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Distribution and predictors of urinary concentrations of phthalate metabolites and phenols among pregnant women in the Healthy Start Study

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ABSTRACT

Background: Phthalates and phenols are suspected endocrine disrupting chemicals that may adversely impact fetal outcomes following *in utero* exposure. Understanding predictors of exposure to phthalates and phenols during the prenatal period is important.

Methods: We measured urinary concentrations of 15 phthalate metabolites and 11 phenols in 446 pregnant women enrolled in the Healthy Start pre-birth cohort. Creatinine-adjusted geometric means (GM) for each urinary biomarker were compared across categories of potential sociodemographic and dietary predictors. To assess the independent relationship between each significant food group predictor and biomarker we used multivariable models, adjusted for sociodemographic predictors.

Results: The phthalate metabolites with the highest concentrations were monoethyl phthalate (GM: 41.1 μg/g creatinine) and monocarboxyisooctyl phthalate (GM: 20.5 μg/g creatinine). Benzophenone-3 (GM: 124.6 μg/g creatinine) and methyl paraben (GM: 119.9 μg/g creatinine) were the phenols with the highest concentrations. Concentrations of the metabolites of di-n-butyl phthalate and di(2-ethylhexyl) phthalate were significantly higher in younger, unmarried or unemployed mothers, those who were overweight or obese, those with lower educational attainment, or those of minority race/ethnicity (p-values < 0.05). Metabolites of di-n-butyl phthalate concentrations were 18% lower in those who consumed milk ≥ 7 times per week (95% CI: 30–4%). Benzophenone-3 and triclosan concentrations were significantly higher in older, married, or employed mothers, those with normal body mass index, higher educational attainment, higher household income, or who were non-Hispanic white (p-values < 0.05). Benzophenone-3 concentrations were 62% higher in those who consumed seafood ≥ 5 times per month (95% CI: 16–127%).

Conclusions: We observed differences in urinary concentrations of phthalates and phenol biomarkers by sociodemographic predictors in an ethnically diverse cohort of pregnant women. These results and future analyses from this prospective cohort will help inform targeted interventions to reduce exposure to these potential endocrine disrupting chemicals during pregnancy.

1. Introduction

Due to their widespread use in numerous consumer and food packaging products, exposure to multiple phthalates and phenols is ubiquitous and has prompted concerns about potential adverse health effects (Calafat et al., 2015, 2009). Previous human studies suggest that some of these compounds may adversely impact human health, particularly during sensitive periods in the life course, such as *in utero* (Bergman et al., 2013; Polanska et al., 2016; Moya et al., 2014; Serrano et al., 2014; Guo et al., 2016; Ipapo et al., 2017; James-Todd et al., 2016).

Evidence suggests that select phthalates and phenols may act as endocrine disrupting chemicals (EDCs) also during pregnancy (Huang et al., 2016; Aker et al., 2016). A recent pregnancy cohort study observed an association between butyl paraben and decreased estradiol (Aker et al., 2016), a reproductive hormone involved in developing oxytocin receptors in the myometrium, which may play a role in preterm birth (Aker et al., 2016; Castracane, 2000). Another study found

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that urinary concentrations of first trimester mono-n-butyl phthalate (MBP) were inversely associated with thyroxine, a key thyroid hormone involved in fetal neuronal development (Huang et al., 2016). Phthalates and phenols acting as EDCs may also influence the development of metabolic disorders in humans, such as type 2 diabetes and overweight/obesity (Song et al., 2016; Russ and Howard, 2016; Stojanoska et al., 2017). Therefore, understanding the extent of exposure to phthalates and phenols during pregnancy and their sources is of public health relevance.

Several previous studies quantified urinary concentrations of phthalate and/or phenol biomarkers during pregnancy (Adibi et al., 2008; Arbuckle et al., 2015; Braun et al., 2014, 2011; Cantonwine et al., 2014; Casas et al., 2013; Meeker et al., 2013; Philippat et al., 2013; Quiros-Alcala et al., 2013; Smith et al., 2012; Valvi et al., 2015). Some similarities among sociodemographic and dietary predictors of phthalate and/or phenol biomarker concentrations exist; however, predictors vary depending on the study population, and the exposure assessment approach and questionnaire used. The variation in urinary concentrations is likely related to geographical variation in the composition of consumer products, cultural differences regarding diet and behavior, and study design (e.g., year and season of data collection, timing of urine sample collection, time interval between repeated measures). Exposure characterization is essential for informing any intervention aimed at reducing/eliminating EDC exposure, such as a recent community-based participatory intervention that was developed to reduce EDCs exposures in adolescent girls (Harley et al., 2016). In sensitive populations, such as pregnant women and their offspring, identifying sociodemographic and dietary patterns of exposure to phenols and phthalates may provide insight into how to reduce exposure during pregnancy.

