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Association between urinary phthalate metabolites and renal function in late pregnant women

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Abstract

Evidence about associations of phthalates metabolites with increased serum uric acid (SUA) levels in pregnant women remains unknown. To address this, we conducted a cross-sectional population-based study including 851 pregnant women from Zunyi birth cohort in southwest China. Multiple linear regression models were used to explore single relationships between ten urinary phthalate metabolites with SUA and estimated glomerular filtration rate (eGFR). And then, the overall relationship of phthalate mixture with SUA and eGFR were determined by principal component analysis (PCA) and quantile g-computation (Q-g) analysis. The multivariable linear regression showed that mono-butyl phthalate (MBP), mono-octyl phthalate (MOP) and mono-benzyl phthalate (MBzP) were positively associated with SUA, while mono (2-ethylhexyl) phthalate (MEHP) and mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) were associated with increased eGFR level. Moreover, PCA analysis suggested that phthalate mixture was positively associated with SUA, and MOP, MBzP and MEHP appeared to be the major contributors. Furthermore, Q-g regression showed that each quantile increase in phthalate mixture was associated with 3.27% higher SUA (95% CI 0.21%, 6.41%). Our results imply that phthalate metabolites were associated with higher SUA in late pregnant women, and MBP, MBzP and MOP might be the major drivers. So, a health perinatal duration should be seriously taken to counteract the environment-related dysregulated kidney function.

Keywords Phthalates, Serum uric acid, Glomerular filtration rate, Pregnancy women

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Introduction

In recent years, phthalates, commonly used as plasticizers in personal care products, food packaging, and other consumer goods, have raised health concerns. The National Health and Nutrition Examination Survey (NHANES) of 2015–16 revealed that over 90% of women of childbearing age had detectable levels of at least one urine phthalate metabolite, highlighting widespread exposure [1]. These metabolites have also been found in various bodily secretions and excreta [2], prompting increased concern among pregnant women due to potential risks to fetal health. Epidemiological studies have linked pre-gestational and perinatal exposure to phthalates with adverse birth outcomes, underlining the threat they pose to maternal and infant well-being by disrupting essential biological functions [3–5].

Animal studies suggest that phthalates contribute to renal dysfunction by inducing oxidative stress and apoptosis, leading to renal fibrosis [6–8, 28]. Similarly, epidemiological research has identified potential negative impacts on renal function [9]. Kang et al. found positive associations between phthalate and urinary albumin creatinine among Korean female population [10]; Similarly, the positive relationships between phthalate metabolites and parameters of renal dysfunction: albumin creatinine ratio (ACR), β2-microglobulin (B2M), and N-acetyl-β-d-glucosaminidase (NAG) were also uncovered [11]. However, there has been no consistent results about the effect of phthalates on eGFR, which is the surest indicators for renal function. Some studies showed a positive correlation between eGFR and phthalates [12, 13], but others found their negative association [14, 15].

Given the altered glomerular hyperfiltration and profound physiological changes during pregnancy, pregnant women's renal function is expected to be greater susceptibility to phthalates exposure, especially for late pregnant women. Therefore, maintaining balanced renal function is important for the health of the mother and delivery. However, to our best knowledge, only two studies explored the influence of phthalate on the renal function of pregnant women: One study found that exposure to phthalate increased the level of microalbumin and NAG in the third trimester [16]; And another one reported that it is more likely to cause an increased renal injury indicators when pregnant women during the third trimester are exposed to both phthalates and melamine simultaneously [17]. Despite the recognition of microalbumin and NAG as early markers of renal injury, routine prenatal screenings seldom include these tests. Instead, serum uric acid (SUA) and serum creatinine levels, which are commonly measured during pregnancy, may offer alternative indicators of phthalate exposure effects for kidney injury. Considering that elevated SUA has been associated with an increased risk of renal dysfunction during pregnancy [19, 20], highlighting the need to identify potential influencing factors to safeguard maternal and fetal health.

Although some evidences have implied that phthalates exposure associates with increased SUA levels in the general population, whether this association also exists in pregnant women has yet been studied. This study, therefore, seeks to examine the relationship between urinary concentrations of phthalate metabolites and kidney function among late-stage pregnant women in the Zunyi birth cohort. Considering the high multicollinearity among phthalate metabolites, we employed Quantile-g computation (Q-g) to assess the potential adverse effects of chemical mixtures. Additionally, we conducted subgroup analyses to determine if lifestyle factors might influence the relationship between phthalate exposure, SUA, and eGFR, aiming to identify particularly susceptible populations. Our findings aim to enrich the understanding of how phthalate metabolites affect kidney function during pregnancy, providing crucial insights for future research and public health policies.

Methods

Study population

The Zunyi Birth Cohort study was carried out in four hospitals within the Zunyi region of Southwest China, including the First and Second Affiliated Hospitals of Zunyi Medical University, People's Hospital of Meitan County, and People's Hospital of Xishui County, starting from May 2020 and April 2022. The primary objective of this cohort is to assess the impact of environmental factors on pregnant women and their fetuses, with detailed methodologies previously described [21]. Women aged 18 to 45 years, experiencing a singleton pregnancy, were initially recruited. After excluding individuals lacking comprehensive data on uric acid, creatinine, phthalate metabolites, covariates, and chronic kidney disease, 851 participants were selected for further analysis, as shown in flowchart (Additional file 1: Figure S1). All participants provided informed consent, with the study receiving ethical approval from Zunyi Medical University (Ethics Approval No. KLL-2019-006).

