during pregnancy, parity, and sampling season. Notably, the concentration of MEHHP in the urine samples from pregnant women aged ≥ 30 years was the highest. MEP, MEHP, ΣLMW, and ΣDEHP were the most abundant metabolites present in the urine samples collected from study participants in the overweight BMI group. Compared with their high-annual-income counterparts, low-annual-income participants exhibited substantially lower concentrations of MiBP, MBP, MOP, MBZP, MEHP, and ΣDEHP, whereas middle-annual-income participants had lower concentrations of MiBP, MB2P, MEHP, and ΣDEHP. The concentration of MEHP in urine samples from participants in the passive smoking group was higher than that in the no passive smoking group. Multiparous participants exhibited higher concentrations of MEHP and lower concentrations of MEHHP than nulliparous participants. Phthalate metabolite concentration was observed to be related to the sampling season. LMW metabolites (i.e., MMP, MEP, MiBP, MBP, and ΣLMW) exhibited the highest concentrations in urine samples collected in participants enrolled during the summer period. By contrast, MEHHP concentration in urine samples was lowest for participants enrolled during the summer, and MOP concentration in urine samples was lowest for participants enrolled during the spring. In this study, no statistically significant correlation was observed between phthalate metabolite exposure level and maternal education or drinking bottled water during pregnancy.

### Correlations between phthalate metabolite concentrations

In order to assess the variations in the potential sources of phthalate metabolite exposure, the correlations between urinary concentrations of individual phthalate metabolites in 1003 pregnant women were identified by Spearman’s rank correlation coefficient analysis. A significant correlation among phthalate metabolites was recognized; specifically, there was a strong correlation between the

### Table 2 Distribution of urinary phthalate metabolite concentrations [unadjusted(μg/L) and creatinine-adjusted (μg/g creatinine)] among pregnant women (N = 1003)

| Phthalate metabolites | DR (%) | GM  | 25th | 50th | 75th | 95th |
|-----------------------|--------|-----|------|------|------|------|
| MMP                  | UAa    | 76  | 0.86 | 0.15 | 1.63 | 4.47 |
|                      | CAa    |     | 1.13 | 0.17 | 1.79 | 6.28 |
| MEP                  | UAa    | 97.8| 8.49 | 4.01 | 8.64 | 20.78|
|                      | CAa    |     | 11.09| 4.17 | 11.85| 30.22|
| MiBP                 | UAa    | 99.6| 24.07| 12.57| 24.61| 47.28|
|                      | CAa    |     | 31.44| 14.77| 32.34| 71.07|
| MBP                  | UAa    | 100 | 64.64| 30.45| 62.45| 130.80|
|                      | CAa    |     | 84.42| 34.64| 84.24| 202.32|
| MOP                  | UAa    | 87.1| 0.14 | 0.04 | 0.13 | 0.28 |
|                      | CAa    |     | 0.18 | 0.08 | 0.17 | 0.40 |
| MBzP                 | UAa    | 77.5| 0.08 | 0.04 | 0.16 | 0.78 |
|                      | CAa    |     | 0.10 | 0.04 | 0.08 | 0.23 |
| MEHP                 | UAa    | 93.7| 7.18 | 2.46 | 6.78 | 37.84|
|                      | CAa    |     | 9.38 | 2.95 | 9.60 | 50.25|
| MEOHPP               | UAa    | 87.4| 5.47 | 2.24 | 6.31 | 11.92|
|                      | CAa    |     | 7.14 | 2.57 | 7.24 | 18.99|
| MEHHP                | UAa    | 93.7| 4.96 | 3.51 | 7.63 | 14.63|
|                      | CAa    |     | 6.48 | 3.72 | 9.14 | 20.09|
| ΣLMW                 | UAa    | 379.76| 177.81| 355.32| 758.45| 2449.65|
|                      | CAa    |     | 495.99| 208.27| 497.86| 1182.32| 4199.32|
| ΣDEHP                | UAa    | 115.01| 47.65| 106.16| 272.97| 1040.99|
|                      | CAa    |     | 150.22| 58.07| 140.40| 359.23| 1622.26|

