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Predictors and long-term reproducibility of urinary phthalate metabolites in middle-aged men and women living in urban Shanghai

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Abstract

Phthalate esters are man-made chemicals commonly used as plasticizers and solvents, and humans may be exposed through ingestion, inhalation, and dermal absorption. Little is known about predictors of phthalate exposure, particularly in Asian countries. Because phthalates are rapidly metabolized and excreted from the body following exposure, it is important to evaluate whether phthalate metabolites measured at a single point in time can reliably rank exposures to phthalates

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over a period of time. We examined the concentrations and predictors of phthalate metabolite concentrations among 50 middle-aged women and 50 men from two Shanghai cohorts, enrolled in 1997-2000 and 2002-2006, respectively. We assessed the reproducibility of urinary concentrations of phthalate metabolites in three spot samples per participant taken several years apart (mean interval between first and third sample was 7.5 years [women] or 2.9 years [men]), using Spearman's rank correlation coefficients and intra-class correlation coefficients. We detected ten phthalate metabolites in at least 50% of individuals for two or more samples. Participant sex, age, menopausal status, education, income, body mass index, consumption of bottled water, recent intake of medication, and time of day of collection of the urine sample were associated with concentrations of certain phthalate metabolites. The reproducibility of an individual's urinary concentration of phthalate metabolites across several years was low, with all intra-class correlation coefficients and most Spearman rank correlation coefficients ≤ 0.3. Only mono(2-ethylhexyl) phthalate, a metabolite of di(2-ethylhexyl)phthalate, had a Spearman rank correlation coefficient ≥ 0.4 among men, suggesting moderate reproducibility. These findings suggest that a single spot urine sample is not sufficient to rank exposures to phthalates over several years in an adult urban Chinese population.

Keywords

Phthalates; reproducibility; predictors; food contaminants; personal care products

1. Introduction

Phthalate esters are man-made chemicals used as plasticizers and solvents in a variety of consumer products, and human exposure is widespread (Guo and others 2011; Silva and others 2004; Wittassek and others 2007). Sources of phthalate exposure may include contaminated food and drinking water, personal care products, building materials and indoor air, as well as certain medications and medical devices (Autian 1973; Duty and others 2005; Guo and Kannan 2011; Guo and others 2013; Guo and others 2012; Kelley and others 2012; Wormuth and others 2006). Moreover, sources and predictors of exposure may vary between populations and geographic areas, and few studies have examined predictors of exposure in Asian populations (Guo and others 2011).

The widespread exposure of humans to phthalates is of concern because adverse health effects have been reported in animal studies, including endocrine disruption (Wakui and others 2013) and reproductive and developmental toxicity (Ahmad and others 2013; Martino-Andrade and Chahoud 2010). Human epidemiologic studies have reported associations of phthalate exposure with asthma and allergic symptoms and with diabetes in adults (Kuo and others 2013; North and others 2014), as well as with altered neurodevelopment and genital development in children (Braun and others 2013; Miodovnik and others 2014).

Measurement of phthalates exposure in humans is complicated by the rapid metabolism and excretion of these compounds. For example, after 24 hours, 67% of an oral dose of di(2-ethylhexyl) phthalate (DEHP[1]) is excreted as five major metabolites in urine (Koch and others 2006). Previous studies have therefore typically quantified the urinary concentrations of monoester metabolites of phthalates to characterize recent exposure (Anderson and others 2001; Koch and Calafat 2009). In epidemiologic studies of diseases with long latency periods, including cancer, the relevant window of exposure may be many years prior to diagnosis. It is therefore important to know how well a single measurement of urinary phthalate metabolites may characterize typical exposures over time. Temporal variability in individual concentrations of urinary phthalate metabolites may be caused by changes in individual behaviors, such as dietary patterns or the use of personal care products, as well as by changes in the composition of commercial products, and consequently the presence of phthalates in indoor and outdoor environments.

Previous studies have evaluated the intra-individual variability of urinary phthalate metabolite measurements, but have generally used repeated samples taken over a relatively short period of time, i.e. days or weeks to months (Baird and others 2010; Frederiksen and others 2013; Hoppin and others 2002; Meeker and others 2012; Peck and others 2010; Preau and others 2010). One recent study reported intra-individual variability in urinary phthalate metabolites over a 1 to 3 year period among U.S. women enrolled in the Nurses' Health Study (Townsend and others 2013). Our study examines intra-individual variability among men and women over a longer period of time (approximately 2 to 8 years) in order to inform studies of possible environmental factors contributing to diseases with long latency periods. Moreover, most previous studies have been conducted in U.S. and European populations. If the sources of exposure to phthalates differ between geographic regions, the temporal variability in measured urinary concentrations of phthalate metabolites may also differ. The aim of the present study was to estimate the predictors of urinary phthalate metabolite concentrations and their intra-individual variability over several years in an adult urban Chinese population.

2. Materials and Methods

2.1 Study Population

The 100 participants in this study were residents of urban Shanghai and were enrolled in one of two population-based cohort studies: the Shanghai Women's Health Study (SWHS; N=74,942; enrollment 1997-2000) or the Shanghai Men's Health Study (SMHS; N=61,582; enrollment 2002-2006). Details of the recruitment and eligibility for the parent cohorts have been reported previously (Cai and others 2007; Zheng and others 2005). The SWHS recruited women aged 40-70 and the participation rate was 92.7% (Zheng and others 2005). The SMHS recruited men aged 40-74 and the participation rate was 74.1% (Cai and others 2007). From these two cohorts, 1,101 individuals were randomly selected and invited to participate in a physical activity substudy in 2005-2008 and 56% of those agreed (N=619) (Peters and others 2010). Among participants in the physical activity substudy, 50 male and

[1]Abbreviations: BMI, body mass index; BzBP, benzylbutyl phthalate; CI, confidence interval; DBP, dibutyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DEP, diethyl phthalate; DiBP, di-isobutyl phthalate;; HMWP, high molecular weight phthalate; ICC, intra-class correlation coefficient; LMWP, low molecular weight phthalate; LOD, limit of detection; MBP, mono-n-butyl phthalate; MiBP, mono-isobutyl phthalate; MEP, monoethyl phthalate; MBzP, monobenzyl phthalate; MCNP, mono(carboxynonyl) phthalate; MCOP, mono(carboxyoctyl) phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; NHANES, National Health and Nutrition Examination Survey; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.

50 female participants were randomly selected within strata of age and year of enrollment for urinary phthalate metabolite measurement in the present study. This study was approved by the Institutional Review Boards of the participating research institutions. The participation of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute human subjects research.

2.2 Questionnaires

At the time of enrollment in the SWHS, women completed a self-administered questionnaire that elicited information on their health history and demographic characteristics. The questionnaire was followed within 2-3 days by an in-person interview to collect additional information about smoking, physical activity and other lifestyle variables. Men enrolled in the SMHS participated in an in-person interview to collect similar information. Additionally, a brief interview was conducted with both men and women at the time of the first urine sample collection which elicited information on prescription medication use in the 24 hours prior to the collection. Weight was measured at enrollment and again between the second and third urine sample collections.

2.3 Urine Samples

Participants (88% of women and 89% of men) provided first urine samples at the time of initial enrollment in the parent cohort. A physical activity substudy was conducted within the parent cohorts in 2006-2007 and 86% of participants in the substudy provided two additional urine samples, for a total of three samples. The second urine sample was collected an average of 6.7 years (standard deviation [SD]: 0.7 years) after the first sample for women, and 2.2 years (SD: 0.3 years) for men. The third sample was collected approximately 9 months after the second sample for both sexes (SD: 1 month). Urine specimens were collected in sterilized polypropylene cups containing 125 mg of ascorbic acid. Samples were stored on ice until processed within 6 hours of collection, and were subsequently maintained at -70 to -80 °C.

2.4 Laboratory Analyses

From each of the three stored urine samples per participant, a 750 microliter aliquot was packed on dry ice and shipped overnight to the CDC in Atlanta, GA. Ten blinded, pooled quality control samples were also included along with the subject samples. Eleven phthalate metabolites were measured using previously published laboratory methods (Kato and others 2005; Silva and others 2008): mono-n-butyl phthalate (MBP), mono-isobutyl phthalate (MiBP), monoethyl phthalate (MEP), monobenzyl phthalate (MBzP), mono(carboxynonyl) phthalate (MCNP), mono(carboxyoctyl) phthalate (MCOP), mono(3-carboxypropyl) phthalate (MCPP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP). The limits of detection (LOD) were as follows: 0.4 μg/L (MBP, MEP), 0.2 μg/L (MBzP, MCNP, MCOP, MCPP, MECPP, MEHHP, MEOHP, MiBP), 0.5 μg/L (MEHP). For two of the phthalate metabolites a correction factor was applied to the measured values (0.72 for MBzP and 0.66 for MEP) in order to adjust for detected impurities in laboratory standards, as recommended by the CDC laboratory (CDC 2012). All three urine samples from each individual were analyzed in the same batch. Interbatch coefficients of variation were calculated for each metabolite and ranged from 2.4% for MBP (geometric mean of pooled quality control samples: 51.4 μg/L) to 19.1% for MEHP (geometric mean of pooled quality control samples: 3.2 μg/L). As expected, coefficients of variation were generally higher for phthalate metabolites present at lower concentrations.

Urinary creatinine was measured at the CDC on a Roche Hitachi Mod P Chemistry Analyzer (Roche, Basel, Switzerland) using the enzymatic method described in Roche's Creatinine Plus Product Application # 11775685216 V17. Quality control pools representing a range of creatinine concentrations were analyzed along with the study samples, and were evaluated using standard statistical probability rules. The LOD of the creatinine assay was 3.5 mg/dL.