Measurement of phthalate metabolites

High-performance gas chromatography mass spectrometry (GC-MS/MS, Agilent 7010b, Santa Clara, CA, USA) was used to quantify ten urinary phthalate metabolites in samples, stored at − 80 °C until analysis, from 851 participants. These included 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), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP). Detailed quality control and procedure has been listed in a prior publication [21]. We presented the retention time, ion pairs, collision energy, recovery rate, precision, determination coefficient, and detection limit in Additional file 1: Table S2.

Renal function measurements

Maternal renal function was evaluated by detecting SUA and creatinine concentrations. Because the most of those participants' age were less than 40, we estimated the eGFR by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 40) (Björk et al., 2020): eGFR $= 144 \times (0.993)^{Age} \times (Scr/62)^{-0.320}$, if the Scr is less than 62 mol/L; eGFR $= 144 \times (0.993)^{Age} \times (Scr/62)^{-1.209}$, if the Scr is greater than 62 mol/L. Scr represents the measured serum creatinine, and MA means age at the time of blood sample collection. The unit of eGFR is showed in ml/min/1.73 m^2. Well-trained technicians utilized full-automatic biochemical analyzer (BECKMAN-AU5800) to test serum creatinine and uric acid, and used a fully automatic urine analysis workstation to test urine creatinine (URIT-1600).

Covariates

Based on the published literature and the possible biological mechanism, we included the following covariates: Maternal age, pregestational body mass index (BMI), maternal educational level, parity, household income, seasons for sample collection, urine creatinine, and gestational age; Regular physical exercise was defined as exercising at least once a week for more than 30 min; exposure to smoking is defined as passive smoking for at least half an hour, ethnicity, the diagnosis of gestational diabetes, and gestational hypertension were obtained from the electronic medical records.

Statistical analysis

Continuous data with normal and skewed distribution were described as means ± SD and medians (interquartile range) (IQR), respectively, and categorical variables were described as frequency (percentage). Urinary phthalate metabolites and SUA with skewed distribution were natural ln-transformed. Phthalate metabolites concentrations below the limit of detection (LOD) were assigned the value of LOD/$\sqrt{2}$. Given the link between eGFR and creatinine, we included urine creatinine instead of the adjustment of specific gravity of urine in models for reducing collider problem [14, 23]. Spearman correlation coefficients among ten phthalate metabolites were counted and visualized in heat map by using the "ggcorrplot" and "corrplot" R package.

Multivariable linear regression model was conducted to estimate the association of each urinary phthalate metabolite with SUA and eGFR. The percent changes of SUA were calculated by applying a back transformation of $\{100 \times [\exp(\beta)\text{-}1]\}$ to the corresponding regression coefficients. Trend analysis was calculated by taking the median phthalate metabolites of each quartile into multivariable linear regression model. In addition, the overall associations of phthalate mixture with SUA and eGFR were estimated by Q-g and principal component analysis (PCA). The results of Q-g were interpreted as the changes of parameters of kidney function with per increment of quantile of phthalate mixture level. This method can effectively control the multi-collinearity and simultaneously identify the major contributor, and estimate the overall association [24, 25]. In PCA, varimax rotation was used to divide them into factor 1–3, and identified the main components of ten chemicals. The chemicals accounting for more than 70% of the total variance of each factor were retained [14], then multiple linear regressions were used to identify the relationship of each factor with renal function. Stratified analyses were applied to examine whether any factors such as education level, gestational hypertension, regular physical exercise, and exposure to smoking atmosphere could modify the associations of phthalates with SUA levels. A two-sided p-value < 0.05 was regarded statistically significant. Statistical analyses were conducted by SPSS version 25.0 (IBM Corp. Armonk, NY, USA) or R software (version 4.2.2).

Results

Characteristics of study population and urinary chemicals

Sociodemographic characteristics of the enrolled 851 women are summarized in Table 1. The mean of maternal age was 27.22 ± 4.99, their pre-pregnancy BMI was 22.52 ± 3.56 kg/m^2, and 73.0% of pregnant women were multiparous. 47.5% of pregnant women participated in this study during winter and 3.6% participated during summer. The prevalence rates of pregnancy hypertension and pregnancy diabetes were 12.7% and 21.3% (Table 1).

