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Pregnancy phthalate metabolite concentrations and infant birth weight by gradations of maternal glucose tolerance

Nudrat Noor[a], Kelly K. Ferguson[b], John D. Meeker[c], Ellen W. Seely[d], Russ Hauser[a], Tamarra James-Todd[a,f,*,1], Thomas F. McElrath[e,1]

[a] Departments of Environmental Health and Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, 02115, USA
[b] Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, 27709, USA
[c] Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI, 48109, USA
[d] Division of Endocrine, Diabetes, and Hypertension, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA
[e] Division of Maternal Fetal Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA
[f] Division of Women's Health, Department of Medicine, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA

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ABSTRACT

Background: Higher birth weight is an important adverse outcome associated with hyperglycemia in pregnancy. Recent studies suggest that phthalate exposure is associated with elevated glucose levels in pregnant women, with implications for higher birth weight in the offspring. No study to date has investigated the association between prenatal phthalate exposure on infant high birth weight accounting for the range of pregnancy glucose levels.

Methods: A total of 350 women participating in an ongoing pregnancy cohort had data available on urinary phthalate metabolite concentrations at up to four time points across pregnancy. Urinary phthalate metabolites were averaged across pregnancy and log-transformed, specific gravity-adjusted and analyzed in quartiles. Birth weight was examined continuously (in grams), as well as dichotomized as large for gestational age ($> 90^{th}$ percentile). Glucose levels were assessed based on Results from 50-g glucose challenge tests as a part of screening for gestational diabetes conducted at 24–28 weeks gestation, and grouped into 3 categories < 120 mg/dL, 120– < 140 mg/dL and ≥ 140 mg/dL. Multivariable linear regression was performed, adjusting for potential confounders in the overall population and stratified by pregnancy glucose levels.

Results: Approximately 20% of infants born to women with glucose levels ≥ 140 mg/dL were large for gestational age. Average mono-ethyl phthalate (MEP) concentrations were higher among women who had glucose levels ≥ 140 mg/dL (geometric mean 140.9 μg/L; 95% CI: 91.6–216.8); however, higher MEP concentrations were not associated with higher birth weight. When stratified by maternal glucose levels, there was a suggestive association between higher concentrations of mono-(3-carboxypropyl) phthalate (MCPP) and higher birth weight among women with glucose levels ≥ 140 mg/dL (adj. birth weight: 569.2 g; 95% CI: 14.1, 1178.2).

Conclusions: Higher urinary phthalate metabolite concentrations were not significantly associated with higher birth weight. Counter to our hypothesis, women with higher glucose levels and higher urinary phthalate metabolites did not deliver babies with higher birth weight.

1. Introduction

In the last 20 years, the prevalence of large for gestational age (LGA), defined as infant birth weight greater than the 90^{th} percentile for gestational age, and macrosomia have decreased in the United States; however, approximately 7% and 10% of infants are still born LGA and with macrosomia, respectively (Ferrara, 2007; Donahue et al., 2010; Bowers et al., 2013). A number of short and long-term health consequences are associated with LGA and macrosomia, including an increased risk of infant shoulder dystocia or neonatal intensive care unit

* Corresponding author. Department of Environmental Health, Harvard T.H. Chan School of Public Health, 665 Huntington Ave, Bldg. 1, 14th Floor, Boston, MA, 02115, USA.
E-mail addresses: tjtodd@hsph.harvard.edu (T. James-Todd), tmcelrath@bwh.harvard.edu",0,0,2
>tmcelrath@bwh.harvard.edu (T.F. McElrath).
[1] Co-senior authors.

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(NICU) stay (Gu et al., 2012), as well as increased risk of type 2 diabetes and cardiovascular disease in adulthood (Lord, 2013; Johnsson et al., 2015; Stansfield et al., 2016). One of the major risk factors of LGA and macrosomia includes elevated glucose levels in pregnancy (HAPO Study Cooperative Research Group, 2009; Catalano et al., 2012). In particular, women with higher glucose levels in pregnancy have up to a 2-fold increased risk of delivering LGA infants (Bowers et al., 2013; Gaudet et al., 2014). This increased risk of LGA holds, even for elevated glucose levels not sufficient to make the diagnosis of gestational diabetes mellitus (GDM) (Coustan et al., 2010).