2.5 Statistical Analyses

Urinary concentrations of phthalate metabolites (μg/L) were divided by the concentration of urinary creatinine (g/L) to produce values adjusted for urine dilution (in μg/g creatinine). Samples with measured creatinine concentrations ≤20 mg/dL or ≥ 275 mg/dL were excluded from analyses (n=4). Among the first urine samples, two samples from men (creatinine ≤20 mg/dL) and one sample from a woman (creatinine ≥275 mg/dL) were excluded. Among the second urine samples, one sample from a woman was excluded due to creatinine ≤20 mg/dL. No samples were excluded from the third urine sample collection. Because mean creatinine differed between men and women, women's creatinine was standardized to the distribution of men's creatinine for analyses in which both sexes were pooled together. Some analyses were limited to metabolites with detectable concentrations in at least 50% of samples. Additional exposure variables were defined as the molar sum of related phthalate metabolites. The concentrations (nmol/L) of low molecular weight phthalate (LMWP) metabolites MBP, MEP, MiBP were summed to produce the variable ΣLMWP. The concentrations of high molecular weight phthalate (HMWP) metabolites MBzP, MCNP, MCOP, MECPP, MEHHP, MEHP, and MEOHP were summed to produce the variable ΣHMWP. The variable ΣDEHP was defined as the sum of the metabolites MECPP, MEHHP, MEHP, and MEOHP. The variable ΣDBP was defined as the sum of MBP and MiBP.

Phthalate metabolite concentrations below the LOD were replaced with the LOD divided by √2. For statistical tests requiring a normal distribution, phthalate metabolite concentrations were natural-log transformed. The Satterthwaite t-test was used to evaluate differences in mean concentrations of phthalate metabolites between categories of binary predictor variables. Dose-response relationships with log-transformed phthalate metabolite concentrations were evaluated using least squares regression for each of the following continuous variables: age, income, education and body mass index (BMI). Education was entered in dose-response models as a continuous value corresponding to the estimated years of schooling completed (no formal education, 0; elementary school, 5; junior high school, 9; high school, 12; professional high education, 14; college or above, 16). For income, the midpoint of each reported category (or the lower bound plus 1/3 of the lower bound for the highest category) was assigned as a continuous value for the purpose of this analysis.

Intra-individual reproducibility of phthalate metabolite concentrations over time was evaluated using two methods: the intra-class correlation coefficient (ICC) and Spearman's rank correlation coefficient. Reproducibility was assessed separately for men and women. For each metabolite, ICCs were calculated for the variability among the log-transformed sample 1, sample 2 and sample 3 concentrations (or log-transformed molar sums of concentrations). While random effects models have been previously recommended for certain ICC calculations, in our data the within-subject variation in the repeated measurements was larger than the between-subject variation for some phthalate metabolites, leading to non-identifiability of the variance terms during the estimation process. Therefore, we employed an alternative method using the INTRACC macro by Robert Hamer (http://support.sas.com/kb/25/031.html). The ICCs were calculated using general linear models with fixed effects of individual subject and sampling round. The method yields an unbiased estimator, which may occasionally produce negative estimates of the non-negative ICC value (Rao and Subrahmaniam 1971). For any negative ICC estimates produced, the estimated value was replaced by the arbitrary non-negative value 0.01. Confidence intervals were generated using Shrout and Fleiss's method (Shrout and Fleiss 1979).

Spearman correlation coefficients were calculated between the first sample urinary phthalate metabolite concentrations and the average of the second and third sample concentrations. The average of the second and third sample concentrations was used because the time elapsed between these samples was relatively short compared to the time elapsed since the collection of the first sample, and the average is likely to provide a better estimate of typical exposure during the later period. A sensitivity analysis was performed by restricting to samples collected in the morning only. Additionally, we performed supplemental analyses examining the Spearman correlation coefficients and ICCs between second and third sample concentrations. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

3. Results

3.1 Characteristics of study participants

Characteristics of the study participants (Table 1) resembled those of the full cohorts of men (Cai and others 2007) and women (Zheng and others 2005). Men were, on average, older than women, with mean ages at enrollment of 56 years (men) and 50 years (women). A higher proportion of women (22%) than men (10%) had completed elementary school only or had no formal education. Men reported a much higher proportion of current smokers (62%) than did women (4%). None of the women were pregnant at enrollment.

3.2 Urinary phthalate metabolite concentrations

The average time elapsed between the first and third urine sample was 5.2 years (SD: 2.4 years, range: 2.5 to 8.3 years), and was shorter for men (2.9 years, SD: 0.3 years, range: 2.5 to 3.9 years) than for women (7.5 years, SD: 0.7 years, range: 4.8 to 8.3 years). Among the first urine samples, approximately two thirds were collected in the afternoon; nearly all other samples were collected in the morning (94% of second and 97% of third samples).

The following nine phthalate metabolites were detected in at least 50% of individuals at the three sampling times (Table 2): MBP, MiBP, MEP, MBzP, MCPP, MECPP, MEHHP, MEHP and MEOHP. Additionally, MCOP was detectable in the majority of men for all three rounds of sampling, and in the majority of women for the second and third samples, but was detectable in only 32.7% of women for the first sample. MCNP was detectable in less than 50% of samples from each sex and round of sampling.

Among men, the creatinine-adjusted geometric mean concentrations of most phthalate metabolites were relatively similar between the first and third samples, although there were decreases of at least 25% for MBP, MBzP and MCPP, and decreases of 20-30% in ΣLMWP and ΣDBP (Table 2). There was an increase of greater than 50% in the creatinine-adjusted geometric mean concentration of MCOP between the first and third samples among men. There was greater variability over time for some metabolites among women, corresponding to a longer average time elapsed between the first and third samples. Among women, there were decreases of greater than 50% between the first and third samples of MBP, MBzP, MCPP and ΣDBP, and decreases of at least 25% for MiBP, MEP and ΣLMWP.

The creatinine-adjusted urinary concentrations of several phthalate metabolites in these samples differed from concentrations in the U.S. general population (National Health and Nutrition Examination Survey, NHANES) from comparable years, and there were consistent differences for the first and third samples (Table 3). The first and third sample geometric mean concentrations of MBP and MiBP were substantially higher in the Shanghai sample than in the comparable NHANES samples, while the concentrations of MEP, MBzP, MCOP, and MCPP were lower in the Shanghai sample, some by a factor of 10 or more. The geometric mean concentrations of DEHP metabolites (MECPP, MEHHP, MEHP and MEOHP) were similar between the Shanghai and NHANES populations.

3.3 Predictors of urinary phthalate metabolite concentrations

The creatinine-adjusted geometric mean urinary concentrations of phthalate metabolites were related to a number of demographic and lifestyle characteristics. Some predictors differed between the first (Table 4) and third samples (Table 5). In the first sample, the mean concentration of MEP was higher among women, while MCOP was higher among men (Table 4). By contrast, in the third urine sample, the mean concentrations of MBP, MiBP, MCPP, and MECPP were higher among men, and the sex difference in MEP was no longer significant (Table 5).

Age as a binary variable was associated with first sample concentrations of MEHP and MCPP, such that individuals aged 50 and younger had significantly higher concentrations. Age as a continuous variable showed significant inverse linear associations with MEHP concentrations in both the first sample (β= -0.03, p=0.02) and the third sample (β= -0.03, p=0.04). Age less than or equal to 57 (the median age at third sample collection) was associated with higher third sample concentrations of MCOP and MEHP. Post-menopausal status in women was associated with lower first sample concentrations of DEHP metabolites. We did not examine associations with menopausal status using third sample concentrations because only three women remained pre-menopausal at the time of the third sample.

Socioeconomic variables were predictive of urinary concentrations of certain phthalate metabolites. The level of education completed was not significantly associated with the first or third sample concentrations of any phthalate metabolites when considered as a binary variable (greater than middle school vs. less than or equal to middle school). However, years of education treated as a continuous variable showed a positive linear association with urinary concentrations of MBP (β=0.03, p=0.03), MiBP (β=0.05, p=0.01) and MEHP (β=0.06, p=0.03) in the third sample only. Low income was associated with higher first sample concentration of MCOP, and income as a continuous variable showed an inverse linear association with MCOP in the first sample (β= -0.0003, p=0.04). For third sample concentrations of phthalate metabolites, there were no significant associations with income.

A BMI at enrollment of less than 25 kg/m^3 was associated with higher first sample concentrations of DEHP metabolites, and BMI as a continuous variable was inversely associated with first sample concentration of MEHP (β= -0.08, p=0.06). Third sample concentrations of MBP and MCPP were higher among those with BMI less than 25 kg/m^3 and there were inverse linear associations between continuous BMI and third sample concentrations of MBP (β= -0.06, p=0.004), MBzP (β= -0.09, p=0.01), and MEHP (β= -0.08, p=0.046). Current versus former/never smoking among men was not associated with concentrations of any phthalate metabolite in either first or third samples, nor was smoking at least 13 cigarettes per day among male smokers. Consumption of bottled water among women (which largely refers to water in glass carafes rather than plastic bottles) was not associated with any phthalate metabolites in the first sample; however, third sample concentrations of certain DEHP metabolites (MECPP, MEHHP, MEOHP) were higher among women who did not consume bottled water.

Self-reported intake of medication in the 24 hours prior to the first urine sample collection was associated with lower concentrations of MBP and MiBP. Recent intake of medication was not assessed for the third sample collection. Urine collection in the afternoon was associated with higher first sample concentration of ΣLMWP as well as higher concentration of MEHP (although this difference was non-significant). This comparison was not made for third samples because most samples were collected in the morning.

