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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

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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.

Keywords

phthalates; pregnancy; maternal obesity; quantile regression

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. 2007), and cesarean delivery (Weiss et al. 2004), as well as stillbirth and congenital anomalies (Chu et al. 2007). 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-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; Hedderson et al. 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), monoethylhexyl- 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; Stahluht 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 overexpression 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.

Methods

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. 2014). 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.

Phthalates concentration assessment

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. 2006); 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: $P_c=P[(1.015-1)/SG-1]$, 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).

Outcomes

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. BMI was assessed continuously and categorically. For categorized BMI, the National Heart Lung and Blood Institute's criteria were used (BMI <25, 25–30, >30 kg/m^2).

Early pregnancy gestational weight gain. GWG was calculated as the difference in weight in kg between the second and the first prenatal visits as an indicator of early gestational weight gain (median time period between 1st and 2nd trimester weight measurements: 7.4 gestational weeks). For early pregnancy GWG, we further excluded n=2 women with unlikely extreme values of GWG (i.e. > or < than 3-sd unit). In addition to continuous GWG, early GWG was divided into inadequate, adequate, and excess GWG, using the criteria of the Institute of Medicine (Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines 2009; Fontaine et al. 2012). The entire trajectory of gestational weight (i.e. also including weight measurements taken at the 3rd and 4th medical visits) was investigated in a secondary analysis.

Covariates

All analyses were adjusted for established risk factors of maternal obesity potentially associated with urinary phthalate metabolite concentrations. These included maternal age (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian, other), alcohol consumption (yes/no), smoking (yes/no), and educational level (college or more vs <college). Statistical models for GWG were additionally adjusted for baseline BMI (continuous). Proportion of missing data was negligible (<5% for all covariates), and all multivariable analyses were conducted as complete-case.

Statistical analysis

We calculated baseline characteristics of the study population, as well as the SG-adjusted geometric means and 25th and 75th percentiles of each phthalate metabolite, for the overall population and stratified by 1st trimester BMI and early GWG categories. Analyses focusing on phthalates and BMI were cross-sectional as these were assessed at the same time point. On the other hand, analyses of GWG were prospective.

In addition to the classical mean regression, we used quantile regression to investigate the associations between urinary phthalate metabolite concentrations and the entire distribution of 1st trimester BMI and early GWG. By focusing on the percentiles of the outcome, quantile regression evaluates shifts in the shape of the outcome distribution, rather than its location, and allows for detection of associations that primarily occur at the tails of the distributions (Koenker and Hallock 2001). To evaluate distribution shifts in the lower tail, median, and higher tail of 1st trimester BMI and early GWG, we specifically focused on the 25th, 50th, and 75th percentiles, respectively. For each of these percentiles we built a linear quantile regression model and presented multivariable-adjusted statistical associations with 95% confidence intervals (CI).

All exposure measures of SG-adjusted phthalate metabolites were *log*-transformed due to right-skewedness. To flexibly evaluate the exposure-outcome associations we adopted two approaches that allowed for detection of non-linear associations. First, we calculated shifts in the mean and percentiles of BMI and early GWG across quartiles of phthalate metabolite concentrations, using the lowest quartiles as referent groups. This model was replicated in two sensitivity analyses, where 1) baseline BMI was not included in the model; and 2) the outcome was investigated in terms of gestational weight adequacy (Bodnar et al 2011). Next, we evaluated urinary phthalate metabolite concentrations as continuous predictors by using restricted cubic splines transformation (Durrleman and Simon 1989). Splines models were graphically presented for only those metabolites showing significant results in the categorical models, and using the lowest reported concentration as referent value. Linearity of the dose-responses was evaluated by calculating *p*-values for linearity as reported in previous studies (Orsini and Greenland 2011).

As a secondary analysis we incorporated information on maternal weight at the third and fourth study visits to evaluate weight trajectories over the entire pregnancy as a function of first trimester phthalate metabolite concentration. Because of the high correlation between individual weight measures we used linear mixed models, to evaluate the trajectory over time of mean weight, and mixed quantile regression, to evaluate trajectories over time of the 25^{th}, 50^{th}, and 75^{th} percentiles of weight (Geraci and Bottai 2014).

All analyses were performed in Stata, version 14, with the exception of the mixed quantile regression models that were evaluated with the R package *lqmm* (Geraci 2016).

Results

Baseline characteristics of the study population are presented in Table 1. The proportion of obese and overweight women was higher among non-Hispanic Black and Asian women. First trimester BMI and early GWG were higher among less educated women. Distributions of age, smoking, and alcohol consumption were similar across levels of 1^{st} trimester BMI and early GWG. Urinary phthalate metabolite concentrations of MEP, MnBP, MBzP, and MCPP were higher among obese women. MiBP, and MBzP were lower among those with excess GWG (Table 2).