The distributions of ten urinary phthalate metabolites concentrations were shown in Table 2. MECPP had the highest median concentration with the value of 71.14 μg/L. Besides, the median concentration of MBzP was the lowest with the value of 0.06 μg/L. Besides, a

Table 1 Characteristics of study subjects ($N=851$) in the study

Characteristics	N	Mean ± SD or percent (%)
Age (years)		27.22 ± 4.99
BMI (kg/m^2)		22.5 ± 3.6
Annual household income (Yuan)		
< 100000	71	8.3
100000–150000	550	64.6
≥ 150000	220	25.9
Unknow	10	1.2
Education		
Middle school or below	482	56.6
High school and middle special school	260	30.6
College degree or above	109	12.8
Exposure to smoking status		
< = 2 day/week	38	4.5
3-5 day/week	57	6.7
6-7 day/week	756	88.8
Han nationality		
Yes	835	98.1
Gestational diabetes mellitus		
Yes	181	21.3
Gestational hypertension		
Yes	108	12.7
physical activity during pregnancy		
Yes	112	13.2
Sample collection season		
Spring	249	29.3
Summer	31	3.6
Fall	167	19.6
Winter	404	47.5
Parity		
Nulliparous	230	27.0
Multiparous	621	73.0
Skin care products		
Daily use	652	76.6
Not daily use	199	23.4
Cosmetics		
Daily use	754	88.6
Not daily use	97	11.4
Urinary creatinine, mg dL^{-1} median (IQR)		5.87(3.15, 11.50)
Estimated glomerular filtration rate, ml/min/1.73 m2 1.73 m^{-2}		132.87 ± 8.85
Serum uric acid, mg dL^{-1} median (IQR)		283.00 (243, 329.0)
hyperuricemia	81	9.5
Abnormal serum creatinine	1	0.1

BMI body mass index, *SD* standard deviation, *IQR* interquartile range

positive correlation between the majority of phthalate metabolites was found with correlation coefficient ranged from 0.01 to 0.8 (Fig. 1).

The association between individual phthalate metabolites and SUA

Table 3 displayed the association of urinary phthalate metabolites with SUA after adjusting for covariates. A onefold increase in MBP, MOP, and MBZP concentrations were associated with increments of 1.51% (95% CI 0.10, 3.05), 1.92% (95% CI 0.50, 3.25), and 1.41% (95% CI 0.20, 2.74) in SUA, respectively. Moreover, there was a positive trend of MBZP and MOP with SUA (P-trend < 0.05). In addition, MEHP and MEHHP, but not other phthalate metabolites, showed the positive associations with eGFR (Table 4).

Q-g computation and PCA analysis

As shown in Fig. 2, of Q-g regression displayed that with each quartile increase of phthalate mixture, the mean estimated changes in SUA and eGFR were 3.27% (95% CI 0.21%, 6.41%) and 0.0870 (95% CI − 0.8823, 1.0563), respectively. We found that MBP, MBZP, MOP, MEHHP, and MIBP (all weights > 10%) were the dominant phthalate metabolites for the positive association with SUA, while MEP, MEHP and MEOHP (all weights > 10%) mainly contributed to negative associations with SUA (Fig. 2A). No significant association was found between phthalate mixture with eGFR (Fig. 2B).

The details of varimax-rotated factor loadings were displayed in Additional file 1: Table S1. MMP, MEP, MIPB and MBP were highly loaded in factor 1. MEHP, MOP and MBZP were highly loaded in factor 2, and MEOP, MEHHP and MECPP were highly loaded in factor 3. Both the multiple-factor and single factor model consistently indicated factor 2 was significantly positively associated with SUA. However, no any statistical significance between eGFR and these factors was presented (Table 5).

Subgroup analyses

The results of subgroup analysis of phthalate metabolites and SUA are presented in Table 6. For pregnant women without regular exercise, onefold increase in MOP and MBzP were associated with 2.43% and 1.71% increase of SUA; for pregnant women who are exposed to smoking for ≥ 6 days per week, onefold increase in MBP and MOP were associated with 1.82% and 2.12% increase of SUA. The results of subgroup analysis of phthalate metabolites and eGFR presented in Additional file 1: Table S3.

Sensitivity analysis

We performed a sensitivity analysis by excluding pregnant women with hyperuricemia and abnormal blood creatinine levels, and the associations of MBP, MOP, and MBZP with SUA (Additional file 1: Table S4) and the association of MEHP with eGFR were still robust (Additional file 1: Table S5).

Table 2 Distribution of urinary phthalate metabolite concentrations among pregnant women (*N* = 851)

Phthalate metabolites	Detection rate (%)	GM	Selected percentiles			
Analyte (μg/L)			25th	50th	75th	95th
MMP	78.03%	0.75	0.1577	1.2842	3.1448	15.7018
MEP	99.06%	7.63	3.7655	7.8416	16.9680	55.5253
MIBP	99.88%	21.85	12.2864	21.0838	40.1828	112.6000
MBP	100.00%	53.91	26.9886	52.2072	102.0250	220.8104
MEHP	93.65%	9.10	2.3564	8.7840	61.1521	352.0550
MOP	78.61%	0.18	0.0767	0.1691	0.3434	0.7074
MBzP	61.69%	0.09	0.0286	0.0664	0.2138	0.9942
MEOHP	81.79%	5.42	1.8640	5.8229	12.9289	52.4802
MEHHP	95.89%	5.26	3.2443	6.9182	13.7948	40.1024
MECPP	71.80%	100.46	16.5728	71.1382	267.8368	3828.0591