3.4 Reproducibility of measured urinary phthalate metabolite concentrations over time

The reproducibility of an individual's urinary concentration of phthalate metabolites over several years was assessed in two ways (Table 6). The ICC was used to compare the variation within individuals to the variation between individuals (based on all three sampling rounds for both). ICCs were low for all metabolites; there were no ICC values above 0.3 among men and none above 0.2 among women. The Spearman's rank correlation coefficient was used to assess the consistency of the relative rank ordering of individual phthalate concentrations from the first measurement to the average of the second and third measurements. Among men, only one phthalate metabolite, MEHP, had a Spearman correlation coefficient greater than 0.4 (Spearman correlation coefficients for the other DEHP metabolites ranged from 0.21-0.26). Among women, Spearman correlation coefficients were lower, and none of the metabolites had a Spearman correlation coefficient above 0.3. Results did not change substantially when analyses were restricted to samples collected in the morning only, but the sample sizes were limited (17 males and 12 females; not shown).

Reproducibility of urinary phthalate metabolite concentrations between samples 2 and 3, collected approximately 9 months apart (mean time interval: 0.8 years, SD: 0.1 years for both men and women), was higher than reproducibility between first and third samples for certain metabolites (Supplemental Table 1). Among men, MBP and MBzP had ICCs greater than 0.5. Among women, MiBP and MEP had ICCs greater than 0.4.

4. Discussion

This study reports on the predictors and reproducibility of urinary phthalate metabolite concentrations in a predominantly middle-aged population from urban Shanghai, over a period of approximately 2 to 8 years. The concentrations of several phthalate metabolites in this population differed from the concentrations measured in the U.S. (NHANES) population of comparable years, suggesting different sources or magnitudes of exposure to certain phthalates. Specifically, concentrations of LMWPs MBP and MiBP were higher in the Shanghai population. Both MBP and MiBP are metabolites of low-molecular weight dibutyl phthalates (DBP); MBP may also be derived from exposure to benzylbutyl phthalate (BzBP), of which the primary metabolite is MBzP (CDC 2009). We observed lower urinary concentrations of MEP (the main metabolite of diethyl phthalate [DEP]), MBzP, MCOP (a metabolite of di-isononyl phthalate), and MCPP (a non-specific metabolite of several HMWPs and a minor metabolite of DBP) than in the comparable years of NHANES. These differences may reflect the different phthalate content of food and personal care products used in the U.S. and China.

The products primarily responsible for exposure to phthalates in the general population may vary between populations and geographic areas. Inhalation of indoor and outdoor air and dermal absorption from personal care products are believed to be the major sources of exposure to LMWPs, while dietary intake is primarily responsible for exposure to HMWPs such as DEHP (Koch and others 2013; Wormuth and others 2006). A recent study of food products from China found DBP in greater than 60% of food samples tested, along with dimethyl phthalate, DEP, di-isobutyl phthalate (DiBP), BzBP, and DEHP (Guo and others 2012), but the study concluded that dietary exposures likely only accounted for less than 10% of total exposure to DBP in China. Use of personal care products may also be a major source of exposure to phthalates in China. In another study, DEP was found in over 50% of lotions, shampoos, cleansers and other personal care products purchased from Chinese supermarkets in 2012, and DBP, DiBP and DEHP were also commonly detected (Guo and others 2013). In the case of DEP, dermal absorption from personal care products may be responsible for a large fraction of daily exposure (Guo and others 2013).

Dietary intake is believed to account for a large proportion of exposure to DEHP in China, as in European countries and the USA (Guo and others 2013; Rudel and others 2011). MEHP, MEOHP, MEHHP, and MECPP are all metabolites of DEHP, and were present in the Shanghai population at concentrations comparable to those reported in NHANES participants' samples from comparable years. Dietary predictors of exposure in this population, however, were beyond the scope of this study.

The concentrations of several urinary phthalate metabolites declined between the first and third samples. These decreases were most pronounced among women, which corresponds with the longer average time elapsed between the first and third sample collections in women (7.5 years) as compared to men (2.9 years). Phthalate metabolites which showed notable declines over time among women included LMWPs (MEP, MBP, and MiBP), as well as MBzP and MCPP. Given that the principal source of exposure to LMWPs is thought to be non-food products, exposure through personal care products and other consumer products may have declined between 1997 and 2006, either through changes in usage patterns or changes in the compositions of these products. There were also decreases in the geometric mean concentrations of ΣLMWP and ΣDBP among men, corresponding to the period between 2002 and 2006. Temporal trends in exposure to several phthalates, both LMWPs and HMWPs, have been also reported among the US and German general populations (Wittassek and others 2007; Zota and others 2014).

Predictors of urinary phthalate metabolite concentrations included sex, age, education, income, BMI, menopausal status, recent intake of medications, consumption of bottled water, and time of day of urine sample collection. In the third sampling round, MBP, MiBP, MCPP and MECPP were higher among men than women, despite standardization of female creatinine concentrations to the male creatinine distribution in this population. Sex differences in LMWPs may reflect different dietary intake or other sources of exposure. Certain metabolites —MEHP and MCPP in the first sample, and MEHP and MCOP in the third sample—were inversely related with age, which may reflect differences in dietary patterns between older and younger individuals, or other unidentified sources of exposure. First sample concentrations of DEHP metabolites were higher among pre-menopausal women than among post-menopausal women.

BMI at enrollment was inversely associated with concentrations of DEHP metabolites. For the third sampling, continuous BMI was inversely associated with concentrations of MBP and MBzP, and with MEHP but not with other DEHP metabolites. Previous cross-sectional studies have produced varied results. Some have reported positive associations between BMI and MBzP (Wolff and others 2008) and MEP (Duty and others 2005; Hatch and others 2008). In a study of men and women aged 60-80, MBP was inversely associated with BMI (Hatch and others 2008), consistent with our third sample finding.

Socioeconomic status may be associated with certain sources of exposure to phthalates. Lower income was associated with higher first sample urinary concentration of MCOP. Higher levels of education were associated with higher third sample concentrations of MBP, MiBP and MEHP. Women who reported drinking bottled water had lower third sample concentrations of certain DEHP metabolites, suggesting that bottled water intake among women in Shanghai (which includes bottled water from glass carafes) may be associated with other behaviors or characteristics that reduce exposure to DEHP. Recent medication intake (in the 24 hours prior to first urine collection) was associated with lower concentrations of ΣDBP. Interestingly, certain LMWP, including DEP and DBP, have been used in FDA-approved medications in the United States (Hernández-Díaz and others 2009; Kelley and others 2012) and therefore higher concentrations following use of certain medications might be expected. However, the phthalate content of medications used in this Shanghai population was unknown.

Overall, the within-individual variability in phthalate metabolites over our study period was high relative to the between-individual variability, and the reproducibility across repeated samples was low. This is consistent with the relatively rapid excretion of phthalate metabolites (Anderson and others 2011; Anderson and others 2001), as well as the likely episodic nature of the exposures. Our results suggest that a single spot urine measurement of phthalate metabolites will not sufficiently rank phthalate exposures over a period of several years in this population. The reproducibility for certain metabolites tended to be higher among men than among women, perhaps owing to the different use patterns of products responsible for exposure to different phthalates, or to the longer interval between samples for women in this study. It is notable, however, that the majority of first urine samples were collected in the afternoon, while the majority of second and third urine samples were collected in the morning. These differences in timing of collection could lead to underestimation of reproducibility, due to daily patterns in personal care product use or dietary intake.

Previous studies of the variability and reliability of urinary phthalate metabolites over time have examined shorter time intervals than those in our study. Reproducibility in previous studies was generally low to moderate, with some exceptions. Low to moderate ICCs (0.36-0.65) have been reported for LMWPs over weeks to months (Braun and others 2012; Meeker and others 2012; Whyatt and others 2012); the same studies have reported low reproducibility for DEHP metabolites (ICCs: 0.08-0.42). Some studies that restricted to first-morning voids found moderate to high reproducibility, particularly for LMWPs among women (ICCs: 0.51-0.80) (Hoppin and others 2002; Peck and others 2010). Reproducibility of first-morning DEHP metabolites among women remained low (ICCs: 0.13-0.37) (Baird and others 2010; Peck and others 2010). A study collecting both spot and first-morning urine samples reported similarly low to moderate ICCs from both types of samples for most phthalate metabolites (ICCs: 0.13-0.68 for spot urine, 0.20-0.48 for first-morning urine) (Frederiksen and others 2013). Another study of variability over 1 week found high reproducibility for MEP (ICC: 0.91) and low reproducibility for MEHHP (ICC: 0.25) among several first-morning samples (Preau and others 2010); both metabolites had somewhat lower reproducibility among spot samples.

Few studies have examined variability of phthalate metabolites over years rather than days to months. One recent study examined reproducibility in urine samples collected over 1-3 years from U.S. women enrolled in the Nurses' Health Study (Townsend and others 2013). Among their samples, most of which were first-morning voids, the reproducibility over time was low to moderate for the LMWP metabolites (ICCs: 0.30-0.53), as well as for the DEHP metabolites (ICCs: 0.39-0.43) with the exception of MEHP, which was notably lower (ICC: 0.14) (Townsend and others 2013). In our study, reproducibility of DEHP metabolites (ICCs: 0.04-0.20) and LMWPs (ICCs: 0.15-0.30) were poor over several years. Low reproducibility in our study may be due to the longer time interval elapsed between samples, and possibly to the different and changing sources of exposure in Shanghai over the duration of the study. Reproducibility over approximately 9 months between the second and third sampling rounds was low to moderate among LMWPs (ICCs: 0.19-0.64) and remained low among DEHP metabolites (ICCs: 0.01-0.23).