The present study examined the distribution of urinary concentrations of biomarkers of phthalates and phenols in a cohort of pregnant women in Colorado. We explored potential sociodemographic predictors and dietary sources to identify exposure patterns. We also used multivariable models to assess the independent relationship between each significant food group predictor and exposure biomarker.

2. Methods

2.1. Study population and design

We used data obtained from the Healthy Start study, a prospective cohort of pregnant women and their offspring in Colorado. The study design has been previously described (Sauder et al., 2016; Shapiro et al., 2016; Starling et al., 2015). Briefly, women 16 years or older and less than 24 weeks gestation at their first prenatal visit were recruited from the University of Colorado obstetric clinics from 2009 to 2014. Participants were excluded if they were expecting multiple births, had a previous stillbirth, pre-existing diabetes, asthma managed with steroids, cancer, or had a serious psychiatric illness. The present analysis included a convenience sample of 446 pregnant women who provided spot urine samples during an in-person visit at 24–32 weeks gestation (median 27 weeks). Additionally, 24 participants had three spot urine samples collected at two week intervals. All samples were collected into sterile collection cups and were stored at − 80 °C until ready for shipment to the laboratory for their analysis. The study was approved by the Colorado Multiple Institutional Review Board and all participants provided written informed consent prior to the first study visit. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

2.2. Predictors

Potential predictors of urinary biomarker concentrations were selected based on previous studies exploring human exposure to phthalates and phenols (Cantonwine et al., 2014; Casas et al., 2013; Meeker et al., 2013, 2012; Valvi et al., 2015; Arbuckle et al., 2014; Zhu et al., 2016; Kelley et al., 2012). Maternal socio-demographic variables (i.e., age, race/ethnicity, education level, household income, marital status, employment status) and parity were self-reported at the first in-person visit at 15–23 weeks gestation (median 17 weeks). Pre-pregnancy body mass index (BMI) was calculated using maternal pre-pregnancy weight from the medical record or self-report and maternal height measured at the in-person visit. During the second in-person visit at 24–32 weeks gestation (median: 27 weeks), when urine samples were collected, a food propensity questionnaire was administered. The dietary assessment captured patterns of dietary intake during the previous three months. We considered nine food groups: milk, cheese, yogurt, ice cream, soft drinks, processed meat, red meat, seafood, and tofu, based on their importance as predictors in previous studies (Serrano et al., 2014; Cantonwine et al., 2014; Casas et al., 2013). In addition to the food propensity questionnaire, participants were asked at the same study visit about current fish oil supplement use. Fish oil supplement use was included as a potential predictor because phthalates can be used to minimize aftertaste and produce the soft gelatin capsules (Kelley et al., 2012). While urine samples were taken from pregnant women, we explored whether the sex of the fetus is associated with urinary concentrations of the phthalate metabolites and phenols. Previous studies have found that concentrations may vary by sex, and evidence suggests that in utero exposure influences future outcomes in the child (Kobrosly et al., 2014; Watkins et al., 2017). We also selected smoking status at the time of urine sample collection and gestational age at urine sample collection as additional predictors.

2.3. Laboratory analyses

Fifteen phthalate metabolites were measured using previously published laboratory methods (Silva et al., 2007): mono-n-butyl phthalate (MBP), monobenzyl phthalate (MBzP), mono carboxyisononyl phthalate (MCNP), mono carboxyisooctyl 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), monoethyl phthalate (MEP), mono-hydroxybutyl phthalate (MHBP), mono-hydroxyisobutyl phthalate (MHiBP), mono-isobutyl phthalate (MiBP), monomethyl phthalate (MMP), and mono-isononyl phthalate (MNP).

Ten phenols were measured using previously published laboratory methods (Ye et al., 2005): 2,4-dichlorophenol, 2,5-dichlorophenol, bisphenol A, bisphenol S, benzophenone-3, methyl paraben, ethyl paraben, propyl paraben, butyl paraben, and triclosan. Urine creatinine concentrations were measured at the CDC using a Roche/Hitachi Cobas 6000 Analyzer (Roche Diagnostics, Indianapolis, IN).

2.4. Statistical analysis

Descriptive statistics of sociodemographic characteristics for the 446 participants were calculated. Geometric means and 5th and 95th percentiles of the creatinine-adjusted urinary chemical concentrations (μg/g of creatinine) were calculated to describe the distribution of these metabolites.

All urinary chemical concentrations were natural log-transformed to normalize right skewed distributions for the purpose of linear regression analysis and calculation of the intraclass correlation coefficients (ICCs). Concentrations of the individual biomarkers and the molar sums were divided by creatinine concentrations to account for urinary dilution. For phthalate metabolite and phenol concentrations below the method limit of detection (LOD; Supplemental Table 1), we obtained instrument values when possible. For values reported as ‘zero’ concentration, we substituted one-half the minimum reported value for that biomarker (Arbuckle et al., 2015). We calculated five molar sums,