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Urinary phthalate metabolite concentrations and maternal weight during early pregnancy

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ABSTRACT

Background: Phthalates are a class of chemicals that may be associated with obesity in non-pregnant populations. Little is known about the association between pregnancy phthalate exposure and maternal obesity.
Objective: We evaluated the association between early-pregnancy urinary concentrations of specific phthalate metabolites and the distribution of body mass index (BMI, cross-sectional), and early gestational weight gain (GWG, prospective).
Methods: We measured 1st trimester urinary phthalate metabolite concentrations (median 9.9 weeks gestation) in 347 women from the LIFECODES pregnancy cohort (Boston, MA), who delivered term births. All measures were adjusted for specific-gravity and *log*-transformed. We used quantile regression to evaluate shifts in the entire outcome distributions, calculating multivariable-adjusted differences in the associations between these phthalate metabolites and BMI and GWG at the 25th, 50th, and 75th percentiles of these anthropometric outcomes.
Results: Higher concentrations of mono-ethyl phthalate (MEP) were associated with a rightward shift of 2.8 kg/m^2 at the 75th percentiles of BMI (lowest vs highest quartile, 95% CI: 0.2-5.4) and 1.3 kg at the 75th percentiles of early GWG (lowest vs second quartiles, 95% CI: 0.3-2.4). A significant right-shift in the upper tail of BMI was also observed at higher concentrations of mono-benzyl (MBzP), mono-3-carboxypropyl (MCPP), and a summary measure of di-(2-ethylhexyl) phthalate metabolites (ΣDEHP). ΣDEHP was also associated with lower GWG.
Conclusions: Certain phthalates may be associated with shifts in maternal obesity measures, with MEP, MBzP, MCPP, and ΣDEHP being cross-sectionally associated with 1st trimester BMI and MEP and ΣDEHP being positively and inversely associated with early GWG, respectively.

1. Introduction

Maternal obesity is an increasingly common condition and is associated with a large number of adverse pregnancy outcomes (Leddy et al., 2008; Sebire et al., 2001; Guelinckx et al., 2008). Specifically, obese women have higher risk of preeclampsia (Salihu et al., 2012), gestational diabetes mellitus (GDM) (Chu et al., 2007a, 2007b), and cesarean delivery (Weiss et al., 2004), as well as stillbirth and congenital anomalies (Chu et al., 2007a, 2007b). In addition, maternal obesity can have a long-term impact on the future health of both the mother and the offspring, especially in terms of heart disease, hypertension, and diabetes (Sridhar et al., 2014; Freeman 2010; Gilmore et al., 2015). Together with the standard obesity measure of body mass index (BMI), another important measure for maternal obesity is gestational weight gain (GWG) (Ferraro et al., 2015). Excessive gestational weight gain is an established predictor of pregnancy and post-

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pregnancy complications, as well as postpartum weight retention, which is known to influence the future risk of obesity (Gunderson 2009; Kirkegaard et al., 2015; Krukowski et al., 2016). Several studies have demonstrated that risks associated with excessive GWG are higher in early pregnancy, suggesting that early GWG may be an important and clinically relevant time period with respect to adverse health outcomes (Fontaine et al., 2012; Ferraro et al., 2015; Hedderson et al., 2010, 2014; Carreno et al., 2012).

In addition to nutritional and behavioral factors, a substantial body of literature suggests that exposures to endocrine disrupting chemicals (EDCs), a class of chemicals capable of interfering with the normal processes of endocrine systems, may increase the risk of obesity (Heindel et al., 2015). Phthalates are a class of EDCs that are used as plasticizers in a variety of consumer products, including food packaging, personal care products, floor tiles, and industrial solvents (Hauser and Calafat, 2005). Phthalates interfere with the endocrine system through different pathways such as by activating peroxisome proliferator-activated receptors (PPARs), which can up-regulate adipogenesis (Desvergne et al., 2009). Animal and non-pregnant population studies have suggested a potential association between obesity and specific phthalate metabolites such as mono-ethyl phthalate (MEP), mono-benzyl phthalate (MBzP), mono-ethylhexyl-phthalate (MEHP), and mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP) (Hao et al., 2012; Hao et al., 2013; Hatch et al., 2008; Stahluht et al., 2007), but have provided inconsistent results, which could in part be due to differences in outcome assessments and inclusion of covariates (Thayer et al., 2012; Tang-Péronard et al., 2011). On the other hand, in pregnant populations, the evidence of an association between phthalate exposure and maternal obesity are limited to a single study (James-Todd et al., 2016).