Strengths of this study include the unique sample of an urban Chinese population, allowing us to identify predictors of phthalate exposure in a relatively understudied group, and the long period of time over which the repeated samples were collected, allowing the assessment of variability and reproducibility over several years. Limitations include the small sample size, especially when stratified by sex, the differences in time of day of collection between the first sample and the second and third samples, and the different timing of collection between men and women, both in the interval between samples and the calendar years of the first collection.

5. Conclusions

The results of our study suggest that a single spot urine measurement is not sufficient to rank individuals' usual exposures to phthalates over a period of several years. The within-individual variability of phthalate metabolite concentrations was high relative to between-individual variability and the reproducibility was low in both men and women. This finding is particularly important for studies of diseases of long latency, such as cancer, when researchers would like to assess environmental exposures that may have occurred years earlier.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- We identify predictors of urinary phthalate metabolites in an urban Chinese cohort.
- The reproducibility of phthalate metabolite concentrations over 2-8 years was low.
- A single spot urine sample may be insufficient to rank exposures over years.

Table 1

Characteristics at enrollment[a] of participants randomly selected from the Shanghai Women's and Shanghai Men's Health Studies [values are numbers (percentages)].

Characteristic	Total (n = 100)	Women (n = 50)	Men (n = 50)
Age at enrollment			
40-49	40 (40)	27 (54)	13 (26)
50-59	33 (33)	13 (26)	20 (40)
60-72	27 (27)	10 (20)	17 (34)
Highest educational level attained			
Elementary school or no formal education	16 (16)	11 (22)	5 (10)
Middle school	38 (38)	19 (38)	19 (38)
High school	30 (30)	13 (26)	17 (34)
Technical school/college or above	16 (16)	7 (14)	9 (18)
Body mass index (kg/m^2) at enrollment			
<20	6 (6)	4 (8)	2 (4)
20-24.99	55 (55)	25 (50)	30 (60)
25-29.99	34 (34)	17 (34)	17 (34)
≥30	5 (5)	4 (8)	1 (2)
Menopausal status			
Premenopausal		26 (52)	
Postmenopausal		23 (46)	
Unknown		1 (2)	
Cigarette smoking status			
Current	33 (33)	2 (4)	31 (62)
Former	4 (4)	0 (0)	4 (8)
Never	63 (63)	48 (96)	15 (30)
Number of cigarettes smoked per day (among current smokers)			
1-6	3 (9)	2 (100)	1 (3)
7-12	11 (33)	0 (0)	11 (35)
13+	19 (58)	0 (0)	19 (61)
Family income in previous year[b]			
"Low"	65 (65)	30 (60)	35 (70)
"High"	35 (35)	20 (40)	15 (30)
Usual source of drinking water[c]			
Tap water only		33 (66)	
Tap water and bottled water		17 (34)	
Any medicine taken in past 24 hours			
Yes	59 (59)	28 (56)	31 (62)
No	41 (41)	22 (44)	19 (38)
Time of day of collection for first urine sample			
7:00am – 8:59am	4 (4)	3 (6)	1 (2)
9:00am – 11:59am	29 (29)	12 (24)	17 (34)

Characteristic	Total (n = 100)	Women (n = 50)	Men (n = 50)
12:00pm – 2:59pm	12 (12)	6 (12)	6 (12)
3:00pm – 7:59pm	55 (55)	29 (58)	26 (52)
Time of day of collection for second urine sample			
6:00am – 8:59am	71 (71)	38 (76)	33 (66)
9:00am – 11:59am	23 (23)	8 (16)	15 (30)
12:00pm – 2:59pm	4 (4)	2 (4)	2 (4)
3:00pm – 5:59pm	2 (2)	2 (4)	0 (0)
Time of day of collection for third urine sample			
6:00am – 8:59am	66 (66)	32 (64)	34 (68)
9:00am – 11:59am	31 (31)	17 (34)	14 (28)
12:00pm – 2:59pm	2 (2)	0 (0)	2 (4)
3:00pm – 5:59pm	1 (1)	1 (2)	0 (0)

[a]Enrollment was in 1997-2000 for women and in 2002-2006 for men.

[b]"Low" and "high" annual income were defined using cutpoints of 20,000 yuan for women and 12,000 yuan for men, which represent the approximate medians reported by each sex.

[c]This information was collected from women only.

Table 2

Creatinine-adjusted urinary phthalate metabolite concentrations in the Shanghai Men's and Shanghai Women's Health

Phthalate Metabolite (μg/g creatinine)[a]	Sample 1[b]			Sample 2			Sample 3		
	% >LOD[c]	GM	(5th, 95th percentile)	% >LOD	GM	(5th, 95th percentile)	% >LOD	GM	(5th, 95th percentile)
Males	(N=48)			(N=50)			(N=50)		
MBP	100	105	(34.1, 289)	100	66.1	(30.2, 173)	100	65.6	(24.8, 208)
MiBP	100	56.6	(23.2, 139)	100	45.6	(18.3, 114)	100	50.5	(19.3, 143)
MEP	100	9.98	(1.93, 163)	100	13.2	(2.14, 433)	100	10.6	(2.75, 49.0)
MBzP	65	0.566	(<LOD, 3.49)	70	0.450	(<LOD, 4.78)	60	0.407	(<LOD, 4.63)
MCNP	33	*d*	(<LOD, 0.893)	46	*d*	(<LOD, 0.891)	24	*d*	(<LOD, 0.481)
MCOP	75	0.444	(<LOD, 4.37)	88	0.675	(<LOD, 3.12)	88	0.715	(0.220, 14.8)
MCPP	90	0.952	(<LOD, 3.17)	90	0.705	(<LOD, 2.56)	90	0.617	(0.213, 2.09)
MECPP	100	29.3	(12.0, 95.4)	100	26.0	(10.9, 123)	100	30.8	(12.8, 168)
MEHHP	100	21.0	(5.83, 110)	100	18.8	(7.01, 88.6)	100	21.3	(8.73, 99.9)
MEHP	92	4.24	(0.779, 33.2)	90	3.57	(0.663, 19.0)	96	3.40	(1.08, 13.3)
MEOHP	100	12.4	(3.67, 54.9)	100	11.2	(4.37, 53.8)	100	13.0	(5.08, 68.6)
ΣLMWP[e]		8.91	(2.72, 29.8)		7.40	(3.07, 27.0)		6.33	(2.56, 14.5)
ΣHMWP[e]		2.51	(0.884, 10.0)		2.15	(0.818, 9.41)		2.45	(0.976, 11.7)
ΣDEHP[e]		2.30	(0.859, 10.0)		2.05	(0.801, 9.36)		2.34	(0.942, 11.7)
ΣDBP[e]		7.58	(2.58, 17.1)		5.25	(2.37, 10.7)		5.46	(2.16, 14.0)
Females	(N=49)			(N=49)			(N=50)		
MBP	100	151	(48.2, 456)	100	88.9	(44.3, 149)	100	62.5	(26.6, 140)
MiBP	100	61.8	(13.8, 284)	100	49.4	(21.9, 138)	100	41.4	(15.0, 121)
MEP	100	28.5	(3.28, 783)	100	13.9	(2.35, 143)	98	20.0	(2.21, 146)
MBzP	84	1.13	(0.262, 9.30)	59	0.545	(<LOD, 2.81)	50	0.491	(<LOD, 2.65)
MCNP	37	*d*	(<LOD, 0.703)	31	*d*	(<LOD, 1.55)	28	*d*	(<LOD, 0.554)
MCOP	33	*d*	(<LOD, 2.30)	80	0.971	(<LOD, 9.76)	80	0.749	(<LOD, 2.89)
MCPP	90	1.31	(0.328, 4.49)	82	0.857	(<LOD, 3.47)	78	0.535	(<LOD, 1.69)
MECPP	100	32.3	(9.67, 235)	100	32.0	(11.1, 168)	100	31.9	(9.81, 222)
MEHHP	100	22.7	(7.51, 67.5)	100	21.9	(7.93, 101)	100	22.9	(7.26, 154)

Phthalate Metabolite (μg/g creatinine)[a]	Sample 1[b]			Sample 2			Sample 3		
	% >LOD[c]	GM	(5^{th}, 95^{th} percentile)	% >LOD	GM	(5^{th}, 95^{th} percentile)	% >LOD	GM	(5^{th}, 95^{th} percentile)
MEHP	92	4.40	(0.913, 38.9)	82	3.39	(0.840, 20.9)	82	3.44	(0.581, 29.2)
MEOHP	100	14.5	(5.49, 45.3)	100	14.2	(5.79, 74.3)	100	14.4	(5.37, 97.1)
ΣLMWP[e]		14.4	(4.67, 67.7)		7.93	(4.64, 26.7)		7.26	(2.92, 12.5)
ΣHMWP [e]		2.70	(0.846, 11.9)		2.61	(0.973, 13.3)		2.59	(0.845, 17.1)
ΣDEHP[e]		2.55	(0.808, 11.9)		2.49	(0.946, 13.2)		2.51	(0.817, 17.0)
ΣDBP[e]		10.2	(3.23, 34.5)		6.42	(3.83, 12.1)		4.81	(1.82, 9.31)

Abbreviations: geometric mean (GM), limit of detection (LOD), mono-n-butyl phthalate (MBP), mono-isobutyl phthalate (MiBP), monoethyl phthalate (MEP), monobenzyl phthalate (MBzP), mono(carboxynonyl) phthalate (MCNP), mono(carboxyoctyl) phthalate (MCOP), mono(3-carboxypropyl) phthalate (MCPP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl- 5-oxohexyl) phthalate (MEOHP), low molecular weight phthalate sum (ΣLMWP), high molecular weight phthalate sum (ΣHMWP), di(2-ethylhexyl) phthalate sum (ΣDEHP), dibutyl phthalate sum (ΣDBP).

