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Determinants of Phthalate Ex posures in Pregnant Women in New York City

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Declaration of interests

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

Abstract

Previous studies have provided data on determinants of phthalates in pregnant women, but results were disparate across regions. We aimed to identify the food groups and demographic factors that predict phthalate exposure in an urban contemporary pregnancy cohort in the US. The study included 450 pregnant women from the New York University Children's Health and Environment Study in New York City. Urinary concentrations of 22 phthalate metabolites, including metabolites of di-2-ethylhexylphthalate (DEHP), were determined at three time points across pregnancy by liquid chromatography coupled with tandem mass spectrometry. The Diet History Questionnaire II was completed by pregnant women at mid-pregnancy to assess dietary information. Linear mixed models were fitted to examine determinants of urinary phthalate metabolite concentrations. Using partial-linear single-index (PLSI) models, we assessed the major contributors, among ten food groups, to phthalate exposure. Metabolites of DEHP and its ortho-phthalate replacement, diisononyl phthalate (DiNP), were found in >90% of the samples. The sum of creatinine-adjusted DiNP metabolite concentrations was higher in older and single women and in samples collected in summer. Hispanic and non-Hispanic Black women had lower urinary concentrations of summed metabolites of di-n-octyl phthalate (DnOP), but higher concentrations of low molecular weight phthalates compared with non-Hispanic White women. Each doubling of grain products consumed was associated with a 20.9% increase in ΣDiNP concentrations (95%CI: 4.5, 39.9). PLSI models revealed that intake of dried beans and peas was the main dietary factor contributing to urinary ΣDEHP, ΣDiNP, and ΣDnOP levels, with contribution proportions of 76.3%, 35.8%, and 27.4%, respectively. Urinary metabolite levels of phthalates in pregnant women in NYC varied by age, marital status, seasonality, race/ethnicity, and diet. These results lend insight into the major determinants of phthalates levels, and may be used to identify exposure sources and guide interventions to reduce exposures in susceptible populations.

Keywords

Phthalates; Determinants; Birth cohort; Pregnancy; Diet; DEHP

1. Introduction

Phthalates are synthetic chemicals widely used as plasticizers and fragrance stabilizers in the manufacturing of a variety of industrial and consumer products (Wang et al., 2019). Phthalates with high molecular weight (HMW) are mainly used in polyvinyl chloride polymers, food packaging, and building materials, whereas low molecular weight (LMW) phthalates are primarily used in personal care products, as well as medical and dental applications (Fang et al. 2017; Henderson et al. 2020). As phthalates are not covalently bound to these products, they can easily migrate into the surrounding environment, contributing to ubiquitous human exposure via ingestion, inhalation, and dermal absorption (Fang et al., 2017; Maestre-Batlle et al., 2020; Paluselli et al., 2019; Young et al., 2018). Phthalate metabolites are prevalent in human biofluids, with high detection rates in urine, serum, amniotic fluid, breast milk, and semen from populations all around the world (Henderson et al., 2020; Song et al., 2020; Zhu et al., 2019). Pregnant women's phthalate exposure has been related to adverse birth outcomes, as

well as immune dysfunction and metabolic dysregulation of offspring (Jeddi et al., 2016; Kahn et al., 2020; Philips et al., 2017; Radke et al., 2018; Radke et al., 2020; Sears and Braun, 2020). Di-2-ethylhexylphthalate (DEHP), dibutyl phthalate (DBP), and butyl benzyl phthalate (BBP) have been regulated in toys and other childcare products in North America and/or Europe due to health concerns (USEPA, 2012; USFDA, 2012; Ventrice et al., 2013). Yet, regulations on the use of their replacements are still limited because the relevant research on health effects of those replacements is still limited. Notably, several studies have reported decreasing levels of DEHP metabolites but increasing trends in the concentrations of metabolites of ortho-phthalate replacements, i.e, di-isononylphthalate (DiNP) and di-isodecylphthalate (DiDP) in human biospecimens in recent decades (Göen et al., 2011; Mitro et al., 2019; Zota et al., 2014). More research on the sources, determinants, and health effects of these replacements is becoming increasingly important.

Several previous studies have examined demographic and/or dietary determinants of phthalates among pregnant women in Europe, Asia, and North America. Age, race/ethnicity, socioeconomic status, parity, personal care product use, and intake of certain food items were associated with phthalate exposure (Casas et al., 2011; Li et al., 2019; Pacyga et al., 2019; Papadopoulou et al., 2019; Philips et al., 2018; Polinski et al., 2018; Rodríguez-Carmona et al., 2020; Schecter et al., 2013; Serrano et al., 2014; Valvi et al., 2015). While diet is known to be a major source of exposure to HMW phthalates (Guo and Kannan, 2013), the few studies that have investigated specific dietary components among pregnant women have reported inconsistent results about which food groups are associated with phthalates (Yang et al. 2019, Pacyga et al. 2019). Besides, most of the previous studies used one spot urine sample to assess exposure. Considering the high variability of urinary biomarkers of phthalates, repeated measurements of phthalate metabolites are essential to evaluate phthalate exposure throughout pregnancy (Faÿs et al., 2020; Gao et al., 2017; Yazdy et al., 2018).

The New York University Children's Health and Environment Study (NYU CHES) is a contemporary, racial/ethnically diverse birth cohort in New York City (Trasande et al., 2020). Taking advantage of multiple urine samples collected repeatedly over the course of pregnancy in women of this cohort, we examined dietary and demographic factors associated with phthalate metabolite levels, including metabolites of DEHP and the ortho-phthalate replacements.

2. Materials and methods

2.1 Study population

NYU CHES recruited women who were 18 years and older and <18 weeks pregnant, and planned to deliver at three NYU-affiliated hospitals, namely NYU Langone Hospital —Manhattan, Bellevue Hospital, and NYU Langone Hospital—Brooklyn (Trasande et al., 2020). Of the 2,000 pregnant women who were enrolled in NYU CHES between March, 2016 and April, 2019 and delivered a live birth, 1,384 women provided valid information on dietary intake using a food frequency questionnaire (Diet History Questionnaire II). In this group, 809 provided spot urine samples at three time points during pregnancy: <18, 18–24,

and >24 gestational weeks (Deierlein et al., 2021; Liu et al., 2021). We measured urinary concentrations of phthalate metabolites in randomly selected 450 of these women.

All participating women provided written informed consent and the study was approved by the Institutional Review Board of the New York University Grossman School of Medicine.

2.2 Measurement of Phthalate Metabolites

Repeated spot urine samples were collected in early, mid and late pregnancy, at clinics where pregnant women received their prenatal care during pregnancy. Staff provided materials and instructed pregnant women in how to collect a sample. After being fully mixed, each sample was aliquoted into polyethylene containers and stored in −80°C refrigerators. Mean gestational ages at urine collection were 10.9 [standard deviation (SD) = 3.6], 20.7 (SD = 2.0), and 29.0 (SD = 3.3) weeks, with range of 4–18, 16–24, and 25–36 weeks in early, mid and late pregnancy, respectively.