UA, unadjusted; CA, creatinine-adjusted; DR, detectable rate; GM, geometric mean; MMP, mono-methyl phthalate; MEP, mono-ethyl phthalate; MiBP, mono-isobutyl phthalate; MBP, mono-butyl phthalate; MOP, mono-octyl phthalate; MBzP, mono-benzyl phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethyl-5-oxohexyl) phthalate; ΣLMW, the molar sum of three metabolites (MMP, MEP, and MBP); ΣDEHP, the molar sum of three metabolites (MEHP, MEHHP, and MEOHPP); ‘the unit was μg/L; $b$the unit was μg/g creatinine.
Table 3  Associations between LMW metabolite concentrations and demographic, lifestyle, parity, and season categories by multivariable linear regression (ln-transformed, μg/g creatinine) ($N$ = 1003)

| Variables                       | β estimates and 95% confidence intervals |
|---------------------------------|------------------------------------------|
|                                 | MMP           | MEP           | MiBP          | MBP           | ΣLMW          |
| Maternal age                    |               |               |               |               |               |
| <25                             | -0.01 (-0.36, 0.35) | -0.05 (-0.29, 0.20) | 0.10 (-0.09, 0.30) | 0.04 (-0.14, 0.22) | 0.03 (-0.15, 0.21) |
| 25–29                           | Reference     |               |               |               |               |
| ≥30                             | 0.12 (-0.25, 0.50) | 0.17 (-0.08, 0.43) | 0.14 (-0.06, 0.35) | 0.07 (-0.12, 0.26) | 0.11 (-0.07, 0.30) |
| BMI (kg/m²)                     |               |               |               |               |               |
| <18.4                           | 0.23 (-0.26, 0.72) | 0.01 (-0.33, 0.35) | -0.12 (-0.39, 0.15) | -0.07 (-0.32, 0.17) | -0.04 (-0.29, 0.20) |
| 18.5–23.9                       | Reference     |               |               |               |               |
| ≥24                             | 0.01 (-0.33, 0.34) | 0.45 (0.23, 0.68) | 0.16 (-0.03, 0.34) | 0.15 (-0.02, 0.32) | 0.19 (0.02, 0.36) |
| Household income                |               |               |               |               |               |
| <100,000                        | 0.01 (-0.38, 0.59) | 0.02 (-0.31, 0.36) | -0.63 (-0.89, -0.36) | -0.30 (-0.54, -0.05) | -0.22 (-0.46, 0.03) |
| 100,000–150,000                 | -0.14 (-0.51, 0.23) | -0.04 (-0.30, 0.21) | -0.25 (-0.45, -0.05) | -0.12 (-0.31, 0.07) | -0.10 (-0.28, 0.08) |
| ≥150,000                        | Reference     |               |               |               |               |
| Don’t know                      | 0.06 (-0.14, 2.31) | -0.02 (-1.03, 0.64) | -0.19 (-0.86, 0.47) | 0.09 (-0.52, 0.71) | 0.07 (-0.53, 0.68) |
| Education                       |               |               |               |               |               |
| Middle school or below          | 0.22 (-0.28, 0.71) | 0.03 (-0.28, 0.34) | 0.07 (-0.17, 0.32) | 0.10 (-0.13, 0.32) | 0.11 (-0.12, 0.33) |
| High school and middle special  | 0.22 (-0.38, 0.59) | 0.21 (-0.12, 0.55) | 0.04 (-0.23, 0.31) | 0.11 (-0.14, 0.36) | 0.12 (-0.12, 0.36) |
| school                          | Reference     |               |               |               |               |
| College degree or above         | 141           |               |               |               |               |
| Passive smoking                 |               |               |               |               |               |
| Yes                             | 0.07 (-0.40, 0.54) | 0.00 (-0.32, 0.32) | -0.01 (-0.27, 0.25) | 0.08 (-0.16, 0.31) | 0.08 (-0.15, 0.31) |
| NO                              | Reference     |               |               |               |               |
| Drinking bottled water          |               |               |               |               |               |
| Yes                             | -0.19 (-0.75, 0.38) | 0.16 (-0.23, 0.54) | -0.17 (-0.48, 0.13) | -0.06 (-0.34, 0.23) | -0.05 (-0.33, 0.23) |
| NO                              | Reference     |               |               |               |               |
| Parity                          |               |               |               |               |               |
| Nulliparous                     | 397           |               |               |               |               |
| Multiparous                     | 606           | 0.02 (-0.32, 0.35) | -0.06 (-0.29, 0.16) | 0.04 (-0.14, 0.22) | 0.03 (-0.13, 0.20) | 0.01 (-0.16, 0.17) |
| Sampling season                 |               |               |               |               |               |
| Spring                          | 255           | -0.07 (-0.43, 0.30) | 0.50 (0.25, 0.75) | 0.14 (0.22, 0.62) | 0.77 (0.58, 0.95) | 0.76 (0.58, 0.94) |
| Summer                          | 75            | 0.95 (0.37, 1.53) | 1.37 (0.98, 1.77) | 0.18 (0.60, 1.23) | 1.74 (1.45, 2.03) | 1.78 (1.50, 2.07) |
| Fall                            | 232           | 0.93 (0.54, 1.32) | 0.70 (0.44, 0.97) | 0.17 (0.32, 0.74) | 0.66 (0.46, 0.85) | 0.67 (0.48, 0.87) |