GM geometric mean, *MMP* mono-methyl phthalate, *MEP* mono-ethyl phthalate, *MIBP* mono-iso-butyl phthalate, *MBP* monobutyl phthalate, *MEHP* mono-ethylhexyl phthalate, *MOP* mono-n-octyl phthalate, *MBzP* mono-benzyl phthalate, *MEOHP* mono-(2-ethyl-5-oxo-hexyl) phthalate, *MEHHP* mono-(2-ethyl-5-hydroxyhexyl) phthalate, *MECPP* mono-(2-ethyl-5-carboxypentyl) phthalate

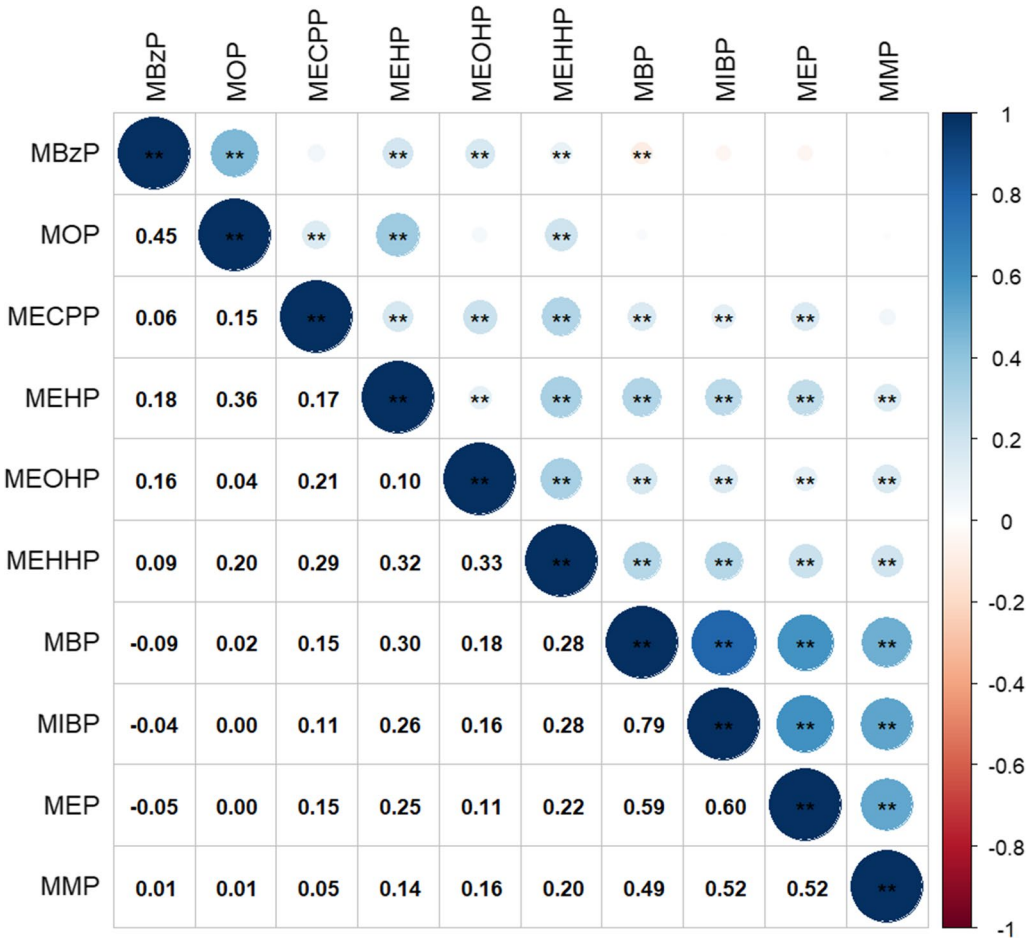

Fig. 1 Spearmon correlation coefficients matrix for the phthalate metabolites concentrations visualized as heatmap. **P* < 0.05; ***P* < 0.01; ****P* < 0.001

Table 3 Association of urinary phthalate metabolites with UA in pregnant women (N = 851)

Phthalate metabolites	% Change (95% CI) by continuous PAEs	Relative change (95% CI) by quartile of PAEs				*P* trend
		Q1	Q2	Q3	Q4	
MMP	0.10(− 0.60, 0.80)	ref	− 1.29(− 5.45, 2.94)	0.50(− 3.63, 4.92)	0.60(− 3.54, 4.92)	0.662
MEP	− 0.20(− 1.29, 1.01)	ref	2.12(− 2.08, 6.50)	0.40(− 3.73, 4.81)	0.03(− 4.21, 4.39)	0.860
MIBP	1.11(− 0.40, 2.63)	ref	2.94(− 1.29, 7.25)	2.74(− 1.49, 7.27)	3.46(− 0.90, 7.90)	0.144
MBP	**1.51(0.10, 3.05)**	ref	3.67(− 0.60, 8.11)	2.63(− 1.59, 7.14)	**4.92(0.40, 9.53)**	0.053
MEHP	0.10(− 0.50, 0.70)	ref	− 2.37(− 6.39, 1.71)	− 0.30(− 4.40, 3.98)	0.04(− 4.11, 4.39)	0.739
MOP	**1.92(0.50, 3.25)**	ref	3.98(− 0.20, 8.44)	2.84(− 1.39, 7.25)	**5.76(1.41, 10.41)**	**0.018**
MBZP	**1.41(0.20, 2.74)**	ref	2.22(− 2.76, 7.36)	**4.50(0.50, 8.65)**	**4.39(0.30, 8.65)**	**0.025**
MEOHP	− 0.10(− 1.19, 1.01)	ref	0.81(− 3.34, 5.13)	− 0.60(− 4.69, 3.67)	0.40(− 3.73, 4.81)	0.974
MEHHP	0.10(− 0.80, 0.90)	ref	2.33(− 1.88, 6.72)	3.87(− 0.40, 8.22)	2.84(− 1.39, 7.25)	0.135
MECPP	0.30(− 0.50, 1.11)	ref	0.10(− 4.11, 4.50)	1.71(− 2.37, 6.08)	1.51(− 2.66, 5.87)	0.404