Phthalate metabolites were measured in each urine sample. Prior to chemical analysis, the urine sample was thawed and prepared in a laboratory according to a standardized procedure. Liquid chromatography with tandem mass spectrometry (LC-MS/MS) was used to quantify 22 phthalate metabolite concentrations (Guo et al., 2011; Guo et al., 2014). Briefly, the method involved spiking of stable isotope analogues of phthalate metabolites, solid phase extraction of 0.5 ml of urine, and analysis by LC-MS/MS. The 22 phthalate metabolites, their corresponding 14 parent phthalates, and phthalic acid, the final common metabolite of phthalate acid esters and a marker of overall phthalate exposure, are listed in Table S1 (Supplemental materials). For the purpose of this study, we restricted our analyses to phthalate metabolites that were detected in >50% of the samples. For these metabolites, the values below the limit of detection (LOD) were replaced with $\mathrm{LOD}/\sqrt{2}$. Concentrations of creatinine were also determined by HPLC-MS/MS. Urinary phthalate concentration was divided by urinary creatinine concentration t o account for urinary dilution. The laboratory participated in several external quality assurance schemes (including German-External Quality Assurance Scheme and Centers for Disease Control and Prevention-Biomonitoring Quality Assurance Support Program) to validate the methods (Guo et al., 2011; Guo et al., 2014). Quality Assurance/Quality (QA/QC) control steps, including method blank, spiked blank, and matrix-spiked sample/duplicates were implemented in the chemical analysis procedures.

We grouped phthalate metabolites on the basis of their parent diester or usage as shown in Table S1. We then summed the molar concentrations of metabolites to yield concentrations of three parent phthalates that had multiple metabolite contributors: DEHP and two of its ortho-phthalate replacements, DiNP and di-n-octyl phthalate (DnOP). Phthalate metabolites with molecular weights <250 daltons were grouped as low molecular weight phthalates (ΣLMW, nmol/l); phthalate metabolites with molecular weights ≥250 daltons were grouped as high molecular weight phthalates (ΣHMW, nmol/) (Wolff et al., 2008). To estimate likely dietary phthalate exposure (ΣFood packaging phthalates), we summed molar concentrations of metabolites that are commonly used in food packaging materials, including metabolites of DEHP (Pacyga et al., 2019), DiNP (Fisher et al., 2019), diisobutyl phthalate (DiBP) (García

Ibarra et al., 2018), DnOP (Pacyga et al., 2019), and benzylbutyl phthalate (BzBP) (Pacyga et al., 2019).

2.3 Demographic information

We used questionnaires administered during prenatal visits and at birth to collect information on sociodemographic variables (i.e., race/ethnicity, educational level, marital status, employment, household income, insurance) and alcohol consumption, which have been shown in the literature to be associated with urinary phthalate concentrations (Bloom et al., 2019; Li et al., 2019; Rodríguez-Carmona et al., 2020; Tranfo et al., 2013; Wang et al., 2019). Electronic health records provided data on women's age at enrollment, pre-pregnancy weight and height, and parity. Pre-pregnancy body mass index (BMI) was computed based on pre-pregnancy weight and height. The cotinine was measured in urine samples using liquid chromatography/tandem mass spectrometry (LC/MS/MS) method. We used 0.013 ng/mL (the LOD of urinary cotinine measurement) as the cut-off for any tobacco exposure during pregnancy. Sampling season was computed based on the date of urine sample collection, and was divided into four seasons.

2.4 Dietary survey

Participants self-reported their dietary habits over the past year using the Diet History Questionnaire II (DHQ-II, validated in English and translated into Spanish) at mid-pregnancy [median (interquartile range) = 26.9 (10.1) weeks] (Institute, 2020). DHQ-II asks about 124 commonly consumed food items and includes both frequency and portion size questions. The forms, codebook, and programs used for categorizing the items of DHQ-II are available on the website of the U.S. National Cancer Institute (Institute, 2020). Ten food groups were created from the DHQ-II data based on the U.S. Department of Agriculture's (USDA) MyPyramid Equivalents Database (MPED) and Food Patterns Equivalents Database (FPED) (USDA, 2020): vegetables (cup equivalents), fruit (cup equivalents), grains (ounce equivalents), dairy (cup equivalents), meat (ounce equivalents), seafood (ounce equivalents), eggs (ounce equivalents), nuts and seeds (ounce equivalents), dried beans and peas (cup equivalents), and soy products (ounce equivalents). The details of how foods were queried were described in our previous study (Deierlein et al., 2021).

2.6 Statistical analyses

Means (SD) or frequencies (percentage) were used to describe participant characteristics. Median (25^{th} percentile, 75^{th} percentile) urinary concentrations of each phthalate metabolite and each group of phthalates were used to describe their distributions. The intra-class correlation coefficient (ICC) for each phthalate metabolite across the three prenatal time points was calculated using a two-way mixed effect model to evaluate the variability of the chemical across pregnancy (Koo and Li, 2016). Spearman correlation coefficients were calculated for mean concentrations across pregnancy of each pair of phthalate metabolites.

First, crude associations of each determinant (demographic factors and food groups) with each summed phthalate concentration (ΣDEHP, ΣDiNP, ΣDnOP, ΣLMW, ΣHMW, and ΣFood packaging phthalates) were analyzed across pregnancy using linear mixed models (LMMs). Then, we reran the adjusted models including all determinants a s

independent variables to mutually adjusted for them. In all analyses, creatinine-adjusted phthalate concentrations and food intakes were natural log-transformed because of their skewed distributions. We assessed the linearity of relationships between food groups and phthalate metabolite levels by partial-linear single-index (PLSI) models with mixed-effects (see below). If there were non-linear associations, quadratic terms were included in the LMMs for optimization. Ten food groups were included in the model because dietary was regarded as important sources of phthalate exposure. For the selection of demographic factors, we included the demographic factors related to phthalate exposure levels in previous epidemiological researches, including age (Polinski et al., 2018; Wenzel et al., 2018), pre-pregnancy BMI (Polinski et al., 2018; Wenzel et al., 2018), race/ethnicity (Polinski et al., 2018), employment status (Polinski et al., 2018), parity (Lyden et al., 2020), marital status (Polinski et al., 2018; Wenzel et al., 2018), and sampling seasons (Li et al., 2019; Shu et al., 2018). Because socioeconomic factors are also reported to be predictors of phthalate exposure in previous studies (Kobrosly et al., 2012; Lyden et al., 2020), we also included factors, such as educational levels, hospital sites, annual household income, insurance, and employment status in the model. Variance inflation factors (VIF) indicated that there was no multi-collinearity between household income, employment status, educational level, insurance, and hospital site, therefore we kept all the socioeconomic indicators in the final models. Metabolism of phthalates in human can be catalyzed by cytochrome P450 (Stajnko et al., 2022), which can be influenced by tobacco smoke exposure (Czekaj et al., 2005). Therefore, cotinine, a biomarker of tobacco smoke exposure, was considered as factor related to metabolism and included in the final model. Regression coefficients (β) were transformed to percent changes in phthalate concentrations to improve the interpretability of our results (Barrera-Gómez and Basagaña, 2015). To test the robustness of the associations, we performed the analysis using raw phthalate metabolite levels as dependent variables and additionally including urinary creatinine as a covariate.