LMW metabolite including MMP, MEP, MiBP, MBP, and ΣLMW. Bold font indicates $p$ value < 0.05. Levels of biomarkers in the following groups: Maternal age 25–29 years, BMI 18.5–23.9 kg/m², annual household income ≥150,000 yuan, college degree or above, non-passive smoking, non-drinking bottled water, nulliparous and winter (sampling season), were set as reference
Table 4  Associations between HMW metabolite concentrations and demographic, lifestyle, parity, and season categories by multivariable linear regression (ln-transformed, μg/g creatinine) (N = 1003)

| Variables                        | N  | MOP   | MBzP  | MEHP  | MEOHP | MEHHP | ΣDEHP |
|----------------------------------|----|-------|-------|-------|-------|-------|-------|
| **Maternal age**                 |    |       |       |       |       |       |       |
| <25                              | 342| −0.05 (−0.23, 0.13) | −0.04 (−0.24, 0.16) | −0.25 (−0.60, 0.09) | 0.15 (−0.07, 0.37) | 0.24 (−0.06, 0.55) | −0.03 (−0.23, 0.17) |
| 25–29                            | 405|       |       |       |       |       |       |
| ≥30                              | 256| 0.15 (−0.04, 0.34) | −0.01 (−0.22, 0.20) | 0.14 (−0.22, 0.51) | 0.01 (−0.22, 0.25) | **0.40 (0.08, 0.72)** | 0.15 (−0.07, 0.36) |
| BMI (kg/m²)                      |    |       |       |       |       |       |       |
| <18.5                            | 105| −0.15 (−0.40, 0.10) | −0.22 (−0.49, 0.06) | 0.19 (−0.29, 0.66) | −0.18 (−0.49, 0.13) | −0.24 (−0.66, 0.18) | −0.05 (−0.33, 0.23) |
| 18.5–23.9                       | 615|       |       |       |       |       |       |
| ≥24                              | 283| 0.07 (−0.10, 0.24) | −0.02 (−0.21, 0.16) | **0.67 (0.34, 0.99)** | −0.01 (−0.22, 0.20) | 0.21 (−0.08, 0.49) | **0.26 (0.07,0.45)** |
| **Annual household income**      |    |       |       |       |       |       |       |
| <100,000                         | 174| **−0.42 (−0.67, −0.18)** | **−0.49 (−0.76, −0.22)** | **−0.49 (−0.96, −0.02)** | −0.17 (−0.47, 0.14) | −0.23 (−0.65, 0.19) | **−0.41 (−0.68, −0.13)** |
| 100,000–150,000                  | 582| **−0.21 (−0.40, −0.02)** | **−0.21 (−0.42, −0.01)** | **−0.48 (−0.84, −0.12)** | −0.17 (−0.40, 0.06) | −0.22(−0.54,0.10) | **−0.30 (−0.51, −0.09)** |
| ≥150,000                         | 231|       |       |       |       |       |       |
| Don't know                       | 16 | 0.11 (−0.51, 0.73) | 0.29 (−0.39, 0.97) | −0.42 (−1.61, 0.77) | 0.43 (−0.33, 1.20) | 0.49 (−0.55, 1.53) | −0.07 (−0.77, 0.62) |
| **Education**                    |    |       |       |       |       |       |       |
| Middle school or below           | 596| −0.02 (−0.25, 0.20) | −0.13 (−0.38, 0.12) | −0.10 (−0.54, 0.33) | −0.22 (−0.50, 0.06) | 0.19 (−0.20, 0.57) | −0.11 (−0.36, 0.15) |
| High school and middle special school | 266| 0.19 (−0.06, 0.44) | −0.20 (−0.47, 0.08) | −0.04 (−0.51, 0.44) | −0.21 (−0.51, 0.10) | 0.17 (−0.25, 0.59) | −0.08 (−0.36, 0.20) |