The bold to highlight the statistically significant *P* values

Adjusting maternal age at deliver, BMI, annual household income, education, exposure to smoking, parity, nationality, gestational diabetes mellitus, gestational hypertension, physical exercise during pregnancy, gestational week at the time of Uric Acid measurement, sample collection season

Table 4 Association of urinary phthalate metabolites with eGFR in the pregnant women (N = 851)

Phthalate metabolites	Exp (β) (95% CI)	Exp (β) (95% CI) by quartile of PAEs				*P* trend
		Q1	Q2	Q3	Q4	
MMP	0.031(− 0.203, 0.265)	ref	0.177(− 0.944, 1.298)	− 0.495(− 1.595, 0.605)	0.394(− 0.717, 1.505)	0.855
MEP	0.312(− 0.069, 0.692)	ref	− 0.133(− 1.227, 0.962)	0.104(− 0.999, 1.207)	0.829(− 0.282, 1.939)	0.072
MIBP	0.160(− 0.346, 0.666)	ref	− 0.603(− 1.707, 0.501)	0.909(− 0.196, 2.015)	− 0.047(− 1.165, 1.070)	0.526
MBP	0.054(− 0.432, 0.539)	ref	0.521(− 0.578, 1.620)	− 0.116(− 1.220, 0.988)	− 0.143(− 1.282, 0.996)	0.965
MEHP	**0.278(0.075, 0.481)**	ref	− 0.314(− 1.412, 0.785)	0.401(− 0.700, 1.501)	0.917(− 0.207, 2.042)	**0.027**
MOP	− 0.249(− 0.708, 0.211)	ref	− 0.117(− 1.227, 0.993)	0.148(− 0.951, 1.248)	− 0.487(− 1.615, 0.642)	0.381
MBZP	− 0.105(− 0.526, 0.316)	ref	0.316(− 1.156, 1.789)	− 0.091(− 1.195, 1.013)	− 0.073(− 1.202, 1.056)	0.881
MEOHP	− 0.175(− 0.544, 0.194)	ref	− 1.055(− 2.167, 0.056)	1.046(− 0.056, 2.147)	− 0.869(− 2.003, 0.266)	0.237
MEHHP	**0.306(0.015, 0.596)**	ref	0.327(− 0.789, 1.443)	0.136(− 0.970, 1.242)	0.191(− 0.927, 1.308)	0.385
MECPP	− 0.042(− 0.324, 0.240)	ref	0.180(− 0.980, 1.340)	0.256(− 0.850, 1.361)	− 0.203(− 1.320, 0.913)	0.959

The bold to highlight the statistically significant *P* values. Adjusting age, BMI, annual household income, education, exposure to smoking, parity, nationality, gestational diabetes mellitus, gestational hypertension, regular physical exercise during pregnancy, gestational week at the time of eGFR measurement, sample collection season

Discussion

Our findings reveal significant associations between increased SUA levels and higher concentrations of mono-butyl phthalate (MBP), mono-octyl phthalate (MOP), and mono-benzyl phthalate (MBzP) in third-trimester pregnant women. Both PCA and Q-g regression underscore the positive correlation of mixed phthalate metabolites with SUA, highlighting MBP, MBzP, and MOP as primary contributors. This evidence supports the hypothesis that phthalate metabolites may adversely affect kidney function. Notably, the detectable rates of ten phthalate metabolites in our cohort ranged from 61.7 to 100%, indicating widespread exposure among pregnant women in Southwest China and underling the need for further research to evaluate its safety implications for perinatal health.

To date, limited research has focused on the impact of phthalates on renal function in pregnant women. Our study aligns with two prior epidemiological investigations identifying phthalates as nephrotoxic agents during pregnancy. One cohort study linked urine phthalate levels with increased ACR and NAG among late-stage pregnant women in Taiwan [16]. Another study observed elevated levels of NAG and ACR due to combined exposure to phthalates and melamine, compared to exposure to either agent alone [17]. Urinary NAG is a sensitive marker of renal tubular injury [32], and the definition of microalbuminuria is urine ACR higher than 3.5 mg/mmol. While urinary NAG is a recognized marker for renal tubular injury, routine prenatal screenings seldom include NAG and microalbumin tests. Instead, SUA and