To assess the joint effect of food groups and to identify the main dietary contributors to phthalate exposure, we utilized PLSI mixed-effects model with a random intercept (Wang et al., 2020). The PLSI model integrates all dietary factors as a single index by a linear combination of the exposures and assesses the association between the single index and outcome using a nonparametric link function. PLSI allows the associations between exposures and outcomes to be in the positive or negative direction, provides explicit and interpretable quantification of the relative direction and importance of the exposures. Importantly, PLSI can deal with repeated measures data, which is suitable for the present study. Dietary factors were normalized before being entered into the PLSI model. The relative importance of each component was calculated by variance contribution to the single index.

Out of 2,000 participants in the cohort, 450 (20.5%) had data on both diet and urinary phthalate metabolite levels. To account for potential selective inclusion, we applied inverse probability weighting (IPW) by calculating the individual probability of being included in this analysis via logistic regression based on the distribution of the above-mentioned covariates. Among the 450 individuals included in the analysis, there were fewer than 5% missing values for each covariate; as such, we imputed missing values with the population

mean for continuous variables and the category with the largest proportion for categorical variables.

We used the method "effective number (Me)" of testing to control the family-wise error rate (FWER). As an extension of the conventional Bonferroni adjustment, Me-based method replaced M (M represents the actual number of markers being tested) by a smaller value called the effective number of independent markers (Me), resulting in a new α as α/Me (Li et al., 2012). In the present study, we defined the threshold of significance as *P* value <0.0167, which was obtained by dividing 0.05 by "effective number of tests (Me)" based on eigenvalues of the correlation matrix among pairs of the main phthalate groups (Li et al., 2012), namely ΣDEHP, ΣDiNP, ΣDnOP, and ΣLMW. We did not consider ΣHMW or ΣFood packaging phthalates in our calculation of the adjusted *P* value because of substantial overlap among components of the groups, i.e., ΣHMW and ΣFood packaging phthalates mainly consist of ΣDEHP, ΣDiNP and ΣDnOP. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Analyses using PLSI models were performed in R (version 3.3.2; R Development Core Team).

3 Results

3.1 Descriptive

Participant characteristics are presented in Table 1. Among 450 women included in this analysis, Hispanic women accounted for approximately half of the study population (52.4%), followed by non-Hispanic White women (29.6%). Mean age of women at enrollment was 31.6 years (SD = 5.5). Nearly half of pregnant women received a high school degree or less (45.1%) and were nulliparous (48.2%). The majority of participants were married/partnered (89.6%) and employed during pregnancy (66.0%). The women included in this subset had similar demographic characteristics compared with the entire NYU CHES cohort (Supplemental Materials, Table S2).

Out of the 22 phthalate metabolites, 16 were detected in >50% of the samples, including metabolites of dimethyl phthalate (DMP), diethyl phthalate (DEP), DBP, DEHP, DiNP, and DnOP (Table 2). The metabolites of DEP and DEHP had the highest levels in urine compared with other phthalates (median mono-ethyl phthalate (MEP) = 34.2 ng/mL; ΣDEHP = 69.4 nmol/L). Mono-(carboxyisooctyl) phthalate (MCiOP), a metabolite of DiNP, was detected in >98% of the samples. Among the three metabolites of DnOP we measured, mono-(3-carboxypropyl) phthalate (MCPP) had the highest detection rate: 90%. ICCs of the majority of phthalate metabolites were in the range of 0.2 – 0.6, indicating weak to moderate reproducibility and reliability across pregnancy. Most of the phthalate metabolites were weakly correlated with each other, except DEP and DiBP metabolites (MEP, MiBP) were moderately correlated with the metabolites of DEHP (MECPP, MCMHP, mEOHP, MEHHP, MEHP) (Supplemental Materials, Table S3).

3.2 Demographic and dietary determinants of phthalate concentrations

The results of single-determinant analysis (Table S4) were mostly consistent with adjusted models that included all demographic and dietary factors. We found that age, race/ethnicity,

marital status, sampling season, and alcohol consumption were associated with one or more phthalate metabolite groupings in both single-determinant analysis and mutually-adjusted models (Table 3). Hospital site, educational level and insurance type were significant determinants of phthalate metabolites in the single-determinant analysis, but no such associations were observed in the mutually-adjusted models. The associations of each demographic factor with the different phthalate metabolite groups usually were in the same direction and had similar magnitude, although not all of the estimates reached the threshold of statistical significance. For example, age at enrollment was positively associated with metabolites of ΣDEHP, ΣDiNP, ΣDnOP, ΣHMW, ΣLMW as well as ΣFood packaging phthalates, whereas pre-pregnancy BMI was negatively associated with each of the groups. Among these the only significant finding was that each year increase in age was associated with a 2.6% increase in ΣDiNP levels (95% Confidence Interval (CI) = 0.8%, 4.4%). In comparison with non-Hispanic White women, Hispanic and non-Hispanic Black women had higher concentrations of ΣLMW, but non-Hispanic Black women had lower ΣDnOP levels. Compared with being married or partnered, being single was associated with higher levels of all groups of phthalates, although the associations were significant only for ΣDiNP (43.7%, 95% CI = 9.4%, 88.6%), ΣHMW (41.4%, 95% CI = 17.5%, 70.3%) and ΣFood packaging phthalates (28.6%, 95% CI = 7.3%, 54.2%). With winter as reference, sampling in summer was associated with higher levels of ΣDiNP (23.1%, 95%CI = 3.7%, 46.2%). Pregnant women who had history of alcohol consumption had lower levels of ΣDEHP (−26.7%, 95% CI = −36.2%, −15.8%) and ΣDnOP (−20.7%, 95% CI = −32.4%, −7.1%). Although no significant associations were observed between other demographic factors and phthalate metabolite levels, we observed consistent directionality among associations of the phthalate groups and alcohol consumption, tobacco use, hospital site, and insurance type. Consistent with models using creatinine-corrected phthalate concentrations as dependent variables, race/ethnicity, marital status, and alcohol consumption were significant determinants of phthalate metabolites in the models using raw phthalate metabolite levels and including urinary creatinine as covariate (Table S5). In an alternative approach, we performed multiple-imputation to replace values below the detection limit based on the distribution (left-censored data) of the chemical levels (Chen et al., 2011), the results calculated by multiple-imputed data were essentially unchanged compared with the substitution strategy, yielding robust associations. Sensitivity analyses using models without adjustment for gestational age at time of dietary survey showed similar results.