| **College degree or above**      |    |       |       |       |       |       |       |
| Passive smoking                  |    |       |       |       |       |       |       |
| Yes                              | 117| −0.04 (−0.28, 0.20) | −0.09 (−0.35, 0.18) | **0.49 (0.03, 0.95)** | −0.25 (−0.55, 0.04) | −0.03 (−0.43, 0.37) | 0.09 (−0.18, 0.36) |
| NO                              | 886|       |       |       |       |       |       |
| **Drinking bottled water**       |    |       |       |       |       |       |       |
| Yes                              | 927| 0.17 (−0.12, 0.45) | −0.05 (−0.37, 0.26) | −0.04 (−0.59, 0.51) | 0.01 (−0.34, 0.36) | −0.17 (−0.65, 0.31) | −0.10 (−0.42, 0.22) |
| NO                              | 76 |       |       |       |       |       |       |
| **Parity**                       |    |       |       |       |       |       |       |
| Nulliparous                      | 397|       |       |       |       |       |       |
| Multiparous                      | 606| 0.03 (−0.14, 0.20) | 0.05 (−0.14, 0.23) | **0.37 (0.05, 0.69)** | 0.13 (−0.08, 0.34) | **−0.46 (−0.75, −0.18)** | 0.17 (−0.02, 0.36) |
| **Sampling season**              |    |       |       |       |       |       |       |
| Spring                           | 255| **−0.30 (−0.48, −0.11)** | **−0.87 (−1.08, −0.67)** | 0.14 (−0.21, 0.50) | −0.05 (−0.28, 0.18) | **0.60 (0.28, 0.91)** | 0.06 (−0.15, 0.27) |
| Summer                           | 75 | **−0.28 (−0.57, 0.01)** | **−0.69 (−1.01, −0.36)** | 0.33 (−0.04, 0.69) | −0.73 (−1.22, −0.23) | 0.10 (−0.23, 0.43) |       |
| Fall                             | 232| 0.00 (−0.20, 0.20) | **−0.46 (−0.68, −0.25)** | 0.24 (−0.14, 0.62) | **−0.37 (−0.62, −0.13)** | 0.41 (0.08, 0.75) | 0.10 (−0.12, 0.32) |
| Winter                           | 441|       |       |       |       |       |       |

HMW metabolite including MOP, MBzP, MEHP, MEOHP, MEHHP, and ΣDEHP. Bold font indicates p value < 0.05. Levels of biomarkers in the following groups: Maternal age 25–29 years, BMI 18.5–23.9 kg/m², annual household income ≥150,000 yuan, college degree or above, non-passive smoking, non-drinking bottled water, nulliparous, and winter (sampling season), were set as reference.
Fig. 1 Correlation between sampling season and phthalate metabolites.

### Spring vs winter

| Phthalate metabolites | $\beta$ (95% CI) | $P$ |
|-----------------------|------------------|-----|
| $\Sigma$DEHP         | 0.06(-0.15,0.27) | 0.587 |
| MEHHP                | 0.60(0.28,0.91)  | <0.001 |
| MEOHHP               | -0.05(-0.28,0.18)| 0.655 |
| MEHP                 | 0.14(-0.21,0.50) | 0.438 |
| MB$_B$P              | -0.87(-1.08,-0.67)| <0.001 |
| MOP                  | -0.30(-0.48,-0.11)| 0.002 |
| $\Sigma$LMW          | 0.76(0.58,0.94)  | <0.001 |
| MBP                  | 0.77(0.58,0.95)  | <0.001 |
| MIBP                 | 0.42(0.22,0.62)  | <0.001 |
| MEP                  | 0.50(0.25,0.75)  | <0.001 |
| MMP                  | -0.07(-0.43,0.30)| 0.718 |