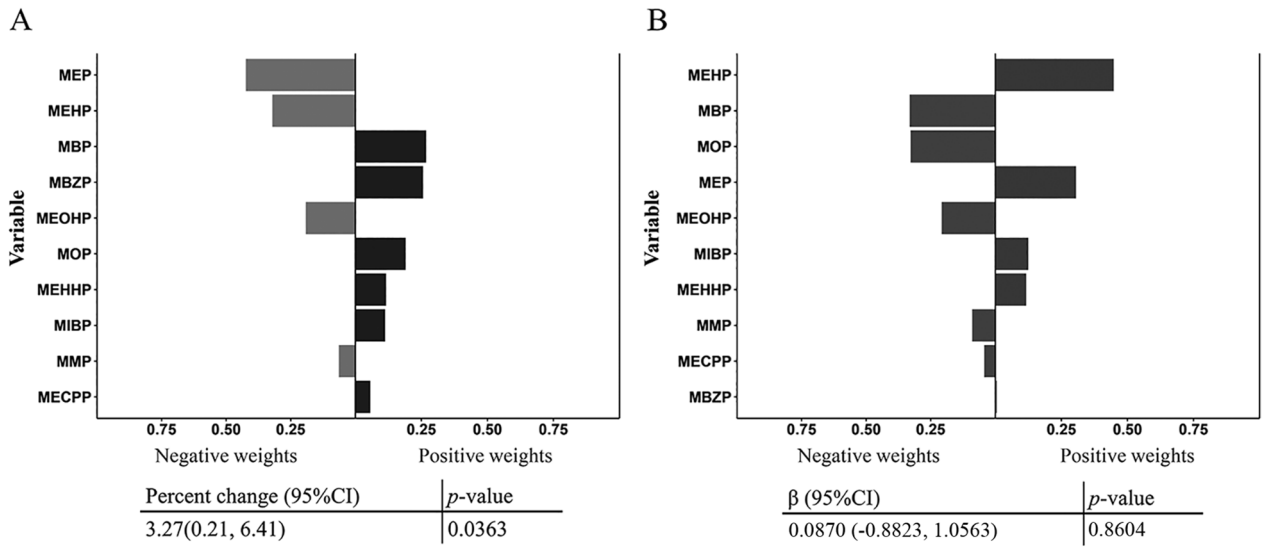

Fig. 2 Estimates the effects of one-quartile increase of phthalate metabolites mixtures in UA (A) and eGFR (B) and scaled weights corresponding to the proportion of the effect for each chemical in Quantile g-computation. Models adjusted for age, BMI, annual household income, education, exposure to smoking, parity, nationality, gestational diabetes mellitus, gestational hypertension, regular physical exercise during pregnancy, sample collection season, gestational week at the time of Uric Acid measurement

Table 5 Associations of PAEs scores with UA and eGFR in the pregnant women principal component analysis

			Single-factor		Multiple-factor	
			β (95% CI)	*P* value	β (95% CI)	*P* value
Total (*n* = 851)	Ln-UA[a]	Factor1	0.008(− 0.007, 0.023)	0.277	0.006(− 0.009, 0.021)	0.452
		Factor2	0.018(0.003, 0.033)	0.020	0.018(0.003, 0.034)	0.018
		Factor3	− 0.002(− 0.017, 0.013)	0.754	− 0.001(− 0.016, 0.013)	0.862
	eGFR[b]	Factor1	0.276(− 0.320, 0.872)	0.363	0.291(− 0.198, 0.780)	0.243
		Factor2	− 0.231(− 0.827, 0.364)	0.445	− 0.011(− 0.503, 0.482)	0.966
		Factor3	0.024(− 0.572, 0.620)	0.937	0.066(− 0.412, 0.544)	0.788

Factor 1 is highly loaded with MMP, MEP, MIBP and MBP. Factor 2 is highly loaded with MEHP, MOP and MBzP. Factor 3 is highly loaded with MEOHP, MEHHP and MECPP

[a] Adjusted for age, BMI, annual household income, education, exposure to smoking, parity, nationality, gestational diabetes mellitus, gestational hypertension, regular physical exercise during pregnancy, sample collection season, gestational week at the time of Uric Acid measurement

[b] Adjusted for age, BMI, annual household income, education, exposure to smoking, parity, nationality, gestational diabetes mellitus, gestational hypertension, regular physical exercise during pregnancy, sample collection season, gestational week at the time of eGFR measurement

serum creatinine, which are regularly measured, offer an alternative means to detect potential kidney injury earlier.

Previous studies suggest that more than 70% of urate excretion occurs via the kidneys, with insufficient uric acid salt excretion being a primary cause of hyperuricemia [33]. Previous studies speculated that phthalate metabolites affect the excrete of SUA by decreasing eGFR or interfering organic anion transporters of the proximal tubular epithelial cell membrane [27]. Our results suggest that phthalates may elevate SUA levels by diminishing eGFR or disrupting organic anion transport across proximal tubular epithelial cell membranes. Notably, MEHP and MEHHP showed positive correlations with eGFR, without a clear negative association with other metabolites.