The 25^{th} and 75^{th} percentiles of BMI were 22 and 28 kg/m^2 and for early GWG, 0.9 and 3.6 kg, respectively. Compared to the first quartiles, significantly higher BMI was observed at higher quartiles of MEP, MBzP, MCPP, and ΣDEHP metabolites (Table 3). The right shift in BMI at higher concentrations of MEP, MBzP, and MCPP, was only statistically significant in the right tail of the distribution, while no significant differences were detected at the 25^{th} percentile. For instance, when comparing women in the highest and lowest MEP quartiles, the 75^{th} percentile of BMI was 2.81 kg/m^2 (95% CI: 0.20–5.42) higher, but only a smaller non-significant increase was observed at the 25^{th} percentiles (β: 0.82 kg/m^2; 95% CI: −0.91, 2.54). In contrast, higher levels of ΣDEHP were associated with a significant right shift in the entire BMI distribution.

Figure 1 depicts the associations between the BMI distribution (i.e. mean, 25th, 50th, and 75th percentile) and urinary concentrations of MEP, MBzP, MCPP, and ΣDEHP, evaluated with restricted cubic splines models. This analysis confirmed that the shifts in BMI distributions were substantially larger in the right tail of BMI. A linear dose-response was only observed in the association between MEP concentrations and the 75th percentile of BMI. Non-linear associations were observed in all other scenarios, with a right shift in the BMI distribution, especially in the right tail, between the lowest and average urinary concentration, and no additional associations at higher levels.

Significant shifts in the distribution of early GWG were detected at high levels of MEP, with the largest difference observed in the right tail of the distribution. While comparing women in the lowest and second quartile of MEP, the difference in early GWG was 1.30 kg (95% CI: 0.26–2.35) at the 75th percentile of the distribution, and 0.82 kg (95% CI: −0.09–1.62) at the 25th percentile (Table 4). On the other hand, lower GWG was observed when comparing participants in the third and first quartiles of ΣDEHP for both the 25th percentile (−0.94 kg; 95% CI: −1.67, −0.22), and 50th percentile (−0.98 kg; 95% CI: −1.74, −0.21) of the outcome distribution. Results were similar when excluding baseline BMI from the potential confounders and when investigating gestational weight adequacy (data not shown). The spline analysis showed that the associations between MEP and the 75th percentile of GWG followed a U-shape, with increasing GWG at low levels of the MEP distribution, and no additional increase at higher concentrations (Figure 2). The dose-response association between ΣDEHP and GWG was described by an inverse U-shape, with similar results throughout the evaluated percentiles.

In a secondary analysis we incorporated all pregnancy measures of gestational weight. This analysis was only performed for MEP, where significant and consistent results with regards of BMI and GWG were observed. Figure 3 presents the longitudinal change in weight over pregnancy across quartiles of baseline MEP concentration. The difference in GWG between women in the lowest and second quartile of MEP largely occurred during the first trimester and remained constant at subsequent prenatal care visits.

Discussion

In a prospective study of pregnant women, we found higher concentrations of MEP to be associated with a right-shift in the higher tails of maternal obesity measures (i.e. first trimester BMI and GWG). Positive cross-sectional associations were also observed between MBzP, MCPP, and ΣDEHP and 1st trimester BMI, while a negative prospective association was detected between ΣDEHP and early GWG. All associations were non-linear and only observed at specific quartiles of the exposures. These findings may provide evidence to suggest an adverse impact of higher phthalate exposure on maternal adiposity measures (i.e. 1st trimester BMI and early GWG and may suggest that higher exposure to phthalate parent compounds during early pregnancy might impact overweight/obese women to a greater extent than their normal weight counterparts.

The association between urinary phthalate metabolite concentrations and obesity has been mainly investigated in animal studies, with positive associations seen for DEHP metabolites

and weight gain (Hao et al. 2013; Hao et al. 2012; Schmidt et al. 2012; Biemann et al. 2014). While several epidemiological studies have focused on childhood phthalate exposure and obesity measures (Deierlein et al. 2016; Trasande et al. 2013; Boas et al. 2010), few observational studies have investigated phthalates and BMI/weight gain in adult women. Of the studies that have evaluated this question, one study found positive associations with MnBP, and MBzP (Song et al. 2014), while another found inverse cross-sectional associations with MEHP (Hatch et al. 2008). Recent studies have investigated phthalate exposure during pregnancy as it relates with the risk of major pregnancy complications such as gestational diabetes and preterm birth (James-Todd et al. 2016; Huang et al. 2016; Philips et al. 2016; Ferguson et al. 2014; Ferguson et al. 2015; Werner et al. 2015). While studies have evaluated pregnancy phthalate metabolite concentrations, to our knowledge, this is among the first study to focus on maternal obesity measures as a primary outcome.

Interestingly, our results indicate that all observed associations are not constant over the entire outcome distributions, but are consistently stronger in the right tails. These differences suggest that women in the higher tails of the outcome distribution (i.e. with higher baseline values of obesity measures) may be more susceptible to pregnancy exposure with respect to certain phthalate metabolites. To detect such shifts occurring in the tails of the outcome distributions, we used quantile regression, which is becoming increasingly popular in the epidemiological literature (Beyerlein 2014; Marrie et al. 2009). Compared to alternative methods to evaluate tails of the distributions, such as categorization or dichotomization of continuous outcome, quantile regression provides important additional properties and modeling advantages, which include not requiring any distributional assumption, as well as not being sensitive to the presence of outliers. In addition, the use of quantile regression has been recommended to fully capture the effects of environmental exposures (Bind et al. 2015; Bind et al. 2016).