### Summer vs winter

| Phthalate metabolites | $\beta$ (95% CI) | $P$ |
|-----------------------|------------------|-----|
| $\Sigma$DEHP         | 0.10(-0.23,0.43) | 0.558 |
| MEHHP                | -0.73(-1.22,-0.23)| 0.004 |
| MEOHHP               | 0.33(-0.04,0.69) | 0.078 |
| MEHP                 | -0.37(-0.93,0.20)| 0.203 |
| MB$_B$P              | -0.69(-1.01,-0.36)| <0.001 |
| MOP                  | -0.28(-0.57,0.01)| 0.061 |
| $\Sigma$LMW          | 1.78(1.50,2.07)  | <0.001 |
| MBP                  | 1.74(1.45,2.03)  | <0.001 |
| MIBP                 | 0.92(0.60,1.23)  | <0.001 |
| MEP                  | 1.37(0.98,1.77)  | <0.001 |
| MMP                  | 0.95(0.37,1.53)  | 0.001 |

### Fall vs winter

| Phthalate metabolites | $\beta$ (95% CI) | $P$ |
|-----------------------|------------------|-----|
| $\Sigma$DEHP         | 0.10(-0.12,0.32) | 0.384 |
| MEHHP                | 0.41(0.08,0.75)  | 0.014 |
| MEOHHP               | -0.37(-0.62,-0.13)| 0.003 |
| MEHP                 | 0.24(-0.14,0.62) | 0.215 |
| MB$_B$P              | -0.46(-0.68,-0.25)| <0.001 |
| MOP                  | 0(-0.20,0.20)    | 0.989 |
| $\Sigma$LMW          | 0.67(0.48,0.87)  | <0.001 |
| MBP                  | 0.66(0.46,0.85)  | <0.001 |
| MIBP                 | 0.53(0.32,0.74)  | <0.001 |
| MEP                  | 0.70(0.44,0.97)  | <0.001 |
| MMP                  | 0.93(0.54,1.32)  | <0.001 |
concentrations of the four LMW phthalates, MMP, MEP, MiBP, and MBP. (the relevant Spearman’s coefficients ranged between 0.534 and 0.855). On the contrary, the correlation between the three DEHP, MEHP, MEOHP, and MEHHP was observed to be weak (the relevant Spearman’s coefficients ranged between 0.228 and 0.444). The results of the mentioned analyses are listed in Table S3.

Discussion

In this study, the concentrations of nine phthalate metabolites were measured in the urine samples of 1003 Chinese pregnant women during their third trimester of pregnancy. The detectable rates of the various analytes were observed to range between 76 and 100%. MBP had the highest median concentration of 62.45 μg/L, followed by MiBP, 24.61 μg/L; MEP, 8.64 μg/L; MEHHP, 7.63 μg/L; MEHP, 6.78 μg/L; MEOHP, 6.31 μg/L; MMP, 1.63 μg/L; MOP, 0.13 μg/L; and MBZP, 0.04 μg/L. We identified several sociocultural characteristics that were associated with nine phthalate metabolites concentrations, with sampling season being the most influential. Besides, maternal age, BMI, passive smoking, income, and parity were also significantly associated with some phthalate metabolites concentrations in this study population.