Comparatively, research on a general American adult population found positive correlations between MECPP, MEHHP, MBzP, and MiBP with SUA levels [27]. Our study corroborates these findings for MBzP and introduces moderate associations with MBP and MOP. Given that evidence from Western populations has limited applicability for exploring the association between phthalate metabolites and SUA levels among Chinese individuals. And, the southwestern region of China is an economically underdeveloped region with

Table 6 Stratified regression analysis of the association of MBP, MOP and MBzP with serum uric acid (n = 851)

Categorical variables	N	MBP			MOP			MBZP		
		% change (95% CI)	*P* value	*P* int	% change (95% CI)	*P* value	*P* int	% change (95% CI)	*P* value	*P* int
Education level										
Middle school or below	482	1.21(− 0.70,3.15)	0.232	0.752	1.51(− 0.30,3.36)	0.100	0.505	0.80(− 0.90,2.43)	0.353	0.551
High school or greater	369	1.51(− 0.70,3.77)	0.179		2.33(0.20,4.50)	0.031		2.12(0.10,4.08)	0.037	
Gestational hypertension										
Yes	108	0.10(− 3.73,4.19)	0.941	0.906	− 2.86(− 7.32,1.82)	0.219	0.021	0.30(− 3.54,4.19)	0.886	0.398
No	743	1.51(− 0.10, 3.15)	0.060		2.43(0.90,3.87)	0.001		1.61(0.20,2.94)	0.021	
Regular physical exercise										
Yes	112	1.31(− 2.76,5.65)	0.533	0.618	− 0.50(− 3.82,3.05)	0.791	0.080	0.50(− 2.66,3.67)	0.776	0.485
No	739	1.31(− 0.30,2.84)	0.115		2.43(0.90,3.98)	0.001		1.71(0.30,3.05)	0.015	
Exposure to smoking atmosphere										
< 6 day/week	95	0.10(− 5.35,5.55)	0.989	0.342	0.50(− 4.02,5.34)	0.822	0.582	2.63(− 1.49,6.93)	0.211	0.442
≥ 6 day/week	756	1.82(0.30,3.36)	0.022		2.12(0.60,3.56)	0.005		1.11(− 0.20,2.43)	0.099	

Adjusting maternal age at deliver, BMI, annual household income, education (not in education-stratified analysis), exposure to smoking (not in exposure to smoking-stratified analysis), parity, nationality, gestational diabetes mellitus, gestational hypertension (not in gestational hypertension-stratified analysis), physical exercise during pregnancy (not in physical exercise-stratified analysis), gestational week at the time of Uric Acid measurement, sample collection season

P-int, *P*-interaction

weak supervision over the use of plasticizers in pregnant women's specialized products. This variation emphasizes the unique environmental and regulatory landscape in Southwest China, necessitating region-specific studies to inform local public health policies. The present study, based on pregnant women in southwest China, reflected that phthalate metabolites were associated with higher SUA. However, the causal relationships between phthalates metabolites and SUA levels are still needed to be clarified by prospectively designed and multicenter studies with larger sample sizes. This study may provide reference for the future development of standards for pregnant women's products in southwest China.

While exploring the relationship between phthalates and eGFR has yielded mixed results, our analysis indicates a discernible, and positive association between certain metabolites and eGFR. The significance of eGFR as a renal function marker, especially considering physiological changes during pregnancy such as glomerular hyperfiltration, merits cautious interpretation of these findings. As MEHP was positively correlated with higher eGFR in a research of 9989 people in the United States [12]; Another study of 538 American adolescents aged 0–17 showed a positive association between low molecular weight phthalates and eGFR [13]. More evidences also observed their negative correlation [14, 15]. In our study, although mixed effects analysis (Q-g and PCA) showed no obviously significant relationship between phthalate metabolites and eGFR, but univariate analysis displayed a positive association of MEHP and MEHHP with eGFR. Thus, the impact of phthalate on eGFR cannot be ignored. In addition, for the general population, eGFR is thought as the most useful marker to reflect the renal function [34]. However, the glomerular hyperfiltration is considered to be the hallmark for the profound physiological change during pregnancy peroid. Since renal vasodilation increases renal plasma flow which further leads to a greater than 50% rise in glomerular filtration rate during pregnancy [35, 36]. Previous studies have found that the optimal range of eGFR in the second trimester is 120–150 ml/min/1.73 m^2. It should be noteworthy that the prevalence of premature delivery and low birth weight infants was significantly higher in pregnant women with an eGFR higher than 150 ml/min/1.73 m^2 [37]. Therefore, the positive correlation between MEHP, MEHHP and eGFR should not be directly interpreted as a potential protective effector.

The health benefits of physical exercises are widely known and recognized. There are a lot of evidence that physical exercise improves the health of pregnant women [38, 39]. In addition, our study highlights lifestyle factors, such as physical activity and exposure to smoke, that may influence the relationship between phthalate exposure and SUA levels. This underscores the importance of addressing modifiable lifestyle factors to mitigate potential health risks. This may be due to the higher renal blood flow of people who exercise regularly [40]. Previous studies on this population showed that the urine concentration of phthalate metabolites in passive smokers was significantly higher [21]. Whether passive smoking and phthalates jointly cause the increased uric acid in pregnant women deserves further studies. These results may indicate that future efforts should be made to improve the unhealthy lifestyles of pregnant women.