As shown in Table 4, each doubling in grains consumption was associated with a 20.9% higher level of ΣDiNP (95%CI = 4.5%, 39.9%). Each doubling of seafood consumption was associated with a 2.1% lower level of ΣDnOP (95%CI = −3.5%, −0.6%). Each doubling of intake of dried beans and peas was associated with 12.1% (95%CI = 3.9%, 20.9%) higher concentration of ΣDiNP. Both ΣDEHP and ΣHMW had non-linear associations with intake of dried beans and peas: the quadratic terms were positive and significant in the models, indicating U-shaped associations. Further, consumption of dried beans and peas was the only dietary component that had a significant association with ΣFood packaging phthalates and the dose-response curve was also U-shaped. There were no significant associations of vegetables, fruit, dairy, meat, eggs, nuts and seeds, or soy products with any phthalate groups. Likewise, daily energy intake was not associated with any of the phthalate groups.

The joint-effect analysis by PLSI model revealed that intake of dried beans and peas was the primary contributor to urinary levels of ΣDEHP, ΣDiNP, and ΣHMW (Table 5). Specifically, intake of dried beans and peas represented 76.3% of the contribution from food groups to urinary levels of ΣDEHP. The intake of grains and seafood contributed 5.0% and 11.6% to the overall effect on ΣDEHP levels, respectively. For ΣHMW, dried beans and peas was the predominant food group contributing to the joint effect, with 63.3%. Although nuts/seeds contributed a large proportion to ΣDiNP, the association was not robust, because the LMM revealed a non-significant association between intake of nuts/seeds and ΣDiNP metabolite concentration.

4 Discussion

We relied on repeatedly measured prenatal urinary phthalate metabolites to identify dietary factors and sociodemographic characteristics associated with phthalate exposure among pregnant women in our contemporary, diverse urban cohort. Being older, being single and sampling in summer were associated with higher urinary ΣDiNP metabolite concentrations. Alcohol consumption during pregnancy was associated with lower ΣDEHP and ΣDnOP concentrations. Hispanic and non-Hispanic Black women had lower ΣDnOP but higher ΣLMW concentrations compared with non-Hispanic White women. Among ten food groups, dried beans and peas contributed most to increased levels of all phthalate groups except ΣLMW. These results help to expand our knowledge regarding the determinants of phthalates, which can help to identify pregnant women at higher risk of exposure for targeted intervention.

We compared phthalate metabolite concentrations between our study sample and pregnant women in other cities or nations. Concentrations of certain phthalates were comparable with levels in pregnant women in California (MiBP, 6.8 vs. 7.2 ng/mL; MBP, 12.1 vs. 12.6 ng/mL), but the pregnant women in the present study had lower levels of benzylbutyl phthalate (BBzP) (2.4 vs. 6.4 ng/mL) and DEHP (MEHHP, 6.27 vs. 12.1 ng/mL) (Shin et al., 2020). As expected, with stronger regulation of legacy phthalates in the United States, pregnant women in NYC were exposed to substantially lower levels of metabolites of DEP, DBP, and DEHP compared with women in Mexico (MEP, 31.7 vs. 123.5ng/mL; MBP: 12.1 vs. 80.4 ng/mL; details in Table S6) and China (MEP, 31.7 vs. 119.0 ng/mL; MBP: 12.1 vs. 79.4 ng/mL; details in Table S6), whereas levels of ortho-phthalate replacements in our pregnancy cohort were similar to the PROGRESS birth cohort from Mexico (MCiNP: 0.7 VS. 0.9 ng/mL)(Gao et al., 2018; Wu et al., 2020). This is in line with national data showing a decrease in DEHP levels in the U.S. general population in recent years and a simultaneous increase in levels of DiNP (Reyes and Price, 2018b).

Consistent with Wenzel et al.'s study (Wenzel et al., 2018), we found that being single was associated with higher concentrations of all groups of phthalate metabolites compared with being married/partnered, although the associations were significant only for ΣDiNP, ΣHMW, and ΣFood packaging phthalates. The higher consumption of convenience foods packaged with plastic materials among single women compared with married/partnered women could be the explanation (Peltner and Thiele, 2018; Yang et al., 2019), as DiNP has been authorized for use in plastic food contact materials (EFSA Panel on Food Contact

Materials et al., 2019). Sampling in warm weather (summer) was also a predictor of higher DiNP levels, as seen in other studies (Li et al., 2019; Shu et al., 2018). As DiNP is used in food contact materials, one possible explanation is that higher environmental temperature might contribute to phthalates migrating into food, resulting in higher urinary DiNP metabolite levels. Also, DiNP is used in PVC flooring, home furnishings, and building materials, and higher temperature might facilitate DiNP emission (Castagnoli et al., 2019). Older age was additionally associated with higher levels of DiNP metabolites in this NYC pregnant population, however, a study conducted among pregnant women from Puerto Rico did not observe similar associations between age and DiNP metabolites (Cantonwine et al., 2014). Although speculative, the different lifestyles of women of relatively older age might be a possible explanation, such as higher frequency of house cleaning and gardening, which may result in more inhalation of DiNP-contaminated dust and more contact with plastic tools.

In this analysis, sociodemographic factors were not associated with levels of DEHP. Hispanic and non-Hispanic Black women had higher ΣLMW levels than non-Hispanic White women, similar to other reports in pregnant women (Polinski et al., 2018) and in the general population (Nguyen et al., 2020). Considering that LMW phthalates are widely used in personal care products, these associations may be explained by differences in personal care product use by race/ethnicity (Taylor et al., 2017). The observed racial/ethnic disparities in phthalate exposure in pregnant women could translate into differential fetal and postnatal growth and development, as higher concentrations of gestational urinary phthalates have been associated with poorer birth outcomes, delayed neurodevelopment, immune dysfunction, and metabolic dysregulation in later life (Bloom et al., 2019; Bornehag et al., 2018; Braun, 2017).

Accounting for the joint effects of 10 food groups via PLSI analysis, we observed that intake of dried beans and peas was the main contributor to DEHP metabolite levels and that this was the only food group substantially associated with DEHP levels. In contrast, The Infant Development and Environment Study (TIDES) reported dairy consumption as a predictor of lower levels of DEHP metabolites (Serrano et al. 2014). In our study, consumption of grains and of dried beans and peas were dietary determinants of higher DiNP metabolite levels in LMMs. This was confirmed via PLSI analysis in which grains and dried beans and peas were the top positive contributors to DiNP levels across pregnancy, accounting for 37% and 14%, respectively. It is not clear why these two specific food groups were strong predictors of DiNP exposure, although DiNP has been authorized for use in plastic food contact materials (EFSA Panel on Food Contact Materials et al., 2019). Other studies have reported associations of various food groups with phthalates, such as a study in Colorado that reported milk consumption as a predictor of DBP and a study in Puerto Rico that found intake of chicken or cheese predicted BBzP exposure in pregnant women (Polinski et al., 2018; Rodríguez-Carmona et al., 2020; Serrano et al., 2014). Dietary factors were not associated with urinary phthalate metabolites in European pregnant women, as neither the Generation R Study nor the HELIX project (consisting of cohorts from six European countries) reported associations between food groups and phthalates (Papadopoulou et al., 2019; Philips et al., 2018). These inconsistencies regarding dietary predictors of phthalates might be explained by the various regulations on the u

se of phthalates in food packaging and distinct dietary patterns across regions, the varied exposure levels and exposure assessment methods (one spot vs. repeated urine samples), dissimilar characteristics of populations, disparate dietary intake assessment methods, as well as distinct sets of covariates in fitted models.