Epidemiological studies focusing on phthalate exposure and obesity have applied standard statistical methods to report shifts in the mean of BMI as a function of phthalate metabolite concentrations (Hao et al., 2012; Hao et al., 2013; Hatch et al., 2008; Stahlhut et al., 2007). Focusing on the mean alone, however, assumes that the exposure-outcome association is constant over the entire outcome distribution, and does not capture effects that primarily occur at the tails of the distribution (Beyerlein, 2014). In environmental health, due to the complexity of biological mechanisms through which environmental chemicals may affect the human body, it may happen that certain chemical exposures could have differential effects based on differing levels of the outcome of interest (Bind et al., 2015). For example, a recent study from Bind et al. found air pollution to be associated with a left shift in gene-specific methylation only in the lower tail of their distribution, suggesting heterogeneity between study participants with respect to the potential epigenetic effects of air pollution exposure (Bind et al., 2015). In the context of phthalates and obesity, a positive association between BMI and PPAR gamma mRNA expression has been observed (Redonnet et al., 2002), thus suggesting that the mechanism by which over-expression of PPAR gamma target genes might be induced by higher phthalate exposure could vary across the distribution of body mass index (BMI). As such, it could be hypothesized that women in the right tail of the BMI distribution might be more susceptible to the potentially obesogenic effects of higher phthalate exposure during pregnancy.

Therefore, the objective of this study was to evaluate, in a prospective cohort of pregnant women, early pregnancy distribution shifts in body size measures commonly used as indicators of maternal obesity (i.e. first trimester BMI and early GWG), as well as weight trajectories over the entire pregnancy, as a function of first-trimester urinary concentrations of specific phthalate metabolites.

2. Methods

2.1. Study population

We used data from the LIFECODES pregnancy cohort, an ongoing prospective study of pregnant women that was started in 2006. LIFECODES enrolls women at the first prenatal visit < 15 gestation weeks (median: 9.9 gestation weeks). Eligible women include those who are: 1) planning to deliver at Brigham and Women's Hospital (Boston, MA); and 2) not pregnant with more than 3 fetuses. All study participants completed a self-administered questionnaire to provide information on socio-demographic and lifestyle factors. Urine and blood samples, together with anthropometric measures, were collected at four time points that coincided with standard prenatal care visits (median: 9.9, 17.3, 26.1, and 35.3 gestation weeks). For the present study, which focuses on early markers of anthropometry in pregnancy, we focus on 1st trimester measures.

Among LIFECODES study participants enrolled between 2006 and 2008, a nested case-control study was conducted, described elsewhere (Ferguson et al., 2014a, 2014b). Our study population included the controls from this case-control study (i.e. those who delivered at term defined as delivery > 37 weeks gestation). Furthermore, women in the present study population were recruited exclusively during the first trimester, as these were women with available information on urinary phthalate metabolite concentrations at the first study visit (n = 347). All women gave their informed consent. The study was approved by the Partners Human Subject Committee at Brigham and Women's Hospital.

2.2. Urinary phthalate metabolite concentrations

Spot urine samples collected at the first study visit were stored at −80 °C and analyzed by NSF International, Inc. (Ann Arbor, MI) following a protocol from the Center for Disease Control and Prevention, described in details elsewhere (Centers for Disease Control and Prevention, 2005). In brief, solid phase extraction and high performance liquid chromatography were used, along with tandem mass spectrometry (Centers for Disease Control and Prevention, 2005). When detection limits were low, samples with levels below the limit were assigned by dividing the limit of detection by the square root of two (Hornung and Reed, 1990).

Nine urinary phthalate metabolites were measured: mono-ethyl phthalate (MEP, metabolite of diethyl phthalate); metabolite of dibutyl phthalate (MnBP, metabolite of di-*n*-butyl phthalate); mono-isobutyl phthalate (MiBP, metabolite of diisobutyl phthalate); metabolite of benzyl butyl phthalate (MBzP, metabolite of butylbenzyl phthalate); mono-(3-carboxypropyl) phthalate (MCPP, metabolite of di-*n*-octyl phthalate), which is a nonspecific metabolite of several high molecular weight phthalates and a minor metabolite of DBP (Calafat et al., 2008); as well as 4 metabolites of di(2-ethylhexyl) phthalate (DEHP): mono-ethylhexyl-phthalate (MEHP); mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP); mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP); and mono-2-ethyl-5-oxohexyl phthalate (MEOHP). Due to the high degree of correlation between these four urinary phthalate metabolites (r > 0.95), we created a summary measure of these four metabolites (ΣDEHP) by adding their molar concentrations.

Since individuals differ in their urinary dilution, we adjusted all phthalate metabolite concentrations for specific gravity (SG) of the individual sample. SG-adjusted urinary concentrations were calculated with the formula: $P_c = P[(1.015\text{-}1)/\text{SG-}1]$, where P was the urinary concentration and 1.015 was the median SG over all samples (Boeniger et al., 1993). We further excluded from the study n = 2 urine samples with SG outside of the normal range (SG > 1.04).

For this study we only used phthalate metabolite concentrations measured at the first medical visit (9.9 median gestation weeks).

2.3. Outcomes

2.3.1. First trimester body mass index

BMI was calculated as weight (kg) divided by squared height (meters^2) based on weight and height taken as a part of standard clinical work-up by trained medical staff at the time of the first prenatal visit.