This investigation, while robust, is not without limitations. Firstly, its cross-sectional nature precludes causal inferences between phthalate exposure and SUA levels. Additionally, the reliance on single urine samples may not fully capture variations in phthalate exposure. Nevertheless, to our certain knowledge, considering our study population has relatively regular lifestyle habits and a stable living environment, we may think that phthalate exposure levels are relatively steady. Thirdly, previous researches have exhibited that purine rich dietary habit has a substantial effect on serum uric acid levels [41]. However, we failed to conduct a complete diet questionnaire in this study. Notably, considering uric acid is not the specific biomarkers of renal function, the positive association between phthalate metabolites and SUA observed in this study couldn't entirely illustrate the significant relationship of phthalate metabolites with renal function. Besides, covariate-adjusted creatinine standardization, which controls for potential confounding by kidney function, was usually employed to adjust urine dilution. Unfortunately, in our population there is no significant correlation between age, BMI, eGFR, and ln transformed urinary creatinine creativity concentration, leading to failure of modeling, so the covariate-adjusted standardization may not be applicable to our study. In addition, due to the limitations of cross-sectional study, the positive association between eGFR and MEHP, MEHHP found in this study might originate from the reverse causation, more prospective studies are needed.

Despite these constraints, our application of PCA and Q-g computation to analyze the data helps overcome issues related to collinearity and multiple comparisons, providing a clearer representation of real-world phthalate exposure scenarios. Besides, we firstly conducted the above association at pregnant women in southwestern region of China, contributing to fill this knowledge gap regarding phthalate exposure positively associated with dysregulated kidney function under the Southwest China human geography scenario. In summary, our study contributes significantly to the understanding of phthalate exposure's impact on kidney function among

pregnant women in Southwest China, filling a critical gap in the literature and laying the groundwork for future longitudinal and interventional research to elucidate causal relationships and develop targeted public health interventions.

Conclusion

In conclusion, our study establishes a clear association between elevated exposure to both individual and combined phthalate metabolites and increased SUA levels. This relationship underscores the potential adverse impact of phthalate exposure on renal health during pregnancy. To substantiate these findings and elucidate the underlying biological mechanisms by which phthalates influence SUA levels, future research should employ longitudinal study designs.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12302-024-00909-6.

Additional file 1: Figure S1. Flowchart. **Table S1.** Varimax-rotated factor loadings of phthalate metabolites in PCA. **Table S2.** Retention time, ion pair, collision energy, determination coefficient, recovery rate, and detection limit of each metabolite. **Table S3.** Stratified regression analysis of the association of MEHP and MEHHP with eGFR (n = 851). **Table S4.** Association of urinary phthalate metabolites with SUA in pregnant women without hyperuricemia and abnormal blood creatinine levels (N=770). **Table S5.** Association of urinary phthalate metabolites with eGFR in pregnant women without hyperuricemia and abnormal blood creatinine levels (N=770). **Table S6.** Association of urinary phthalate metabolites with SUA in pregnant women(N=851). **Table S7.** Association of urinary phthalate metabolites with eGFR in the pregnant women(N=851). **Table S8.** Association of urinary phthalate metabolites with SUA in pregnant women (N=851). **Table S9.** Association of urinary phthalate metabolites with SUA in pregnant women (N=851). **Table S10.** Association of urinary phthalate metabolites with UA in pregnant women (N=851). **Table S11.** Association of urinary phthalate metabolites with eGFR in pregnant women (N=851). **Table S12.** Association of urinary phthalate metabolites with eGFR in pregnant women (N=851). Excluded MIBP. **Table S13.** Association of urinary phthalate metabolites with UA in pregnant women (N=851). Excluded MBP.

Author contributions

Author contributions statement Qifu Hong, Tao Pu (first author): conceptualization, methodology, software, investigation, formal analysis, writing—original draft; Maojie Li: data curation, writing—original draft; Zhongbao Chen: visualization; Rong Zeng: resources; Mingzhe Zhang: software; Lulu Dai: writing—review & editing; Songlin An: investigation; Xubo Shen: supervision; Xuejun Shang: Validation; Kunming Tian, Yuanzhong Zhou (corresponding author): conceptualization, funding acquisition, resources, supervision, writing—review & editing.

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Availability of data and materials

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author, [author initials], upon reasonable request.

Declarations

Ethics approval and consent to participate

After review by the Medical Ethics Committee of Zunyi Medical University, the qualifications and experience of the researchers in this project meet the experimental requirements, and the research plan meets the requirements of scientificity and relevant ethical principles. The research content does not pose potential risks to the subjects and does not constitute harm to them. The recruitment of subjects follows the principles of voluntary and informed consent, and the method of obtaining informed consent is appropriate, which can maximize the protection of subjects' rights and privacy. The degree of risk that subjects may face is appropriate compared to the expected benefits of the study. There is no conflict of interest between the research content and results. Agree that the research team will carry out relevant experiments according to the research plan of the National Key R&D Plan Task Book (2018YFC1004302) as planned.

Competing interests

The authors declare they have no conflict of interest in this paper.

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