We did not observe any dietary factors associated with ΣLMW, which can be explained by their main use in personal care products but not food contact materials (Wang et al., 2019). Unfortunately, we did not have data on specific food contact materials for the foods the women consumed. Future studies with detailed information on food contact materials is essential, as materials used during food production, processing, transportation, storage, preparation, and serving may be more relevant than food categories in investigating determinants of phthalates, especially HMW phthalates such as DEHP, DiNP, and DnOP (Pacyga et al., 2019).

The notable strengths of this study are the availability of repeated measures of urinary phthalate metabolites, which reduced the misclassification of exposure across pregnancy (Faÿs et al., 2020; Gao et al., 2017; Yazdy et al., 2018). In addition, measuring 22 phthalate metabolites (including legacy phthalates and the ortho-phthalate replacements) provided a more comprehensive evaluation of phthalate exposure compared with earlier studies (Christensen et al., 2014; Gao et al., 2018; Li et al., 2019; Qian et al., 2015; Reyes and Price, 2018a). Furthermore, the prospective design and diversity of the study sample provided valuable insights into determinants of phthalates among a pregnant population in a major U.S. metropolitan area.

However, the following limitations should be considered. The participation rate could not be accurately estimated as no information was available on the number of women who were approached. While our models included a wide range of sociodemographic factors that have been shown to be good indicators of personal care product use (Park et al., 2018), we did not have direct information on personal care product use across pregnancy. Similarly, food packaging, preparation, and storage have been reported to be associated with HMW phthalate exposure among pregnant women (Sterrett et al., 2021), but because we lacked information on exposure to these materials, limiting our ability to investigate the more specific origin of these phthalates. Furthermore, the DHQ-II was not the best tool to assess associations of food intakes with short half-life chemicals such as phthalates, as the DHQ-II collects long-term dietary information whereas phthalates are metabolized quickly. However, we used repeated urine samples collected in three trimesters to assess exposure across pregnancy, which roughly corresponds to the period covered by the DHQ-II. Correcting for urine dilution using creatinine may bias the evaluation of phthalate exposure because creatinine is influenced by renal function, protein intake, and physical activity, all of which vary across pregnancy (Carrieri et al., 2001). DHQ-II covers information on neither food packaging materials, food processing, nor recency of food items, limiting our ability to account for important phthalate sources. Considering that phthalates are quickly metabolized and the urinary concentrations of phthalate metabolites might change within a short period of time, a random spot urine sample collected for the present study can be a source of variability in exposure levels. Future studies are needed to explore the determinants of

new non-phthalate plasticizers, e.g., di-(2-ethylhexyl) terephthalate (DEHT) and diisononyl cyclohexanedicarboxylate (DINCH), especially in susceptible populations.

5 Conclusions

Pregnant women in NYC are widely exposed to legacy phthalates and ortho-phthalate replacements, with exposure levels varying by characteristics such as age, marital status, sampling season, race/ethnicity, and diet. Results of this study can provide useful information for regulation of phthalates from dietary sources.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HMW	high molecular weight
LMW	low molecular weight
DEHP	di-2-ethylhexylphthalate
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
DMP	Dimethyl phthalate
MMP	Mono-methyl phthalate
DEP	Diethyl phthalate
MEP	Mono-ethyl phthalate
DBP	Di-n-butyl phtalate
MBP	Mono-n-butyl phthalate
DCHP	Dicyclohexyl phthalate
MCHP	Monocyclohexyl phthalate
DiBP	Diisobutyl phthalate
MiBP	Mono-isobutyl phthalate
DPeP	Di-n-pentyl phthalate
MPeP	Mono-n-pentyl phthalate

DIPrP	Diisopropyl phthalate
MiPrP	Mono-isopropyl phthalate
DEHP	Di(2-ethylhexyl) phthalate
MECPP	Mono-(2-ethyl-5-carboxypentyl) phthalate
MCMHP	Mono-[(2-carboxymethyl) hexyl] phthalate
mEOHP	Mono-(2-ethyl-5-oxohexyl) phthalate
MEHHP	Mono-(2-ethyl-5-hydroxyhexyl) phthalate
MEHP	Mono-(2-ethylhexyl) phthalate
DiNP	Diisononyl phthalate
MiNP	Mono-isononyl phthalate
MCiOP	Mono-(carboxyisooctyl) phthalate
DnOP	Di-n-octyl phthalate
MOP	Mono-octyl phthalate
MCPP	Mono-(3-carboxypropyl) phthalate
MCHpP	Mono-(7-carboxyheptyl) phthalate
BzBP	Benzylbutyl phthalate
MBzP	Mono-benzyl phthalate
DiDP	Di-isodecyl phthalate
MCiNP	Mono-(carboxyisononyl) phthalate
DnHP	Di-n-hexyl phthalate
MHxP	Mono-n-hexyl phthalate
DHpP	Di-n-heptyl phthalate
MHpP	Mono-n-heptyl phthalate
PA	Phthalic acid
LOD	limit of detections
BMI	body mass index
SD	standard deviation
IQR	Interquartile range
ICC	intra-class correlation coefficient

IPW	inverse probability weighting
LMM	liner mixed models
PLSI	partial-linear single-index
NYC	New York City
NYU CHES	the New York University Children's Health and Environment Study
DHQ-II	electronic version of the Diet History Questionnaire II

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Table 1.

Participant characteristics (n=450).

Characteristics	Values
Age at enrollment, mean ± SD, years	31.55 ± 5.45
Pre-pregnancy BMI (kg/m^2)	26.38 ± 5.66
Race/ethnicity, n (%)	
Hispanic	236 (52.44)
Non-Hispanic White	133 (29.56)
Non-Hispanic Black	24 (5.33)
Asian	43 (9.56)
Other, including multiple race	14 (3.11)
Education status, n (%)	
High school degree or less	212 (47.11)
Some college but no degree	24 (5.33)
Bachelor's degree	99 (22.00)
Post-graduate degree	113 (25.11)
Married/living as married, n (%)	403 (89.56)
Annual household income, n (%)	
Less than $49,999	120 (26.67)
$49,999 – $99,999	44 (9.78)
$100,000 or more	145 (32.22)
Don't know	122 (27.11)
Hospital site, n (%)	
NYU Manhattan	195 (43.33)
NYU Brooklyn	119 (26.44)
Bellevue	136 (30.22)
Public insurance, n (%)	252 (56.00)
Employed, n (%)	297 (66.00)
Nulliparous, n (%)	217 (48.22)
Nulligravida	105 (23.33)
Multigravida	111 (24.67)
Alcohol consumption during pregnancy, n (%)	
Never user	169 (37.56)
User, stopped at pregnancy	210 (46.67)
User, continued in pregnancy	71 (15.78)
Twins, n (%)	3 (0.66)
Boys, n (%)	226 (50.22)
Birth weight, mean ± SD, kg	3.33 ± 0.49
Gestational duration at birth, mean ± SD, weeks	39.32 ± 1.54

Missing data, n (%): Pre-pregnancy BMI, 1 (0.22%); Education status, 2 (0.44%); Annual household income, 19 (4.19%); Insurance type, 3 (0.66%); Employment, 1 (0.22%); Infant sex, 7 (1.54%); Birth weight, 12 (2.64%). One nulliparous woman had missing information on gravidity, therefore, the sum of nulligravida women and multigravida women was 216.