The high detection frequency of phthalate metabolites in this investigation confirmed our suspicion that pregnant women were frequently exposed to phthalates. Compared with three published studies in China, the phthalate exposure pattern in our study is similar to theirs, with the geometric mean concentration of MBP being the highest and MBZP being the lowest in urine samples (Gao et al. 2017b; He et al. 2019; Li et al., 2019a), except for MBP, which was significantly higher than their results and there was little difference between the levels of other phthalate metabolites (MEP, MBZP, MEHP, MEHHP, and MEOHP). The population’s relatively high MBP levels indicate that more attention should be directed to economically underdeveloped areas. However, the characteristics of other published international studies were different from ours (Figure S8). There is a lack of MMP and MOP data, according to the comparison results. The concentration of MBP is two to six times higher than that measured in studies conducted in South Korea, Thailand (Lee et al. 2020b), and the European and American countries (Casas et al. 2011; Tefre De Renzy-Martin et al. 2014; Cantonwine et al. 2014; Arbuckle et al. 2014). China is the largest producer of DBP, with an annual production of more than 60,000 tons in 2004 (Guo et al. 2011). Because of the high production and widespread use of DBP in China, human exposure to this compound may be higher than in other countries. In contrast, the median concentration of MBZP determined in our survey was significantly lower than that measured in other regions (Suzuki et al. 2010; Lin et al. 2011; Casas et al. 2011; Tefre De Renzy-Martin et al. 2014; Cantonwine et al. 2014; Arbuckle et al. 2014; Lee et al. 2020a). There is limited evidence that MBZP exposure in China is mainly associated with exposure to cereal, seafood, and cooking oil (Wang et al. 2018a). Therefore, the low level of MBZP exposure obtained here could be related to the dietary structure and sources of our study participants. Remarkably, the herein-measured median concentration of MEP is similar to that reported for the rest of the Asian region, but it is significantly lower than that reported in studies conducted in the European and American regions. In particular, MEP concentrations up to 324 μg/L have been measured in Spain (Casas et al. 2011) and up to 99.2 μg/L in the USA (Cantonwine et al. 2014), which are 11 to 36 times as large as the median concentration measured for the said metabolite in our survey. These striking differences may be related to the more extensive use that women in European and American countries make of. Indeed, these products contain as a component diethyl phthalate (DEP), which is the parent compound of MEP, resulting in their higher MEP levels. Besides, because the samples of the two studies were obtained between 2004 and 2008 and 2010 and 2012, respectively, the high MEP exposure could be due to the lack of public and government awareness of phthalate pollution and toxicity. Furthermore, comparisons should be made with caution since differences between studies (such as study design, sample collection time, different methods of urine dilution adjustment, and population consumption habits) may affect the comparison data. In addition, domestic and global regulatory actions on phthalate metabolites may also cause result variations.

Consistent with previous study (Arbuckle et al. 2014), maternal age was positive correlation with the levels of MEHHP was observed in our study, but other studies have found the opposite relationship (Wenzel et al. 2018). In addition, we found that participants with BMI ≥24 kg/m² had higher levels of MEP, MEHP, ΣLMW, and ΣDEHP in urine samples; the existence of this phenomenon is also supported by previous research data (Hatch et al. 2008; Yaghjyan et al. 2015). The compelling reason for this trend may be that phthalates exhibit a degree of lipophilicity, so they can be stored in the adipose tissue; therefore, people with higher BMI may exhibit higher concentrations of urinary phthalate metabolites (Philips et al. 2017). In addition, foods are an important source of phthalate metabolites exposure (Duala et al. 2020); indeed, study participants with high BMI values tend to have higher food intake than those with low BMI values, which may account for the observed difference in exposure to phthalate metabolites. Compared with their high-annual-income peers, lower-annual-income participants exhibit lower urine levels of MiBP, MBP, MOP,
MBzP, MEHP, and ΣDEHP, a result that is inconsistent with those reported in previously published studies (Wenzel et al. 2018; Wang et al. 2018b). People with lower incomes may be less exposed to cosmetics and food packaging products, which may contribute to the mentioned observation. Multiparous women had lower concentrations of MEHHP than nulliparous women, as has been observed in previous studies that first pregnancies having the higher MEP concentrations (Arbuckle et al. 2014). Other research found that pregnant women who were nulliparous had higher urinary concentrations of almost all phthalate metabolites (Zhu et al. 2016). Related reason was not well understood. Zhu et al. believe that the removal of placenta after delivery can reduce the biological accumulation of chemicals may be one possible explanation (Zhu et al. 2016).