The biological mechanism through which phthalates may affect obesity is complex (Heindel, Newbold and Schug 2015). Phthalates are known to induce the expression of PPAR gamma, modifying the expression of its target genes and the differentiation of these cells into adipocytes (Feige et al. 2007; Hurst and Waxman 2003; Biemann et al. 2012). The association between PPAR polymorphisms and obesity (Yao et al. 2015; Redonnet et al 2002) may partly explain the larger associations observed in the right tail of first trimester BMI and early GWG, as the over-expression of PPAR gamma target genes induced by high levels of pregnancy phthalate exposure would more likely occur and have larger effects in those women with higher obesity levels before pregnancy. Of particular interest, we observed a positive association between BMI and ΣDEHP, but an inverse association when looking at ΣDEHP and GWG. DEHP metabolites are high molecular weight phthalates, which may have different effects from lower molecular weight metabolites such as MEP.

Most associations were non-linear. While different studies have presented suggestive non-linear associations when evaluating phthalate metabolites, these have generally been documented through categorical analyses. Categorizing continuous exposures presents some limitations and often relies on specific assumptions (e.g. step dose-response function, difficulty in detecting within-category differences, subjective choice of cut-off) (Greenland 1995b; Royston et al.2006). In the present study, we used spline transformations, a common

tool to model a continuous covariate relaxing the assumption of linearity and also avoiding the loss of information implied by the use of categories (Greenland 1995a). In agreement with some other studies we observed non-monotonic dose responses, suggesting that EDCs at low-dose exposures might have a greater impact on adverse outcomes as compared to mid-to-higher dose exposures.

This study has several limitations. First, our study used single spot urines to measure early pregnancy urinary phthalate metabolite concentrations with respect to early maternal adiposity measures. However, single spot urines may not accurately classify long-term exposures, particularly pre-conception exposures. Moreover, both exposure and outcome measures are possibly subject to measurement error. Second, by only focusing on early pregnancy phthalate exposure and early markers of maternal adiposity, our study does not provide information on the potential effects of late-pregnancy exposures. Nevertheless, changes occurring during the first trimester of pregnancy are generally regarded as important predictors of maternal measures (Fontaine et al. 2012; Ferraro et al. 2015; Hedderson et al. 2010; Hedderson et al. 2014; Carreno et al. 2012). Third, the analysis of early pregnancy phthalate exposure and BMI (assessed at the first prenatal visit) was cross-sectional. As such, there is the possibility of reverse causation. Specifically, women of higher BMI may also have a higher surface area, potentially leading to greater exposure to topical products containing phthalates. In fact, obese women had significantly higher concentrations of MEP compared to normal BMI women. Fourth, other factors that could influence early GWG and BMI, such as hyperemesis, nausea, and vomiting, or dietary factors, were not available in our data. In particular, future studies should further investigate the role of dietary factors in the observed associations and whether low and high molecular weight metabolites have different effects on maternal obesity. Food is a principal source of certain phthalate metabolites, especially DEHP metabolites. Primary sources of DEHP metabolites such as diet, and of non-DEHP phthalate metabolites such as personal care products, should be investigated as potential confounders as well as effect modifiers of the association. Finally, we only included women with term births, in whom lower concentrations of specific phthalate metabolites, especially DEHP, have been observed (Ferguson et al. 2014). While this allows for the ability to evaluate risk factors independent of preterm birth status, it could also attenuate the associations as women with the highest DEHP exposure would be more likely to be excluded. We were also underpowered to examine possible effect modifications by race/ethnicity and age, and by first trimester BMI in the GWG model.

Despite these limitations, this study had several strengths. First, to our knowledge, the present study is among the first to evaluate the association between urinary phthalate metabolite concentrations and maternal obesity. Second, the use of quantile regression, combined with the application of flexible statistical techniques such as splines, allowed for the evaluation of urinary phthalate metabolite concentrations and distribution shifts in first trimester BMI and early GWG, outcomes that are important to adverse pregnancy outcomes (Marrie et al. 2009). By focusing on the entire distribution of the outcomes we observed associations that would not have been detectable using classical regression methods. Third, this study evaluated two body size measures commonly used as indicators of maternal obesity, which could provide insight into obesity status, as well as weight gain in pregnancy.

Fourth, we were able to evaluate associations between a number of phthalates and a prospective measure of GWG in early pregnancy.