Table 2

Concentrations of urinary phthalates metabolites in all samples or specific stage of pregnancy (n=450).

Phthalates and the urinary metabolites (ng/mL)	% > LOD in all samples	Median (P25, P75) [g]			ICC [h]
		Early pregnancy	Mid pregnancy	Late pregnancy	
Low Molecular Weight (LMW) [a]					
Mono-methyl phthalate (MMP)	62.0	1.76 (<LOD, 5.63)	1.60 (<LOD, 5.46)	1.47 (<LOD, 5.00)	0.62
Mono-ethyl phthalate (MEP)	99.6	34.18 (14.70, 96.80)	31.62 (13.33, 84.60)	31.98 (12.31, 104.00)	0.50
Mono-n-butyl phthalate (MBP)	99.0	12.10 (4.89, 24.55)	12.75 (4.93, 26.76)	11.48 (5.13, 23.56)	0.55
Monocyclohexyl phthalate (MCHP)	5.9	<LOD (<LOD, <LOD)	<LOD (<LOD, <LOD)	<LOD (<LOD, <LOD)	/
Mono-isobutyl phthalate (MiBP)	96.9	6.76 (2.72, 14.90)	7.17 (3.12, 16.23)	7.15 (2.94, 16.70)	0.22
Mono-n-pentyl phthalate (MPeP)	1.3	<LOD (<LOD, <LOD)	<LOD (<LOD, <LOD)	<LOD (<LOD, <LOD)	/
Mono-isopropyl phthalate (MiPrP)	13.7	<LOD (<LOD, <LOD)	<LOD (<LOD, <LOD)	<LOD (<LOD, <LOD)	/
∑LMW [b]	/	359.92 (158.36, 765.79)	325.76 (148.58, 679.37)	331.64 (146.11, 818.11)	0.48
High Molecular Weight (HMW) [a]					
Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)	99.3	6.19 (2.65, 11.63)	6.03 (2.83, 10.89)	5.99 (2.82, 11.59)	0.26
Mono-[(2-carboxymethyl) hexyl] phthalate (MCMHP)	97.4	2.30 (1.13, 5.55)	2.57 (1.24, 5.15)	2.61 (1.23, 5.04)	0.26
Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)	99.5	3.35 (1.59, 6.53)	3.72 (1.82, 6.68)	3.75 (1.81, 6.93)	0.39
Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)	99.5	6.27 (2.69, 12.10)	5.84 (2.94, 10.99)	5.89 (2.74, 11.17)	0.27
Mono-(2-ethylhexyl) phthalate (MEHP)	69.9	1.25 (<LOD, 3.67)	1.27 (<LOD, 3.68)	1.44 (<LOD, 3.45)	0.33
∑DEHP [c]	/	69.38 (31.49, 136.33)	69.13 (34.76, 125.67)	69.08 (35.36, 136.61)	0.34
Mono-isononyl phthalate (MiNP)	55.6	0.76 (<LOD, 3.40)	0.77 (<LOD, 4.17)	0.68 (<LOD, 4.47)	0.61
Mono-(carboxyisooctyl) phthalate (MCiOP)	98.1	1.44 (0.69, 3.22)	1.65 (0.73, 3.12)	1.54 (0.71, 3.11)	0.05
∑DiNP [d]	/	10.10 (4.57, 25.15)	11.23 (4.63, 26.44)	10.58 (4.32, 27.48)	0.18
Mono-octyl phthalate (MOP)	7.3	<LOD (<LOD, <LOD)	<LOD (<LOD, <LOD)	<LOD (<LOD, <LOD)	/
Mono-(3-carboxypropyl) phthalate (MCPP)	90.4	0.82 (0.45, 1.38)	0.80 (0.46, 1.46)	0.81 (0.45, 1.41)	0.03
Mono-(7-carboxyheptyl) phthalate (MCHpP)	52.7	0.15 (<LOD, 1.09)	0.17 (<LOD, 1.12)	0.13 (<LOD, 0.90)	0.13
∑DnOP [e]	/	4.80 (2.61, 10.63)	5.04 (2.64, 10.25)	4.68 (2.51, 9.64)	0.13
Mono-benzyl phthalate (MBzP)	88.6	2.40 (0.71, 6.41)	2.28 (0.62, 7.16)	2.35 (0.72, 6.63)	0.83
Mono-(carboxyisononyl) phthalate (MCiNP)	72.9	0.91 (<LOD, 2.29)	0.73 (<LOD, 1.90)	0.70 (<LOD, 1.89)	0.33

Phthalates and the urinary metabolites (ng/mL)	% > LOD in all samples	Median (P25, P75) [g]			ICC [h]
		Early pregnancy	Mid pregnancy	Late pregnancy	
Mono-n-hexyl phthalate (MHxP)	36.2	<LOD (<LOD, 0.06)	<LOD (<LOD, 0.07)	<LOD (<LOD, 0.06)	/
Mono-n-heptyl phthalate (MHpP)	45.6	<LOD (<LOD, 0.18)	<LOD (<LOD, 0.18)	<LOD (<LOD, 0.15)	/
∑HMW [f]	/	124.56 (59.27, 234.86)	119.92 (54.49, 225.40)	120.00 (57.72, 236.05)	0.45
Phthalic acid (PA)	98.6	17.62 (8.87, 31.34)	16.27 (8.30, 30.60)	16.74 (8.23, 32.03)	0.58

[a] High molecular weight (HMW) phthalates include those with molecular weight equal or over 250 Dalton and low molecular weight (LMW) are those with molecular weight less than 250 Dalton. Units of molar sums are nmol/L; Units of raw chemicals are ng/mL.

[b] ∑LMW was molar sum of MMP, MEP, MBP, MiBP. MCHP, MiPrP and MPeP were excluded because of low detection rates.

[c] ∑DEHP was molar sum of MECPP, MCMHP, mEOHP, MEHHP, MEHP.

[d] ∑DiNP was molar sum of MiNP, MCiOP.

[e] ∑DnOP was molar sum of MCPP, MCHpP. MOP was excluded because of low detection rate.

[f] ∑HMW was molar sum of ∑DEHP, ∑DiNP, ∑DnOP, MBzP, MCiNP. MHxP and MHpP were excluded because of low detection rates.

[h] ICCs were calculated based on two-way mixed effect and K means of multiple raters.

Abbreviation: LOD, limit of detection; ICC: intraclass correlation coefficient.

Table 3

Associations between demographic factors and phthalates metabolite levels in pregnant women, assessed by linear mixed models (n=450).