The results of previously published studies indicated that the distribution of some phthalate metabolites in the environment exhibits seasonal characteristics (Chen et al. 2018; Zhang et al. 2019). Indeed, higher levels of the LMW phthalate metabolites (i.e., MMP, MEP, MiBP, MBP, and ΣLMW) were measured in of our study in participants recruited during the summer. Similar results were obtained for pregnant women, young children, and general population in China (Liao et al. 2018b; Guo et al. 2020; Yang et al. 2021). The reasons for the observed seasonal effects on metabolite concentrations remain unclear. Research results indicate that LMW phthalate metabolites, such as DEP and DBP, are mainly used in cosmetics and PCPs, and use of these products will lead to high exposure to phthalate metabolites (Koniczki et al. 2011; Hsieh et al. 2019). During the summer, women may use PCPs like perfumes, shampoos, nail polish, and sunscreen more frequently than in other seasons, and phthalate metabolites absorbed by skin is more frequent, resulting in higher exposure to LMW phthalate metabolites during the summer. Moreover, the higher temperature in summer would cause an increase in the release of these phthalates due to their volatility (Chen et al. 2018; Zhang et al. 2019), resulting in the human body being exposed to increased amounts of phthalate metabolites. However, different phthalates are affected differently by the temperature (Kashyap and Agarwal 2018). These differences may in part explain the different exposure levels of different metabolites in different seasons, although there may be other reasons for them that we don’t yet understand. Further research in this field is thus necessary.

Our research has some limitations. First, a single urine sample was collected from each study participant for testing, so the measured phthalate metabolite content does not represent the average level during late pregnancy. Second, humans are exposed to phthalates from a variety of sources and pathways, and we only analyzed sociocultural characteristics and sampling season; by this approach, we may be missing other potentially important predictive variables, such as dietary and PCPs use habits. Considering, however, that our sample size is relatively large and the phthalate metabolites are examined according to the same standard, using the same instrumentation, and the same testing personnel, and the quality control of the data is reliable, we have reason to believe that our test data closely reflect the “real” situation of the study population.

Conclusions

The health of pregnant women and fetuses in Zunyi may be generally harmed by the high exposure of phthalate metabolites, especially by MBP. Also, phthalate metabolites present a demographic and seasonal differential distribution among the study population. Targeted measures to reduce phthalates exposure for high-risk pregnant women and high-exposure seasons may have potential benefits for the protection of maternal and fetal health.

Abbreviations DEHP: mono(2-ethylhexyl) phthalate; DBP: di-n-butyl phthalate; BMI: body mass index; GC-MS/MS: high-performance gas chromatography mass spectrometry; MMP: mono-methyl phthalate; MEP: mono-ethyl phthalate; MiBP: mono-isobutyl phthalate; MBP: mono-butyl phthalate; MBzP: mono-benzyl phthalate; MOP: mono-octyl phthalate; MBzP: mono-benzyl phthalate; MEHP: mono(2-ethylhexyl) phthalate; MEOP: mono(2-ethyl-5-oxohexyl) phthalate; MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate; LOD: the limit of detection; LMW: low-molecular-weight; ΣLMW: the total sum of low-molecular-weight phthalates (MMP, MEP, and MBP); ΣDEHP: the total sum of the three metabolites (MEHP, MEOP, and MEHHP); SD: standard deviation; UA: unadjusted; CA: creatinine-adjusted; DR: detectable rate; GM: geometric mean; HMW: high-molecular-weight; CI: confidence interval; PCPs: personal care products; DEP: diethyl phthalate

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Author contribution Juan Liao: formal analysis, investigation, validation, data curation, writing—original draft. derong fang: investigation, data curation. Yijun Liu: data curation, validation. Shimin Xiong: data curation, validation. Xia Wang: methodology, validation. Yingkuan Tian: methodology, validation. Haonan Zhang: methodology, validation. Songlin An: investigation, conceptualization. Caidie He: investigation, conceptualization. Wei Chen: investigation, conceptualization. Xiang Liu: investigation, conceptualization. Nian Wu: data curation, conceptualization. Kunming Tian: investigation, validation. Lingli Wang: investigation, validation. Ya Zhang: investigation, data curation. Hongyu Yuan: investigation, data curation. Li Zhang: investigation, data curation. Quan Li: project administration, investigation, validation, resources. Xubo Shen: Project administration, investigation, validation, resources. Yuanzhong Zhou: project administration, investigation, validation, resources, writing—review and editing, funding acquisition.

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Data availability Data associated with the present study can be accessed on request to the author (630140512@qq.com).

Declarations

Ethical Approval This study was ethically reviewed by the Affiliated Hospital of Zunyi Medical University (batch No.: KLL-2019-006).

Consent to participate All participants agreed to participate in this study and signed the informed consents.

Consent to publish The authors declare that this manuscript does not contain any individual person’s data and material in any form.

Competing interests The authors declare no competing interests.

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