Conclusion

In a pregnancy cohort, we found higher early-pregnancy urinary concentrations of MEP, MBzP, MCPP, and ΣDEHP to be cross-sectionally associated with a right shift in the distribution of first trimester BMI in a non-linear fashion. Suggestive prospective associations between MEP (positive), DEHP metabolites (inverse), and early GWG distribution were also detected. Future studies should further investigate the role of baseline BMI in the prospective association between non-DEHP phthalate exposures and maternal obesity (e.g. as an effect modifier), as well as explore the potential mechanism involved in the obesogenic effects of certain phthalates in pregnant women. If replicated, the present study may suggest that reducing exposure to certain non-DEHP phthalate compounds could be particularly beneficial to women with higher BMI and GWG, with implications for potential reductions in related adverse maternal and child health outcomes. Even the inverse association between DEHP and GWG may suggest important effects that these EDCs could have on weight gain during the potentially sensitive time period of pregnancy.

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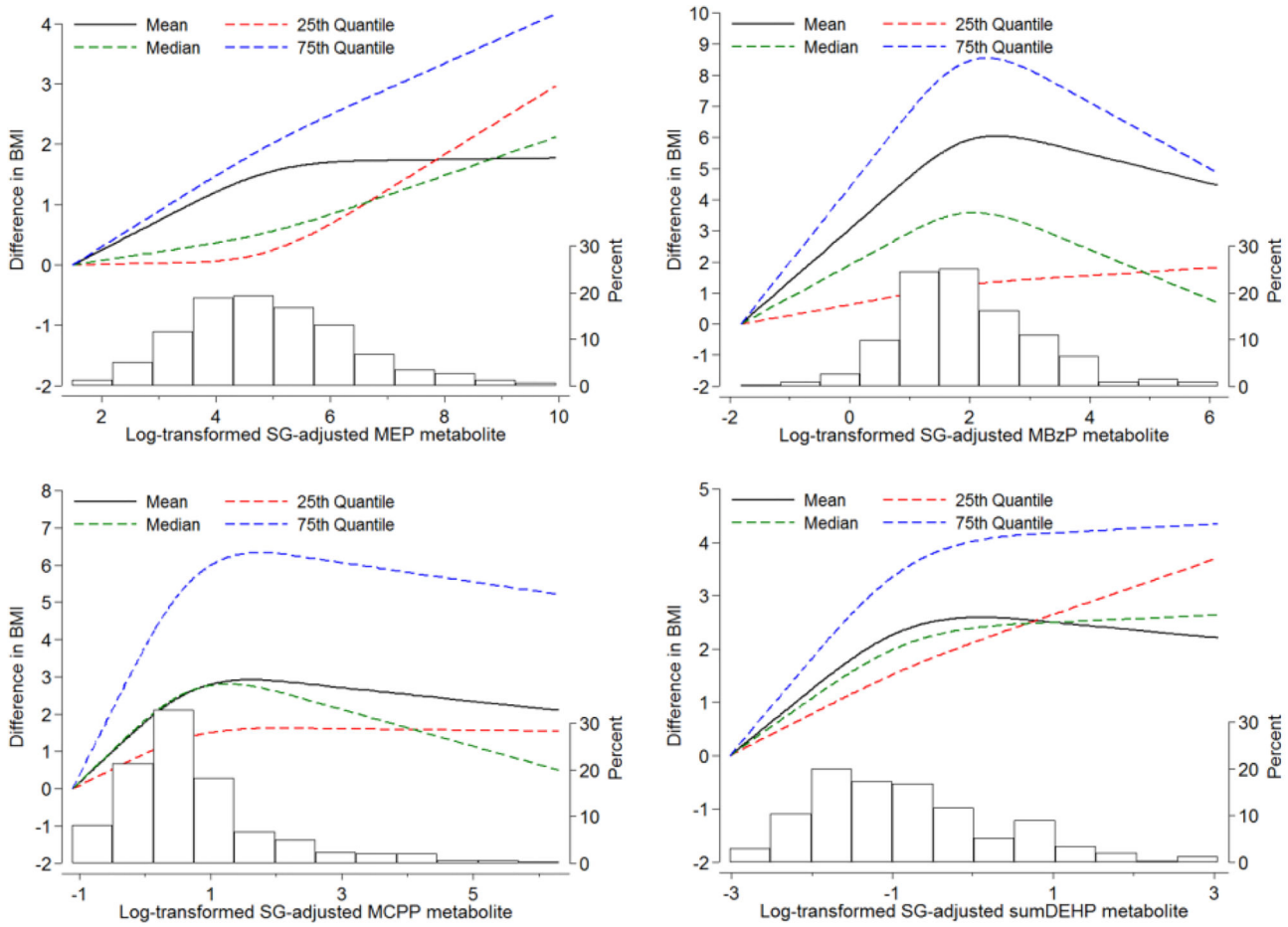

Figure 1. Multivariable-adjusted distribution shifts of BMI as a function of baseline urinary phthalates levels

Phthalates metabolites were flexibly modeled with restricted cubic splines with the lowest concentration serving as referent value. The histograms depict the distribution of phthalate levels in the study population. All models are adjusted for maternal age, race/ethnicity, education, smoking, alcohol. Shifts are at the mean, 25th, 50th, and 75th percentile of the outcome distribution.