Demographic determinants	∑DEHP %Change (95% CI) [a]	∑DiNP %Change (95% CI) [a]	∑DnOP %Change (95% CI) [a]	∑HMW %Change (95% CI) [a]	∑LMW %Change (95% CI) [a]	∑Food packaging phthalates %Change (95% CI) [a]
Age at enrollment	0.89 (−0.36, 2.16)	**2.58 (0.81, 4.39)** *	1.70 (0.24, 3.17)	0.64 (−0.56, 1.86)	0.93 (−0.60, 2.48)	0.94 (−0.23, 2.13)
Pre-pregnancy BMI	−0.51 (−1.62, 0.61)	−1.84 (−3.39, −0.27)	−0.17 (−1.45, 1.13)	−0.12 (−1.19, 0.96)	−0.11 (−1.48, 1.29)	−0.26 (−1.30, 0.79)
Parity						
Nulliparous	Reference	Reference	Reference	Reference	Reference	Reference
Multiparous	1.23 (−11.81, 16.21)	−1.02 (−18.16, 19.71)	−4.99 (−18.98, 11.43)	7.46 (−5.88, 22.69)	15.12 (−2.60, 36.07)	4.92 (−7.81, 19.41)
Race/ethnicity						
Hispanic	−1.97 (−20.01, 20.15)	10.50 (−16.28, 45.85)	−10.66 (−29.44, 13.11)	−1.55 (−19.06, 19.76)	**78.91 (40.11, 128.46)** *	0.14 (−17.30, 21.26)
Non-Hispanic White	Reference	Reference	Reference	Reference	Reference	Reference
Non-Hispanic Black	−7.30 (−31.18, 24.88)	−7.79 (−39.29, 40.07)	**−38.40 (−56.29, −13.20)** *	−3.55 (−27.52, 28.35)	**99.43 (38.35, 187.48)** *	−3.85 (−27.23, 27.05)
Asian	−3.25 (−22.12, 20.19)	−7.21 (−30.47, 23.83)	−8.33 (−28.83, 18.07)	−0.15 (−19.03, 23.13)	10.52 (−14.43, 42.74)	−0.72 (−19.12, 21.87)
Other	−12.74 (−37.22, 21.30)	31.43 (−15.97, 105.56)	23.12 (−16.03, 80.51)	5.04 (−23.53, 44.29)	**81.61 (22.43, 169.40)** *	−0.02 (−26.68, 36.35)
Educational levels						
High school degree or less	−4.22 (−22.79, 18.81)	18.95 (−11.38, 59.67)	−24.73 (−41.37, −3.37)	−2.94 (−21.12, 19.43)	−13.97 (−33.61, 11.49)	−5.46 (−22.80, 15.77)
Some college but no degree	8.83 (−20.20, 48.41)	43.18 (−7.65, 121.97)	−15.28 (−40.70, 21.03)	4.28 (−22.54, 40.38)	10.33 (−24.75, 61.77)	6.49 (−20.30, 42.29)
Bachelor’s degree	Reference	Reference	Reference	Reference	Reference	Reference
Post-graduate degree	5.83 (−11.24, 26.18)	−7.32 (−26.77, 17.31)	1.76 (−17.10, 24.90)	1.02 (−14.76, 19.71)	6.88 (−13.23, 31.65)	0.97 (−14.47, 19.21)
Employment status						
No	3.12 (−9.82, 17.91)	−1.06 (−18.06, 19.47)	−1.78 (−15.83, 14.60)	−2.80 (−14.52, 10.54)	2.39 (−13.16, 20.74)	−0.54 (−12.25, 12.74)
Yes	Reference	Reference	Reference	Reference	Reference	Reference
Marital status						
Married or living as married	Reference	Reference	Reference	Reference	Reference	Reference
Single	15.62 (−4.74, 40.32)	**43.66 (9.42, 88.63)** *	27.31 (1.87, 59.09)	**41.43 (17.46, 70.29)** *	21.63 (−4.14, 54.32)	**28.63 (7.33, 54.16)**
Sampling season						
Winter	Reference	Reference	Reference	Reference	Reference	Reference
Spring	−7.97 (−19.48, 5.19)	12.07 (−4.58, 31.62)	5.98 (−9.68, 24.35)	−7.60 (−18.94, 5.32)	2.59 (−11.36, 18.74)	−8.25 (−19.33, 4.37)

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Demographic determinants	∑DEHP %Change (95% CI) [a]	∑DiNP %Change (95% CI) [a]	∑DnOP %Change (95% CI) [a]	∑HMW %Change (95% CI) [a]	∑LMW %Change (95% CI) [a]	∑Food packaging phthalates %Change (95% CI) [a]
Summer	−6.44 (−18.72, 7.68)	**23.14 (3.69, 46.23)** *	3.87 (−12.14, 22.80)	−5.01 (−17.20, 8.97)	16.22 (−0.53, 35.80)	−5.07 (−17.06, 8.66)
Fall	−4.14 (−15.98, 9.35)	15.28 (−1.63, 35.10)	4.12 (−11.06, 21.89)	−1.56 (−13.48, 11.99)	7.08 (−7.30, 23.68)	−2.28 (−13.93, 10.95)
Alcohol consumption						
Never user	Reference	Reference	Reference	Reference	Reference	Reference
User, stopped or continued at pregnancy	**−26.65 (−36.15, −15.75)** *	−16.15 (−31.17, 2.15)	**−20.75 (−32.40, −7.10)** *	**−27.15 (−36.20, −16.81)** *	−13.53 (−27.20, 2.71)	**−27.24 (−36.06, −17.20)**
Cotinine levels						
Less than 0.013ng/mL	Reference	Reference	Reference	Reference	Reference	Reference
0.013ng/mL or more	0.60 (−10.83, 13.49)	3.47 (−12.29, 22.07)	8.65 (−5.52, 24.94)	2.75 (−8.51, 15.39)	11.95 (−3.20, 29.47)	3.82 (−7.31, 16.28)
Hospital site						
NYU Manhattan	Reference	Reference	Reference	Reference	Reference	Reference
NYU Brooklyn	−16.43 (−36.25, 9.55)	−9.77 (−38.06, 31.45)	−8.33 (−32.91, 25.24)	−17.64 (−36.48, 6.80)	3.90 (−25.31, 44.53)	−15.55 (−34.46, 8.81)
Bellevue	−11.57 (−31.73, 14.53)	−17.23 (−41.89, 17.90)	−16.59 (−38.19, 12.56)	−13.63 (−32.67, 10.78)	29.72 (−4.99, 77.12)	−13.95 (−32.52, 9.73)
Annual household income						
Less than $49, 999	Reference	Reference	Reference	Reference	Reference	Reference
$50, 000 – $100, 000	14.38 (−12.36, 49.26)	10.12 (−23.94, 59.43)	2.92 (−24.27, 39.87)	15.80 (−10.30, 49.51)	34.00 (−3.15, 85.39)	15.56 (−9.93, 48.25)
$100, 000 or more	2.01 (−20.64, 31.14)	−1.59 (−30.92, 40.18)	−9.70 (−32.36, 20.54)	1.54 (−20.19, 29.17)	19.07 (−12.60, 62.21)	0.93 (−20.18, 27.63)
Don’t know	−7.82 (−21.38, 8.10)	−5.46 (−24.67, 18.66)	3.61 (−13.68, 24.36)	−3.68 (−17.29, 12.17)	17.61 (−3.50, 43.35)	−6.70 (−19.57, 8.23)
Insurance						
Public	Reference	Reference	Reference	Reference	Reference	Reference
Private	−8.70 (−25.21, 11.45)	−2.46 (−26.09, 28.73)	−2.79 (−22.77, 22.34)	−8.02 (−24.05, 11.39)	14.53 (−10.20, 46.07)	−9.56 (−24.97, 9.01)

[a]Adjusted for dietary factors, including intakes of vegetable, fruit, grains, dairy, meat, seafood, egg, nuts and seeds, dried beans and peas, soy product and energy intake. ; Chemicals were natural log-transformed. Inverse probability weighting (IPW) was applied in the models to correct the potential selection bias.