[a] Samples with creatinine concentration ≤20 or ≥275 mg/dL were excluded.

[b] First samples were collected during 2003-2004 for men and 1998-2002 for women.

[c] LODs (in μg/L) are MBP: 0.4, MiBP: 0.2, MEP: 0.4, MBzP: 0.2, MCNP: 0.2, MCOP: 0.2, MCPP: 0.2, MECPP: 0.2, MEHHP: 0.2, MEHP: 0.5, MEOHP: 0.2.

[d] GM not calculated (>50% of samples below the LOD).

[e] Molar sums; units are nanomoles per gram creatinine.

Table 3

Comparison of creatinine-adjusted[a] geometric mean (95% CI) urinary phthalate concentrations (μg/g) to concentrations in NHANES.

Phthalate metabolite	Total				Males				Females			
	Current study		NHANES		Current study		NHANES		Current study		NHANES	
	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)
Sample 1[b]	(N=97)		(N=2782)		(N=48)		(N=1371)		(N=49)		(N=1411)	
MBP	126	(109, 146)	17.8	(16.7-19.0)	105	(85.9, 128)	14.4	(13.5-15.4)	151	(123, 186)	21.7	(19.6-23.9)
MiBP	59.2	(51.1, 68.5)	2.54	(2.36-2.73)	56.6	(48.0, 66.8)	2.22	(2.09-2.35)	61.8	(48.3, 79.1)	2.88	(2.61-3.18)
MEP	17.0	(12.2, 23.6)	110	(99.3-122)	9.98	(6.74, 14.8)	97.6	(85.8-111)	28.5	(17.3, 47.0)	123	(110-139)
MBzP	0.802	(0.635, 1.01)	10.2	(9.50-10.9)	0.566	(0.417, 0.769)	9.13	(8.18-10.2)	1.13	(0.808, 1.57)	11.3	(10.2-12.4)
MCNP	*c*		2.66	(2.43-2.91)	*c*		2.53	(2.28-2.82)	*c*		2.79	(2.47-3.15)
MCOP	0.336	(0.264, 0.428)	5.26	(4.54-6.10)	0.444	(0.297, 0.663)	5.01	(4.21-5.97)	*c*		5.51	(4.75-6.39)
MCPP	1.12	(0.926, 1.35)	2.58	(2.35-2.83)	0.952	(0.703, 1.29)	2.35	(2.17-2.56)	1.31	(1.04, 1.64)	2.81	(2.48-3.18)
MECPP	30.8	(25.7, 36.9)	32.6	(29.6-36.0)	29.3	(22.2, 38.8)	29.8	(26.8-33.1)	32.3	(25.4, 41.2)	35.5	(31.6-40.0)
MEHHP	21.8	(18.0, 26.6)	18.8	(17.0-20.7)	21.0	(15.4, 28.7)	17.9	(16.2-19.7)	22.7	(17.6, 29.2)	19.7	(17.3-22.4)
MEHP	4.32	(3.41, 5.46)	4.00	(3.58-4.48)	4.24	(2.96, 6.06)	3.50	(3.08-3.99)	4.40	(3.20, 6.05)	4.54	(4.02-5.13)
MEOHP	13.4	(11.1, 16.2)	12.6	(11.5-13.9)	12.4	(9.22, 16.7)	11.8	(10.7-13.0)	14.5	(11.3, 18.4)	13.5	(11.9-15.2)
Sample 3[d]	(N=100)		(N=2604)		(N=50)		(N=1294)		(N=50)		(N=1310)	
MBP	64.1	(57.6, 71.2)	19.0	(17.7-20.5)	65.6	(55.8, 77.1)	15.5	(14.4-16.8)	62.5	(54.2, 72.2)	23.1	(21.0-25.5)
MiBP	45.7	(40.4, 51.7)	7.21	(6.76-7.70)	50.5	(41.9, 60.8)	6.33	(5.91-6.79)	41.4	(35.2, 48.6)	8.18	(7.46-8.96)
MEP	14.5	(11.0, 19.2)	91.1	(82.6-101)	10.6	(8.31, 13.5)	78.1	(68.5-89.1)	20.0	(12.2, 32.9)	106	(95.5-117)
MBzP	0.447	(0.363, 0.552)	7.29	(6.71-7.93)	0.407	(0.297, 0.558)	6.57	(5.91-7.31)	0.491	(0.369, 0.654)	8.07	(7.29-8.93)
MCNP	*c*		2.44	(2.25-2.65)	*c*		2.32	(2.11-2.55)	*c*		2.57	(2.33-2.83)
MCOP	0.731	(0.594, 0.901)	6.85	(6.05-7.75)	0.715	(0.514, 0.993)	6.01	(5.29-6.84)	0.749	(0.573, 0.978)	7.76	(6.84-8.81)
MCPP	0.575	(0.499, 0.662)	2.79	(2.63-2.96)	0.617	(0.508, 0.750)	2.54	(2.34-2.76)	0.535	(0.434, 0.660)	3.04	(2.84-3.25)
MECPP	31.4	(26.1, 37.8)	33.6	(29.7-38.0)	30.8	(23.6, 40.3)	29.0	(25.3-33.2)	31.9	(24.5, 41.7)	38.7	(34.5-43.3)
MEHHP	22.1	(18.3, 26.6)	22.2	(19.4-25.5)	21.3	(16.3, 27.8)	19.6	(16.8-22.7)	22.9	(17.6, 29.9)	25.2	(22.1-28.6)
MEHP	3.42	(2.74, 4.27)	2.66	(2.37-2.99)	3.40	(2.55, 4.54)	2.33	(2.03-2.68)	3.44	(2.43, 4.86)	3.02	(2.70-3.38)
MEOHP	13.7	(11.5, 16.4)	12.3	(10.7-14.0)	13.0	(10.1, 16.9)	10.5	(9.08-12.2)	14.4	(11.1, 18.5)	14.2	(12.5-16.0)

Abbreviations: confidence interval (CI), geometric mean (GM), National Health and Nutrition Examination Survey (NHANES), mono-n-butyl phthalate (MBP), mono-isobutyl phthalate (MiBP), monoethyl phthalate (MEP), monobenzyl phthalate (MBzP), mono(carboxynonyl) phthalate (MCNP), mono(carboxyoctyl) phthalate (MCOP), mono(3- carboxypropyl) phthalate (MCPP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP).

[a] Samples with creatinine concentration ≤20 or ≥275 mg/dL were excluded.

[b] First samples were collected during 2003-2004 for men and 1998-2002 for women. These are compared to NHANES 2001-2002 except for MECPP (NHANES 2003-2004; N total: 2605, N male: 1250, N female: 1355), MCNP, and MCOP (NHANES 2005-2006; N total: 2548, N male: 1270, N female: 1278).

[c] GM not calculated (>50% of samples below the limit of detection).

[d] Third urine samples were collected during 2006-2007. These are compared to NHANES 2007-2008.

Table 4

Geometric mean (95% CI) creatinine-adjusted first sample urinary phthalate metabolite concentrations (μg/g) by selected characteristics, with female creatinine standardized to male creatinine.

Characteristic	N	MBP		MiBP		MEP		MBzP		MCOP		MCPP		MECPP	
		GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)
Sex															
Female	49	112	(90.5, 139)	45.8	(35.6, 59.0)	21.1	(12.9, 34.7	0.836	(0.600, 1.17)	0.190	(0.146, 0.247)	0.969	(0.766, 1.22	24.0	(18.8, 30.5)
Male	48	105	(85.9, 128)	56.6	(48.0, 66.8)	9.98	(6.74, 14.8	0.566	(0.417, 0.769)	0.444	(0.297, 0.663)	0.952	(0.703, 1.29	29.3	(22.2, 38.8)
p-value[1]		0.66		0.16		0.02		0.09		0.001		0.93		0.27	
Age															
<50	42	118	(95.1, 146)	55.5	(42 5, 72.4)	11.5	(7.27, 18.1	0.694	(0.479, 1.00)	0.295	(0.188, 0.465)	1.20	(0.902, 1.61	30.7	(21.6, 43.7)
>50	55	102.(83.5, 124)	47.6	(40.0, 56.8)	17.5	(11.2, 27.5	0.686	(0.513, 0.918)	0.284	(0.214, 0.378)	0.808	(0.633, 1.03	23.7	(19.8, 28.4)	
p-value[1]		0.32		0.34		0.19		0.96		0.88		0.04		0.19	
Education															
< middle school	52	108	(91.0, 128)	53.0	(43.9, 63.9)	14.0	(8.90, 22.2	0.739	(0.539, 1.01)	0.303	(0.206, 0.444)	0.989	(0.762, 1.28	24.7	(18.9, 32.4)
> middle school	45	109	(85.1, 139)	48.6	(37.9, 62.2)	15.2	(9.57, 24.2	0.637	(0.456, 0.890)	0.274	(0.199, 0.378)	0.928	(0.701, 1.23	28.7	(22.4, 36.8)
p-value[1]		0.97		0.58		0.81		0.52		0.69		0.74		0.41	
Income[2]															
Low	62	108	(91.1, 128)	515	(43.2, 61.4)	153	(101, 230	0 737	(0 542, 1 00)	0 349	(0 244, 0 499)	1 04	(0 825, 1 31	27 7	(215, 35 7)
High	35	109	(83.1, 144)	49.9	(37.4, 66.5)	13.5	(7.91, 22.9	0.613	(0.443, 0.849)	0.207	(0.159, 0.269)	0.833	(0.600, 1.16	24.4	(19.0, 31.3)
p-value[1]		0.94		0.85		0.71		0.41		0.02	‡	0.27		0.47	
BMI															
<25 kg/m3	59	106	(88.2, 129)	50.9	(41.7, 62.1)	13.1	(8.76, 19.7	0.682	(0.522, 0.891)	0.292	(0.208, 0.411)	1.06	(0 823, 1.36	31.6	(24.2, 41.3)
>25 kg/m3	38	112	(88 4, 141)	50.9	(40.1, 64.5)	17.1	(9.98, 29.4	0.701	(0.462, 1.06)	0.284	(0.196, 0.413)	0.825	(0.621, 1.10	20.1	(16.6, 24.5)
p-value[1]		0.76		0.99		0.43		0.91		0.92		0.19		0.01	
Smoking[3]															
Former/never	19	98.1	(66.7, 144)	48.1	(37.9, 61.0)	15.0	(6.65, 33.9	0.674	(0.426, 1.07)	0.361	(0.250, 0.523)	0.879	(0.552, 1.40	29.5	(20.8, 41.8)
Current	29	110	(86.6, 139)	63.0	(50.1, 79.2)	7.63	(5.18, 11.2	0.505	(0.330, 0.772)	0.507	(0.269, 0.957)	1.00	(0.659, 1.53	29.2	(19.2, 44.5)
p-value[1]		0.61		0.10		0.13		0.34		0.35		0.66		0.97	