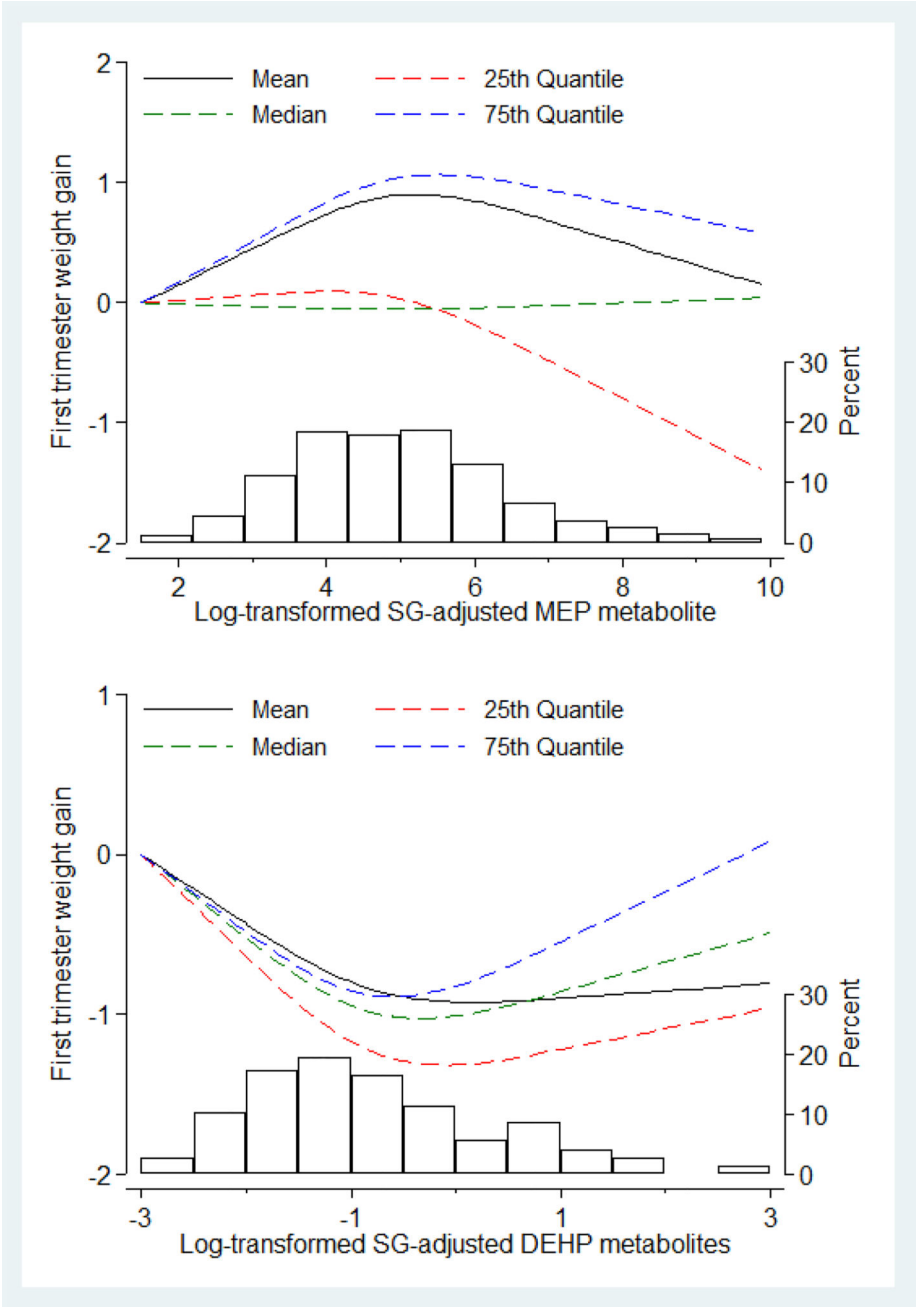

Figure 2. Multivariable-adjusted distribution shifts of early gestational weight gain (GWG, kg) as a function of 1st trimester urinary MEP and ΣDEHP phthalate metabolites levels. Shifts are at the mean, 25th, 50th, and 75th percentile of the outcome distribution

MEP and ΣDEHP concentration were flexibly modeled with restricted cubic splines with the lowest concentrations serving as referent value. The histograms depict the distribution of the metabolite in the study population. Models are adjusted for maternal age, race/ethnicity, education, smoking, alcohol, baseline BMI