*$P < 0.0167$, significant associations after multiple comparison correction.

Abbreviations; BMI: body mass index; CI: confidence interval.

Table 4

Associations between dietary factors and phthalates metabolite levels in pregnant women, assessed by linear mixed models (n=450).

	∑DEHP	∑DiNP	∑DnOP	∑HMW	∑LMW	∑Food packaging phthalates
Dietary factors	**%Change (95% CI)** [a]	**%Change (95% CI)** [a]	**%Change (95% CI)** [a]	**%Change (95% CI)** [a]	**%Change (95% CI)** [a]	**%Change (95% CI)** [a]
Vegetable	3.80 (−3.60, 11.76)	6.72 (−3.80, 18.39)	−3.66 (−11.52, 4.90)	1.99 (−4.99, 9.48)	6.50 (−2.74, 16.62)	2.95 (−3.93, 10.31)
Fruit	2.58 (−3.67, 9.23)	0.43 (−7.86, 9.47)	−1.46 (−8.37, 5.97)	0.23 (−5.65, 6.47)	0.74 (−6.62, 8.67)	2.11 (−3.74, 8.31)
Grains	−2.65 (−12.51, 8.33)	**20.90 (4.51, 39.86)** *	−3.75 (−14.95, 8.92)	−4.94 (−14.23, 5.35)	−0.56 (−12.55, 13.07)	−1.87 (−11.25, 8.49)
Dairy	0.05 (−6.70, 7.29)	6.12 (−3.60, 16.82)	−2.02 (−9.63, 6.23)	0.31 (−6.21, 7.28)	2.82 (−5.50, 11.88)	1.51 (−4.94, 8.39)
Meat	0.54 (−3.02, 4.23)	−5.41 (−9.78, −0.82)	0.43 (−3.73, 4.77)	0.51 (−2.95, 4.08)	1.26 (−2.91, 5.60)	0.43 (−2.95, 3.93)
Seafood	−0.21 (−1.49, 1.07)	0.48 (−1.28, 2.28)	**−2.07 (−3.51, −0.61)** *	−0.50 (−1.72, 0.74)	−1.56 (−3.08, −0.01)	−0.36 (−1.55, 0.85)
Egg	0.94 (−1.66, 3.61)	0.67 (−3.13, 4.62)	2.09 (−0.89, 5.16)	1.46 (−1.03, 4.01)	−1.74 (−4.95, 1.59)	1.43 (−0.98, 3.91)
Nuts and seeds	−0.14 (−1.57, 1.31)	−1.49 (−3.47, 0.54)	0.61 (−1.05, 2.29)	−0.18 (−1.55, 1.21)	−0.10 (−1.86, 1.69)	−0.25 (−1.59, 1.10)
Dried beans and peas	**11.39 (5.42, 17.71)** *	**12.09 (3.88, 20.94)** *	4.37 (−2.07, 11.25)	**9.31 (3.67, 15.26)** *	0.99 (−5.53, 7.97)	**10.76 (5.17, 16.64)** *
Quadratic of beans and peas [b]	**0.44 (0.17, 0.71)** *	0.41 (0.04, 0.78)	0.11 (−0.20, 0.42)	**0.35 (0.10, 0.61)** *	0.02 (−0.30, 0.35)	**0.41 (0.16, 0.66)** *
Soy product	0.46 (−0.28, 1.21)	0.37 (−0.66, 1.42)	0.70 (−0.15, 1.57)	0.63 (−0.08, 1.35)	0.81 (−0.10, 1.73)	0.55 (−0.14, 1.25)
Energy intake (kcal/day)	−8.03 (−25.51, 13.54)	**−24.95 (−43.75, 0.13)** *	**3.13 (−19.18, 31.61)** *	−1.93 (−19.92, 20.10)	−12.26 (−31.93, 13.11)	−9.48 (−25.73, 10.32)

[a] Chemicals were natural log-transformed. Inverse probability weighting (IPW) was applied in the models to correct the potential selection bias.

[b] Because partial-linear single-index (PLSI) model indicated a non-linear relationship between beans and peas consumption and phthalate metabolite levels, quadratic of dried beans and peas were added to improve the goodness fit of models.

* $P < 0.0167$, significant associations after multiple comparison correction.

Table 5

Proportion contributions (%) of all diet factors to phthalates (n=450) [a].

Determinants	∑DEHP [b]		∑DiNP [b]		∑DnOP [b]		∑LMW [b]		∑HMW [b]	
	Estimates	% [c]	Estimates	% [c]	Estimates	% [c]	Estimates	% [c]	Estimates	% [c]
Vegetable	0.09	0.9	0.00	0.0	−0.04	0.1	0.35	11.9	0.09	0.9
Fruit	0.00	0.0	0.06	0.4	0.00	0.0	0.33	11.0	−0.07	0.5
Grain	−0.22	5.0	0.40	16.0	−0.24	5.7	−0.03	0.1	−0.25	6.2
Dairy	0.00	0.0	0.00	0.0	−0.33	10.8	−0.35	12.5	−0.01	0.0
Meat	0.10	0.9	0.02	0.1	0.31	9.6	−0.22	5.0	0.17	2.9
Seafood	0.34	11.6	−0.06	0.4	−0.33	10.9	−0.43	18.6	−0.20	4.0
Egg	−0.04	0.1	−0.20	4.1	0.22	4.8	0.18	3.4	0.17	2.9
Nuts and seeds	−0.03	0.1	−0.52	26.6	0.08	0.7	−0.08	0.6	−0.34	11.8
Dried beans and peas	0.87	76.3	0.60	35.8	0.52	27.4	0.15	2.4	0.80	63.3
Soy product	0.20	4.0	0.12	1.4	0.42	17.4	−0.06	0.3	0.23	5.1

[a] Assessed by partial-linear single-index (PLSI) model. Adjusted for demographic factors, including age, pre-pregnancy BMI, race/ethnicity, educational levels, employment status, marital status, sampling season, alcohol consumption, cotinine levels, hospital site, annual household income, and insurance.

[b] All diet factors and phthalates were natural log-transformed.

[c] Contribution proportions of individual diet factors to phthalate levels.