>13 cigarettes/day among smokers[3]

Characteristic	N	MBP		MiBP		MEP		MBzP		MCOP		MCPP		MECPP	
		GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)
No	12	109	(73.8, 162)	66.8	(48.9, 91.2)	7.20	(3.74, 13.9	0.365	(0.174, 0.763)	0.336	(0.193, 0.587)	0.830	(0.514, 1.34	39.8	(14.7, 108)
Yes	17	110	(79.0, 154)	60.5	(42.6, 85.8)	7.95	(4.66, 13.6	0.635	(0.368, 1.10)	0.678	(0.238, 1.93)	1.15	(0.587, 2.25	23.5	(17.7, 31.2)
p-value[1]		0 98		0 65		0 80		0 20		0 22		041		0 29	
Bottled water[4]															
No	32	108	(83.3, 139)	40.1	(314,512)	21.0	(10.9, 40.5	0.875	(0.612, 1.25)	0.170	(0.129, 0.223)	1.01	(0.774, 1.31	22.0	(17.0, 28.4)
Yes	17	120	(79.3, 183)	59.0	(32.8, 106)	21.4	(9.47, 48.3	0.769	(0.364, 1.62)	0.235	(0.131, 0.422)	0.898	(0.544, 1.48	28.2	(16.4, 48.5)
p-value[1]		0.64		0.21		0.97		0.75		0.30		0.67		0.39	
Menopause[4]															
No	25	109	(80.7, 146)	51.9	(33.8, 79.8)	19.5	(10.2, 37.0)	0.866	(0.525, 1.43)	0.223	(0.147, 0.337)	1.02	(0.756, 1.37)	31.2	(21.2, 46.0)
Yes	23	117	(82.8, 164)	41.4	(31.1, 55.1)	22.5	(9.69, 52.3)	0.848	(0.523, 1.37)	0.160	(0.113, 0.227)	0.900	(0.600, 1.35)	18.5	(14.0, 24.6)
p-value[1]		0.75		0.37		0.78		0.95		0.21		0.62		0.03	
Medication in past 24 hours															
No	39	132	(101, 171)	61.1	(47.6, 78.4)	11.8	(7.26, 19.3)	0.584	(0.413, 0.828)	0.241	(0.182, 0.320)	0.968	(0.707, 1.33)	29.7	(20.3, 43.6)
Yes	58	95.3	(81.1, 112)	45.0	(37.4, 54.2)	16.8	(10.9, 25.8)	0.770	(0.570, 1.04)	0.326	(0.224, 0.475)	0.955	(0.752, 1.21)	24.5	(20.6, 29.1)
p-value[1]		0.04		0.05		0.28		0.23		0.20		0.94		0.36	
Time of day of urine collection															
Morning	31	91.2	(69.3, 120)	43.2	(34.6, 54.0)	10.1	(6.01, 17.0)	0.597	(0.378, 0.943)	0.261	(0.184, 0.369)	0.775	(0.552, 1.09)	24.2	(17.4, 33.6)
Afternoon	66	118	(99.3, 140)	55.0	(45.2, 66.8)	17.3	(11.6, 25.9)	0.738	(0.569, 0.957)	0.303	(0.217, 0.424)	1.06	(0.846, 1.33)	27.7	(22.1, 34.6)
p-value[1]		0.11		0.10		0.10		0.42		0.53		0.12		0.50	

Characteristic	N	MEHHP		MEHP		MEOHP		ΣLMWP		ΣHMWP		ΣDEHP		ΣDBP	
		GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)
Sex															
Female	49	16.8	(13.1, 21.6)	3.26	(2.37, 4.49)	10.7	(8.40, 13.7)	10.6	(8.26, 13.7)	2.00	(1.57, 2.54)	1.89	(1.48, 2.41)	7.53	(6.08, 9.31)
Male	48	21.0	(15.4, 28.7)	4.24	(2.96, 6.06)	12.4	(9.22, 16.7)	8.91	(7.38, 10.8)	2.51	(1.87, 3.36)	2.30	(1.71, 3.08)	7.58	(6.37, 9.02)
p-value[1]		0.26		0.27		0.45		0.26		0.23		0.31		0.96	
Age															
≤50	42	21.7	(14.9, 31.7)	5.38	(3.55, 8.15)	13.4	(9.32, 19.3)	9.83	(7.92, 12.2)	2.72	(1.90, 3.89)	2.46	(1.71, 3.53)	8.26	(6.64, 10.3)

Characteristic	N	MEHHP		MEHP		MEOHP		ΣLMWP		ΣHMWP		ΣDEHP		ΣDBP	
		GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)
>50	55	16.8	(13.7, 20.5)	2.80	(2.16, 3.62)	10.3	(8.49, 12.4)	9.69	(7.72, 12.2)	1.92	(1.60, 2.31)	1.83	(1.52, 2.21)	7.06	(5.92, 8.41)
p-value[1]		0.23		0.01	‡	0.19		0.93		0.09		0.15		0.26	
Education															
≤ middle school	52	18.0	(13.4, 24.3)	3.47	(2.47, 4.88)	11.0	(8.31, 14.6)	10.1	(8.15, 12.5)	2.16	(1.63, 2.87)	1.96	(1.48, 2.60)	7.65	(6.52, 8.97)
> middle school	45	19.7	(15.2, 25.6)	4.01	(2.86, 5.62)	12.1	(9.42, 15.6)	9.38	(7.37, 11.9)	2.32	(1.82, 2.97)	2.23	(1.73, 2.87)	7.45	(5.90, 9.39)
p-value[1]		0.65		0.54		0.62		0.65		0.70		0.49		0.85	
Income[2]															
Low	62	19.7	(15.1, 25.7)	4.22	(3.12, 5.72)	12.1	(9.37, 15.7)	9.66	(8.02, 11.6)	2.41	(1.87, 3.11)	2.19	(1.70, 2.83)	7.53	(6.43, 8.82)
High	35	17.3	(12.9, 23.1)	2.96	(2.02, 4.34)	10.5	(8.03, 13.8)	9.92	(7.36, 13.4)	1.96	(1.50, 2.55)	1.90	(1.45, 2.49)	7.59	(5.84, 9.85)
p-value[1]		0.50		0.15		0.45		0.88		0.26		0.44		0.96	
BMI															
<25 kg/m3	59	21.6	(16.0, 29.1)	4.66	(3.30, 6.58)	13.4	(10.2, 17.8)	9.39	(7.67, 11.5)	2.64	(2.00, 3.49)	2.45	(1.85, 3.25)	7.44	(6.22, 8.89)
≥25 kg/m3	38	15.1	(12.4, 18.5)	2.61	(2.01, 3.38)	9.06	(7.46, 11.0)	10.3	(7.98, 13.4)	1.72	(1.43, 2.09)	1.61	(1.33, 1.95)	7.73	(6.23, 9.60)
p-value[1]		0.05		0.01	†	0.02		0.56		0.01		0.01		0.78	
Smoking[3]															
Former/never	19	21.6	(14.8, 31.6)	3.93	(2.44, 6.31)	12.5	(8.58, 18.1)	9.31	(6.33, 13.7)	2.38	(1.67, 3.39)	2.31	(1.61, 3.31)	6.85	(4.95, 9.47)
Current	29	20.7	(13.0, 33.0)	4.46	(2.63, 7.55)	12.4	(7.93, 19.3)	8.66	(7.03, 10.7)	2.60	(1.67, 4.04)	2.29	(1.47, 3.56)	8.10	(6.58, 9.98)
p-value[1]		0.89	0.71	0.98	0.73	0.75	0.98	0.37							
≥13 cigarettes/day among smokers[3]															
No	12	30.8	(10.8, 88.0)	6.76	(2.24, 20.4)	16.2	(5.70, 45.8)	8.99	(6.85, 11.8)	3.28	(1.19, 9.07)	3.21	(1.15, 8.93)	8.50	(6.53, 11.1)
Yes	17	15.6	(10.6, 23.1)	3.32	(1.96, 5.64)	10.2	(7.25, 14.4)	8.44	(6.10, 11.7)	2.20	(1.52, 3.20)	1.80	(1.29, 2.52)	7.83	(5.65, 10.9)
p-value[1]		0.20		0.22		0.38		0.75		0.43		0.26		0.68	
Bottled water[4]															
No	32	15.3	(11.6, 20.1)	2.82	(1.98, 4.02)	9.76	(7.52, 12.7)	10.4	(7.63, 14.3)	1.79	(1.39, 2.31)	1.71	(1.32, 2.22)	6.94	(5.49, 8.79)
Yes	17	20.1	(11.6, 34.7)	4.29	(2.19, 8.38)	12.8	(7.48, 21.8)	11.0	(6.85, 17.8)	2.46	(1.46, 4.14)	2.27	(1.32, 3.91)	8.76	(5.55, 13.8)
p-value[1]		0.36		0.26		0.35		0.84		0.26		0.33		0.35	
Menopause[4]															
No	25	22.4	(15.2, 33.0)	5.61	(3.61, 8.74)	13.9	(9.55, 20.3)	10.2	(7.44, 14.1)	2.70	(1.88, 3.88)	2.54	(1.74, 3.72)	7.83	(5.68, 10.8)
Yes	23	12.7	(9.27, 17.4)	1.93	(1.34, 2.78)	8.32	(6.16, 11.2)	11.3	(7.29, 17.6)	1.49	(1.12, 1.99)	1.42	(1.06, 1.89)	7.33	(5.35, 10.0)