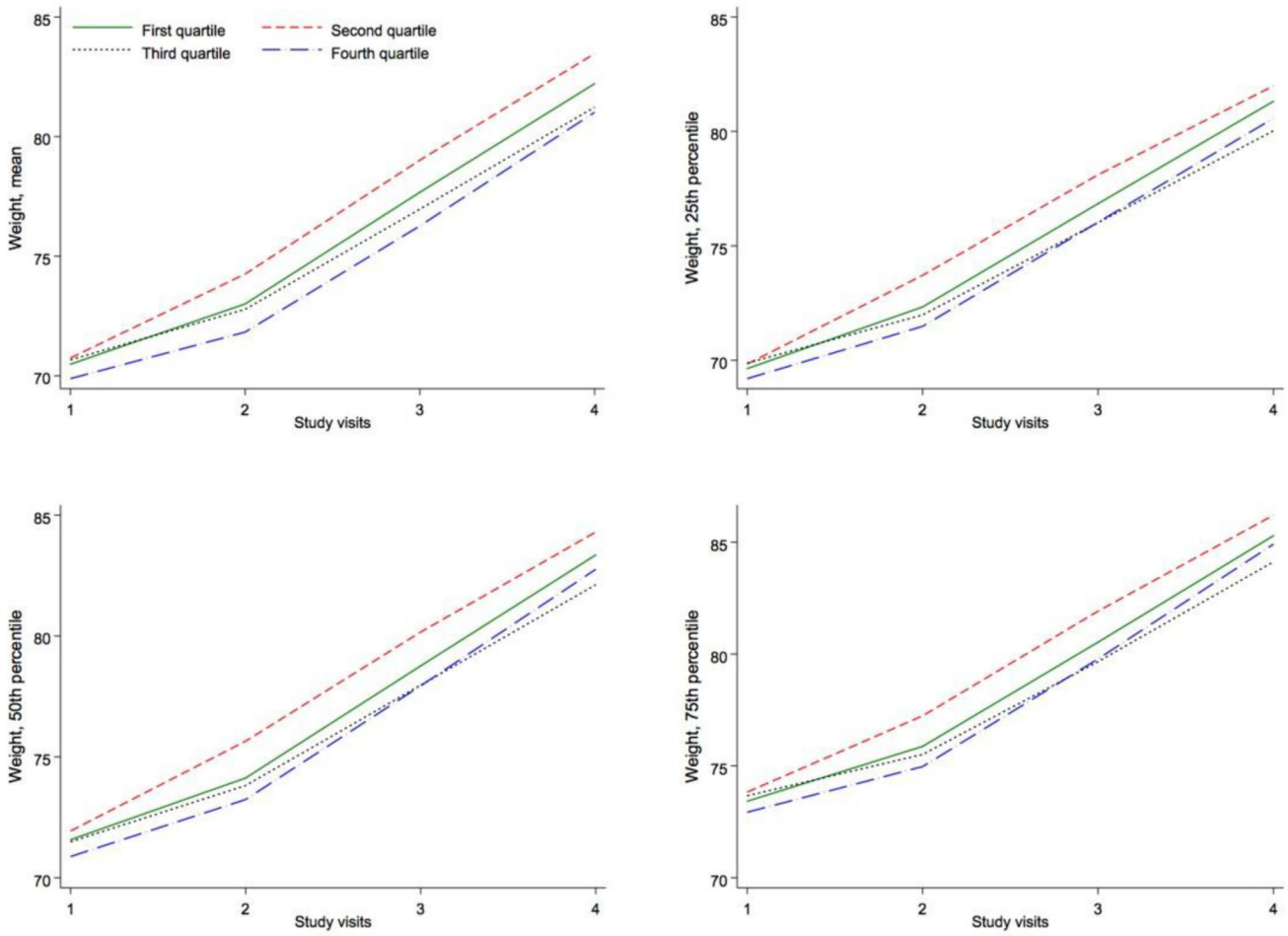

Figure 3. Multivariable-adjusted trajectories of the distribution of gestational weight (kg) across pregnancy over quartiles of log-transformed SG-adjusted MEP metabolite concentration

Mean trajectory estimated with linear mixed models. Trajectories of the 25th, 50th, and 75th percentiles estimated with mixed quantile regression. All models adjusted for maternal age, race/ethnicity, education, smoking, alcohol, baseline BMI. Median gestation weeks, Visit 1: 9.9; Visit 2: 17.3; Visit 3: 26.1; Visit 4: 35.3.

Table 1

Baseline characteristics of the study population overall and by levels of 1st trimester BMI and early gestational weight gain (GWG)

				BMI				GWG	
Characteristics	**Overall**		**<25**	**25–30**	**>30**		**Inadequate**	**Adequate**	**Excess**
N (%) *	347 (100)		187 (54)	92 (27)	64 (19)		120 (39)	166 (53)	25 (8)
Maternal age, mean (sd)	32.0 (5.5)		32.2 (4.9)	32.0 (6.3)	31.3 (5.7)		30.8 (5.5)	32.7 (5.3)	31.9 (5.5)
Race/ethnicity, n (%)									
Caucasian	205 (59)		130 (70)	46 (50)	27 (42)		66 (55)	106 (64)	14 (54)
Non-Hispanic black	54 (16)		19 (10)	17 (18)	18 (28)		18 (15)	25 (15)	3 (12)
Hispanic	19 (5)		10 (5)	9 (10)	0 (0)		9 (8)	7 (4)	3 (12)
Asians	50 (14)		19 (10)	14 (15)	16 (25)		21 (17)	20 (12)	4 (16)
Unknown/other	19 (5)		9 (5)	6 (6)	3 (5)		6 (5)	8 (5)	1 (4)
College or higher education, n (%)	141 (41)		92 (51)	38 (41)	11 (18)		46 (39)	79 (48)	7 (27)
Alcohol use during pregnancy, n (%)	19 (6)		11 (6)	6 (6)	2 (3)		6 (5)	12 (7)	1 (4)
Smoking status, n(%)	8 (2)		0 (0)	3 (3)	4 (6)		2 (2)	4 (2)	1 (4)

* Numbers may not sum up to 347 because of missing values of BMI or GWG

Table 2

Urinary phthalate metabolite levels at baseline by levels of 1st trimester BMI and early gestational weight gain (GWG)

Phthalates metabolite, geometric mean (25th–75th percentile)	Overall Population	BMI <25	25<BMI<30	BMI>30	Inadequate GWG	Adequate GWG	Excess GWG
MEP, μg/l	137.8 (48.6–345)	113.0 (42.5–295.7)	138.1 (46.6–290.5)	236.3 (81.0–560.8)	135.2 (44–363.8)	131.8 (46.6–295.7)	148.9 (53.4–263.7)
MnBP, μg/l	17.3 (10.8–26.2)	16.7 (10.6–25.1)	15.6 (10.8–23.8	22.2 (12.2–31.1)	19.0 (11.0–32.8)	15.5 (10.7–22.6)	20.4 (9.7–31.5)
MiBP, μg/l	7.3 (4.5–11.1)	7.0 (4.4–10.5)	7.9 (4.6–13.9)	7.5 (5.6–11.7)	7.5 (4.5–11.1)	7.3 (4.3–11.1)	5.9 (3.3–11.9)
MBzP, μg/l	7.0 (3.5–13.4)	6.3 (3.1–13.2)	6.7 (3.2–10.4)	9.9 (5.2–16.7)	8.1 (3.6–19.7)	6.5 (3.3–12.4)	5.3 (2.5–7.3)
MCPP, μg/l	2.1 (1.0–3.1)	1.9 (0.9–2.7)	2.1 (1.1–3.2)	2.8 (1.2–4.0)	2.2 (1.1–3.5)	2.2 (1.1–3.1)	2.3 (1.0–4.8)
ΣDEHP, μmol/l	0.4 (0.2–0.8)	0.4 (0.2–0.8)	0.5 (0.2–1.2)	0.5 (0.2–0.7)	0.4 (0.2–0.8)	0.4 (0.2–1.0)	0.3 (0.2–0.5)

Table 3

1st trimester urinary phthalate metabolite concentrations and distribution shifts in 1st trimester BMI

	Multivariable adjusted*			
Log-transformed SG-adjusted phthalate metabolites	**Mean BMI**	**25th Percentile**	**Median BMI**	**75th percentile**
MEP				
Q1	Ref			
Q2	1.83 (0.19, 3.47)	0.04 (−1.62, 1.70)	0.87 (−0.92, 2.65)	1.61 (−0.90, 4.12)
Q3	1.41 (−0.28, 3.11)	0.13 (−1.59, 1.84)	0.72 (−1.13, 2.57)	2.06 (−0.53, 4.66)
Q4	1.60 (−0.10, 3.31)	0.82 (−0.91, 2.54)	1.44 (−0.41, 3.30)	2.81 (0.20, 5.42)
MnBP				
Q1	Ref			
Q2	−0.3 (−1.93, 1.24)	−0.73 (−2.23, 0.77)	−0.21 (−1.96, 1.55)	−0.55 (−3.03, 1.92)
Q3	0.94 (−0.76, 2.63)	−0.15 (−1.76, 1.46)	−0.06 (−1.94, 1.81)	0.88 (−1.76, 3.53)
Q4	0.09 (−1.64, 1.82)	0.33 (−1.31, 1.97)	−0.04 (−1.96, 1.87)	0.16 (−2.54, 2.85)
MiBP				
Q1	Ref			
Q2	0.76 (−0.88, 2.4)	0.19 (−1.63, 2.01)	1.27 (−0.41, 2.94)	1.39 (−1.4, 4.19)
Q3	0.92 (−0.78, 2.62)	−0.05 (−1.95, 1.84)	0.28 (−1.46, 2.02)	1.83 (−1.07, 4.73)
Q4	0.91 (−0.79, 2.61)	−0.07 (−1.97, 1.82)	0.86 (−0.88, 2.6)	1.07 (−1.83, 3.97)
MBzP				
Q1	Ref			
Q2	1.24 (−0.4, 2.88)	0.23 (−1.4, 1.86)	1.12 (−0.41, 2.64)	1.45 (−1.24, 4.14)
Q3	2.26 (0.63, 3.89)	1.05 (−0.57, 2.67)	1.94 (0.43, 3.46)	3.61 (0.94, 6.28)
Q4	1.62 (−0.06, 3.3)	1.04 (−0.64, 2.71)	0.31 (−1.26, 1.87)	1.73 (−1.02, 4.49)
MCPP				
Q1	Ref			
Q2	1 (−0.59, 2.59)	0.33 (−1.14, 1.80)	1.06 (−0.89, 3.00)	2.52 (0.11, 4.94)
Q3	1.79 (0.18, 3.39)	0.96 (−0.52, 2.45)	1.17 (−0.79, 3.14)	3.46 (1.01, 5.91)
Q4	1.6 (−0.04, 3.25)	1.37 (−0.16, 2.89)	1.2 (−0.81, 3.22)	3.28 (0.77, 5.79)
ΣDEHP				
Q1	Ref			
Q2	1.93 (0.34, 3.52)	1.4 (0.12, 2.68)	1.03 (−0.98, 3.03)	3.29 (1.09, 5.49)
Q3	1.2 (−0.41, 2.8)	1.23 (−0.06, 2.52)	1.08 (−0.95, 3.11)	2.68 (0.45, 4.9)
Q4	1.5 (−0.17, 3.18)	2.32 (0.97, 3.67)	1.51 (−0.61, 3.63)	1.68 (−0.64, 4.01)