Characteristic	N	MEHHP		MEHP		MEOHP		ΣLMWP		ΣHMWP		ΣDEHP		ΣDBP	
		GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)
p-value[1]		0.02		<0.001		0.03		0.70		0.01		0.01		0.76	
Medicine in past 24 hours															
No	39	20.0	(13.4, 30.0)	4.33	(2.70, 6.96)	12.7	(8.62, 18.7)	10.8	(8.41, 13.8)	2.38	(1.62, 3.50)	2.30	(1.56, 3.41)	9.22	(7.26, 11.7)
Yes	58	18.0	(14.7, 22.0)	3.35	(2.62, 4.27)	10.8	(8.94, 13.0)	9.13	(7.42, 11.2)	2.15	(1.79, 2.58)	1.94	(1.62, 2.33)	6.61	(5.65, 7.72)
p-value[1]		0.63		0.33		0.45		0.31		0.63		0.43		0.02	
Time of day of urine collection															
Morning	31	15.2	(10.7, 21.6)	2.66	(1.73, 4.09)	9.59	(6.89, 13.3)	7.68	(5.92, 9.96)	1.85	(1.33, 2.57)	1.76	(1.25, 2.46)	6.33	(4.99, 8.03)
Afternoon	66	20.7	(16.3, 26.4)	4.34	(3.27, 5.76)	12.6	(9.95, 15.8)	10.9	(8.99, 13.2)	2.44	(1.94, 3.07)	2.25	(1.79, 2.84)	8.21	(6.96, 9.68)
p-value[1]		0.14		0.06		0.18		0.03		0.17		0.22		0.07	

Abbreviations: body mass index (BMI), confidence interval (CI), geometric mean (GM), mono-n-butyl phthalate (MBP), mono-isobutyl phthalate (MiBP), monoethyl phthalate (MEP), monobenzyl phthalate (MBzP), mono(carboxyoctyl) phthalate (MCOP), mono(3-carboxypropyl) phthalate (MCPP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), low molecular weight phthalate sum (ΣLMWP), high molecular weight phthalate sum (ΣHMWP), di(2-ethylhexyl) phthalate sum (ΣDEHP), dibutyl phthalate sum (ΣDBP).

[1] p-value for Satterthwaite t-test; ‡ and † represent $p<0.05$ and $p<0.1$, respectively, in linear regression models testing dose-response (age, education, income, and BMI only)

[2] High income was defined as ≥ 1,000 yuan/month for males and ≥20,000 yuan/year for females

[3] Males only

[4] Females only

Table 5

Geometric mean (95% CI) creatinine-adjusted third sample urinary phthalate metabolite concentrations (μg/g) by selected characteristics, female creatinine standardized to male creatinine.

Characteristic	N	MBP		MiBP		MEP		MBzP		MCOP		MCPP		MECPP	
		GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)
Sex															
Female	50	41.8	(36.2, 48.3)	27.6	(23.5, 32.5)	13.4	(8.19, 21.8)	0.328	(0.246, 0.438)	0.500	(0.382, 0.655)	0.358	(0.290, 0.442)	21.3	(16.3, 27.9)
Male	50	65.6	(55.8, 77.1)	50.5	(41.9, 60.8)	10.6	(8.31, 13.5)	0.407	(0.297, 0.558)	0.714	(0.514, 0.993)	0.617	(0.508, 0.750)	30.8	(23.6, 40.3)
p-value[1]		<0.0001		<0.0001		0.39		0.31		0.10		0.0002		0.05	
Age															
≤57	52	50.8	(43.3, 59.7)	39.1	(32.9, 46.5)	9.62	(7.09, 13.0)	0.404	(0.302, 0.541)	0.757	(0.560, 1.02)	0.475	(0.389, 0.580)	29.0	(21.4, 39.3)
>57	48	54.1	(45.6, 64.2)	35.5	(28.6, 44.0)	15.0	(9.47, 23.6)	0.328	(0.240, 0.448)	0.463	(0.346, 0.619)	0.464	(0.366, 0.588)	22.4	(17.9, 28.1)
p-value[1]		0.60		0.49		0.11		0.32		0.02		0.89		0.18	
Education															
≤ middle school	54	48.9	(41.5, 57.6)	34.0	(28.7, 40.2)	10.8	(7.68, 15.3)	0.362	(0.283, 0.462)	0.602	(0.441, 0.824)	0.477	(0.386, 0.589)	24.3	(18.0, 32.8)
> middle school	46	56.7	(48.0, 66.9)	41.7	(33.5, 52.0)	13.3	(8.57, 20.5)	0.370	(0.256, 0.534)	0.592	(0.442, 0.793)	0.462	(0.369, 0.578)	27.3	(21.8, 34.2)
p-value[1]		0.20	‡	0.14	‡	0.47		0.92		0.94		0.84		0.53	
Income[2]															
Low	65	50.4	(43.3, 58.5)	36.9	(31.4, 43.3)	11.0	(8.30, 14.7)	0.329	(0.259, 0.417)	0.565	(0.433, 0.738)	0.487	(0.402, 0.590)	23.8	(18.6, 30.5)
High	35	56.2	(46.8, 67.6)	38.1	(29.5, 49.3)	13.6	(7.64, 24.3)	0.445	(0.293, 0.675)	0.664	(0.461, 0.955)	0.440	(0.340, 0.569)	29.4	(21.9, 39.5)
p-value[1]		0.35		0.83		0.51		0.21		0.48		0.52		0.27	
BMI[3]															
<25 kg/m3	56	60.0	(50.7, 71.0)	38.9	(32.5, 46.5)	12.1	(9.29, 15.7)	0.413	(0.305, 0.558)	0.644	(0.484, 0.859)	0.559	(0.473, 0.661)	28.4	(21.4, 37.8)
≥25 kg/m3	41	44.2	(37.9, 51.5)	35.3	(28.1, 44.2)	11.7	(6.68, 20.5)	0.311	(0.230, 0.421)	0.564	(0.403, 0.792)	0.394	(0.301, 0.515)	23.1	(17.8, 29.9)
p-value[1]		0.01	‡	0.50		0.92		0.19	‡	0.55		0.03		0.28	
Smoking[4]															
Former/never	19	72.7	(54.8, 96.4)	49.3	(31.8, 76.6)	13.0	(8.46, 20.0)	0.458	(0.235, 0.896)	0.581	(0.355, 0.950)	0.557	(0.376, 0.826)	28.5	(21.8, 37.1)
Current	31	61.6	(50.2, 75.5)	51.2	(43.4, 60.3)	9.32	(6.92, 12.6)	0.378	(0.271, 0.528)	0.811	(0.516, 1.27)	0.657	(0.528, 0.819)	32.4	(21.4, 48.9)
p-value[1]		0.33		0.87		0.19		0.60		0.31		0.45		0.59	

≥13 cigarettes/day among smoker[4]

Characteristic	N	MBP		MiBP		MEP		MBzP		MCOP		MCPP		MECPP	
		GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)
No	12	61.6	(49.9, 76.2)	52.2	(38.2, 71.3)	6.63	(3.78, 11.6)	0.410	(0.221, 0.760)	0.933	(0.367, 2.37)	0.596	(0.411, 0.864)	37.2	(15.6, 88.6)
Yes	19	61.6	(44.6, 85.0)	50.5	(41.0, 62.3)	11.6	(8.22, 16.3)	0.360	(0.234, 0.553)	0.743	(0.439, 1.26)	0.699	(0.520, 0.941)	29.7	(18.6, 47.4)
p-value[1]		0.99		0.85		0.08		0.71		0.65		0.47		0.62	
Bottled water[5]															
No	33	45.4	(38.3, 53.9)	26.8	(22.2, 32.5)	14.1	(8.95, 22.2)	0.313	(0.212, 0.462)	0.579	(0.408, 0.820)	0.407	(0.322, 0.516)	26.5	(18.6, 37.7)
Yes	17	35.5	(27.0, 46.7)	29.3	(21.1, 40.5)	12.1	(3.49, 41.7)	0.360	(0.232, 0.557)	0.377	(0.245, 0.580)	0.278	(0.180, 0.428)	14.0	(9.95, 19.8)
p-value[1]		0.12		0.64		0.81		0.62		0.11		0.11		0.01	