* Adjusted for maternal age, race/ethnicity, education, smoking, alcohol

Table 4

1st trimester urinary phthalate metabolite concentrations and distribution shifts for early gestational weight gain (GWG, kg)

Log-transformed SG-adjusted phthalate metabolites	Mean GWG	25th Percentile	Median GWG	75th percentile
MEP				
Q1	Ref			
Q2	0.94 (0.24, 1.64)	0.82 (−0.09, 1.72)	0.84 (0.07, 1.62)	1.3 (0.26, 2.35)
Q3	−0.06 (−0.78, 0.65)	−0.18 (−1.1, 0.74)	0.01 (−0.78, 0.8)	0.39 (−0.68, 1.45)
Q4	−0.1 (−0.83, 0.63)	−0.8 (−1.73, 0.14)	0.16 (−0.65, 0.96)	0.4 (−0.69, 1.48)
MnBP				
Q1	Ref			
Q2	0.27 (−0.41, 0.94)	0.26 (−0.6, 1.13)	0.45 (−0.25, 1.15)	0.62 (−0.45, 1.7)
Q3	−0.14 (−0.86, 0.58)	0 (−0.93, 0.92)	0.05 (−0.69, 0.8)	0.21 (−0.94, 1.36)
Q4	−0.3 (−1.03, 0.44)	−0.6 (−1.53, 0.34)	−0.51 (−1.27, 0.25)	−0.16 (−1.33, 1.01)
MiBP				
Q1	Ref			
Q2	0.12 (−0.58, 0.82)	0.64 (−0.19, 1.46)	−0.01 (−0.81, 0.78)	0.16 (−0.9, 1.22)
Q3	0.42 (−0.31, 1.15)	0.39 (−0.47, 1.25)	0.07 (−0.77, 0.9)	0.87 (−0.23, 1.97)
Q4	0.35 (−0.37, 1.07)	0.72 (−0.13, 1.57)	−0.02 (−0.84, 0.8)	0.08 (−1.01, 1.17)
MBzP				
Q1	Ref			
Q2	0.17 (−0.54, 0.88)	0.39 (−0.57, 1.35)	0.28 (−0.5, 1.06)	0.5 (−0.52, 1.51)
Q3	−0.21 (−0.93, 0.5)	−0.05 (−1.02, 0.91)	−0.12 (−0.91, 0.66)	0.02 (−1, 1.04)
Q4	−0.28 (−1.01, 0.44)	−0.23 (−1.21, 0.75)	−0.3 (−1.1, 0.5)	−0.38 (−1.42, 0.66)
MCPP				
Q1	Ref			
Q2	0.08 (−0.61, 0.77)	0.01 (−0.83, 0.84)	−0.16 (−0.91, 0.6)	0.2 (−0.84, 1.24)
Q3	−0.46 (−1.17, 0.26)	−0.38 (−1.24, 0.48)	−0.68 (−1.46, 0.09)	−0.26 (−1.33, 0.81)
Q4	0.22 (−0.49, 0.93)	0.14 (−0.71, 0.99)	−0.04 (−0.81, 0.73)	0.46 (−0.6, 1.52)
ΣDEHP				
Q1	Ref			
Q2	0.49 (−0.18, 1.16)	0.33 (−0.38, 1.04)	0.23 (−0.53, 0.98)	0.3 (−0.79, 1.39)
Q3	−0.58 (−1.26, 0.1)	−0.94 (−1.67, – 0.22)	−0.98 (−1.74, – 0.21)	−0.67 (−1.77, 0.44)
Q4	−0.42 (−1.14, 0.3)	−0.41 (−1.17, 0.35)	−0.42 (−1.22, 0.39)	−0.27 (−1.43, 0.9)

*Adjusted for maternal age, race/ethnicity, education, smoking, alcohol, baseline BMI