Characteristic	N	MEHHP		MEHP		MEOHP		ΣLMWP		ΣHMWP		ΣDEHP		ΣDBP	
Sex															
Female	50	15.3	(11.7, 20.0)	2.29	(1.62, 3.25)	9.60	(7.43, 12.4)	4.85	(3.67, 6.40)	1.73	(1.33, 2.24)	1.67	(1.29, 2.18)	3.21	(2.79, 3.70)
Male	50	21.3	(16.3, 27.8)	3.40	(2.55, 4.54)	13.0	(10.1, 16.9)	6.33	(5.45, 7.34)	2.45	(1.89, 3.18)	2.34	(1.80, 3.04)	5.46	(4.65, 6.42)
p-value[1]		0.08		0.08		0.09		0.09		0.06		0.07		<0.0001	
Age															
≤57	52	20.0	(14.6, 27.3)	3.48	(2.46, 4.94)	12.4	(9.15, 16.8)	5.07	(4.38, 5.87)	2.32	(1.72, 3.13)	2.23	(1.65, 3.01)	4.19	(3.58, 4.89)
>57	48	16.2	(13.1, 20.0)	2.20	(1.67, 2.90)	10.0	(8.24, 12.2)	6.10	(4.56, 8.15)	1.81	(1.47, 2.23)	1.74	(1.41, 2.15)	4.19	(3.48, 5.05)
p-value[1]		0.27		0.04	‡	0.25		0.26		0.17		0.18		0.99	
Education															
≤ middle school	54	17.5	(13.1, 23.4)	2.48	(1.79, 3.44)	10.8	(8.12, 14.3)	5.04	(4.41, 5.76)	1.96	(1.47, 2.61)	1.88	(1.40, 2.51)	3.89	(3.34, 4.52)
> middle school	46	18.7	(14.7, 23.8)	3.21	(2.35, 4.40)	11.7	(9.34, 14.7)	6.19	(4.55, 8.42)	2.19	(1.75, 2.73)	2.11	(1.68, 2.64)	4.58	(3.80, 5.52)
p-value[1]		0.71		0.25	‡	0.64		0.22	‡	0.54		0.53		0.18 ‡	
Income[2]															
Low	65	16.7	(13.1, 21.3)	2.71	(2.03, 3.62)	10.4	(8.24, 13.1)	5.10	(4.47, 5.82)	1.92	(1.51, 2.43)	1.84	(1.45, 2.34)	4.08	(3.53, 4.71)
High	35	20.9	(15.3, 28.4)	2.96	(2.02, 4.31)	12.8	(9.54, 17.2)	6.45	(4.39, 9.48)	2.35	(1.76, 3.15)	2.26	(1.69, 3.04)	4.41	(3.56, 5.47)
p-value[1]		0.26		0.71		0.27		0.25		0.27		0.28		0.54	
BMI[3]															
<25 kg/m3	56	20.3	(15.2, 27.0)	3.26	(2.38, 4.46)	12.5	(9.48, 16.5)	5.74	(5.05, 6.53)	2.29	(1.74, 3.02)	2.21	(1.67, 2.92)	4.64	(3.96, 5.43)
≥25 kg/m3	41	16.2	(12.8, 20.6)	2.32	(1.65, 3.27)	10.1	(7.99, 12.7)	5.33	(3.76, 7.56)	1.86	(1.46, 2.36)	1.78	(1.39, 2.27)	3.68	(3.05, 4.44)
p-value[1]		0.23		0.14	‡	0.24		0.69		0.25		0.24		0.06	

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Characteristic	N	MEHHP		MEHP		MEOHP		ΣLMWP		ΣHMWP		ΣDEHP		ΣDBP	
Smoking[4]															
Former/never	19	18.9	(15.3, 23.3)	2.84	(2.07, 3.90)	11.5	(9.41, 14.0)	7.05	(5.19, 9.58)	2.23	(1.80, 2.75)	2.12	(1.70, 2.64)	5.81	(4.08, 8.27)
Current	31	22.9	(15.0, 34.9)	3.80	(2.47, 5.86)	14.1	(9.37, 21.2)	5.92	(5.04, 6.94)	2.60	(1.73, 3.91)	2.49	(1.65, 3.76)	5.26	(4.45, 6.21)
p-value[1]		0.41		0.27		0.36		0.30		0.49		0.48		0.60	
≥13 cigarettes/day among smokers[4]															
No	12	27.3	(11.6, 64.2)	4.81	(2.24, 10.3)	16.1	(7.05, 36.7)	5.76	(4.61, 7.19)	3.00	(1.30, 6.94)	2.90	(1.24, 6.75)	5.21	(4.09, 6.64)
Yes	19	20.4	(12.4, 33.6)	3.27	(1.86, 5.76)	13.0	(7.98, 21.1)	6.02	(4.75, 7.63)	2.38	(1.48, 3.82)	2.26	(1.40, 3.65)	5.29	(4.15, 6.75)
p-value[1]		0.53		0.39		0.63		0.77		0.60		0.59		0.92	
Bottled water[5]															
No	33	19.0	(13.5, 26.8)	2.58	(1.64, 4.07)	11.8	(8.51, 16.5)	4.59	(3.86, 5.46)	2.12	(1.51, 2.97)	2.05	(1.46, 2.89)	3.33	(2.82, 3.94)
Yes	17	10.1	(6.78, 14.9)	1.83	(1.03, 3.24)	6.39	(4.46, 9.16)	5.40	(2.42, 12.0)	1.17	(0.820, 1.67)	1.13	(0.787, 1.62)	2.99	(2.25, 3.97)
p-value[1]		0.02		0.33		0.01		0.68		0.02		0.02		0.49	

Abbreviations: body mass index (BMI), confidence interval (CI), geometric mean (GM), mono-n-butyl phthalate (MBP), mono-isobutyl phthalate (MiBP), monoethyl phthalate (MEP), monobenzyl phthalate (MBzP), mono(carboxyoctyl) phthalate (MCOP), mono(3-carboxypropyl) phthalate (MCPP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), low molecular weight phthalate sum (ΣLMWP), high molecular weight phthalate sum (ΣHMWP), di(2-ethylhexyl) phthalate sum (ΣDEHP), dibutyl phthalate sum (ΣDBP).

[1] p-value for Satterthwaite t-test; ‡ and † represent p<0.05 and p<0.1, respectively, in linear regression models testing dose-response (age, education, income, and BMI only)

[2] High income was defined as ≥1,000 yuan/month for males and ≥20,000 yuan/year for females

[3] Measured between second and third urine sample collections.

[4] Males only

[5] Females only

Table 6

Measures of reproducibility for urinary phthalate metabolite concentrations.

Phthalate Metabolite (μg/g creatinine)	Males				Females			
	n	ICC[1]	(95% CI)	Spearman correlation coefficient[2]	n	ICC[1]	(95% CI)	Spearman correlation coefficient[2]
MBP	48	0.30	(0.14, 0.45)	0.26	48	0.15	(0.02, 0.30)	0.24
MiBP	48	0.21	(0.07, 0.36)	0.26	48	0.16	(0.02, 0.30)	0.06
MEP	48	0.15	(0.01, 0.30)	0.17	48	0.15	(0.02, 0.30)	0.00
MBzP	48	0.18	(0.04, 0.32)	0.05	48	0.11	(-0.01, 0.24)	0.08
MCOP	48	0.01[3]	(-0.15, 0.09)	0.21	48	0.09	(-0.01, 0.21)	0.11
MCPP	48	0.18	(0.05, 0.32)	0.14	48	0.11	(0.00, 0.24)	0.14
MECPP	48	0.06	(-0.07, 0.20)	0.21	48	0.13	(-0.01, 0.28)	0.25
MEHHP	48	0.05	(-0.08, 0.19)	0.26	48	0.04	(-0.09, 0.19)	0.09
MEHP	48	0.20	(0.06, 0.35)	0.43	48	0.20	(0.06, 0.35)	0.21
MEOHP	48	0.04	(-0.08, 0.19)	0.21	48	0.04	(-0.09, 0.18)	0.11
ΣLMWP[4]	48	0.14	(0.01, 0.28)	0.22	48	0.03	(-0.08, 0.15)	-0.02
ΣHMWP[4]	48	0.03	(-0.10, 0.17)	0.21	48	0.07	(-0.06, 0.22)	0.13
ΣDEHP[4]	48	0.05	(-0.08, 0.20)	0.25	48	0.07	(-0.06, 0.22)	0.12
ΣDBP[4]	48	0.26	(0.12, 0.41)	0.28	48	0.12	(0.01, 0.25)	0.20

Abbreviations: confidence interval (CI), intraclass correlation coefficient (ICC), mono-n-butyl phthalate (MBP), mono-isobutyl phthalate (MiBP), monoethyl phthalate (MEP), monobenzyl phthalate (MBzP), mono(carboxyoctyl) phthalate (MCOP), mono(3-carboxypropyl) phthalate (MCPP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), low molecular weight phthalate sum (ΣLMWP), high molecular weight phthalate sum (ΣHMWP), di(2-ethylhexyl) phthalate sum (ΣDEHP), dibutyl phthalate sum (ΣDBP).

[1] Sample 1, sample 2, and sample 3

[2] Sample 1 and the average of samples 2 and 3

[3] As described in the Methods, a negative estimate was obtained but replaced by an arbitrarily small value in this instance.

[4] Molar sums; units are nanomoles per gram creatinine.