While traditional lifestyle factors, such as diet are certainly involved in LGA and macrosomia (defined as birth weight above 4000 g), a growing body of literature suggests that environmental chemicals also play a role in altered glucose levels during pregnancy, as well as altered fetal growth (James-Todd, Meeker et al., 2016; Chiu et al., 2017; Bellavia et al., 2018). One class of environmental chemicals associated with glucose levels are phthalates (Stahlhut et al., 2007; Svensson et al., 2011; James-Todd et al., 2012; Huang et al., 2014), which are used as plasticizers (Xie et al., 2016). Phthalates are ubiquitous within the environment, with use in a variety of consumer products, including personal care products, food packaging, and common household and industrial products (Hauser and Calafat, 2005; Koniecki et al., 2011). Certain phthalates, such as di-2-ethylhexyl phthalate are considered to be reproductive toxicants due to their associations with a variety of adverse maternal and infant outcomes (Swan, 2008; Diamanti-Kandarakis et al., 2009), including associations with altered fetal growth (Ferguson et al., 2016) and lower birth weight (Huang et al., 2009; Zhang et al., 2009; Casas et al., 2016; Ferguson et al., 2016; Watkins et al., 2016), anogenital distances (Swan, 2008; Dorman et al., 2018), and preterm birth (Ferguson, McElrath et al., 2014; Ferguson, McElrath et al., 2014). Although several recent studies have shown associations between certain urinary phthalate metabolites and low birth weight (Huang et al., 2009; Zhang et al., 2009; Casas et al., 2016; Ferguson et al., 2016; Watkins et al., 2016), studies have not accounted for maternal glucose levels as a potential effect modifier of the association between phthalates and birth weight. These associations may be particularly important, given that glucose is thought to be a major substrate for fetal growth (Coustan et al., 2010).

Therefore, we sought to evaluate the association between urinary phthalate metabolite concentrations on higher infant birth weight, stratifying by gradations of maternal glucose levels. We used data from a Boston-based pregnancy cohort—the LIFECODES study (McElrath et al., 2012). Given the association between phthalates and elevated maternal glucose levels (James-Todd, Meeker et al., 2016), our inquiry seeks to provide needed information about an important downstream sequela of maternal glucose intolerance—high birth weight—as it relates to a number of studies showing associations between phthalates and obesity (Holtcamp, 2012; Thayer et al., 2012).

2. Methods

2.1. Study population

The study population consisted of pregnant women participating in the LIFECODES pregnancy cohort, a large prospective study based at the Brigham and Women's Hospital (Boston, MA)(McElrath et al., 2012). Participants were recruited during their first prenatal visit (median: 9.9 weeks gestation). At baseline, information on socio-demographic factors was collected via a questionnaire. Blood and urine samples were collected at four time points during pregnancy (i.e. median: 9.9 weeks gestation; 17.9 weeks gestation; 26.1 weeks gestation and 35.3 weeks gestation). We utilized a subset of the population, who had available data on urinary phthalate metabolite concentrations, as a part of a nested case-control study among women who delivered between 2006 and 2008. Our subset included 350 term births (infants delivered at ≥37 weeks gestation) in order to assess exposure to phthalates across the full-course of pregnancy. There were 49 women with missing information on glucose levels, which resulted in a sample of 301 for the descriptive analysis, which was stratified by maternal glucose levels. For the multivariable analysis, we excluded women with a clinical diagnosis of GDM (n = 24), since standard treatment for GDM could impact infant birth weight (Crowther et al., 2005; Landon et al., 2009). The total sample size for our multivariable analysis consisted of 277 women. More detailed information about the LIFECODES pregnancy cohort and the nested case-control study can be found elsewhere (McElrath et al., 2012; Ferguson, McElrath et al., 2014). Institutional review board approval was obtained from Brigham and Women's Hospital as well as the University of Michigan, with the latter providing approval for the nested case-control study that generated the urinary phthalate metabolite data.

2.2. Urinary phthalate metabolite concentrations

Urine samples collected at the 4 time periods were stored at 4°C until processed within 3 h of collection, after which they were stored at −80°C. Nine urinary phthalate metabolites were measured at each time point, these included: mono-ethyl phthalate (MEP)(metabolite of di-ethyl phthalate); mono-butyl phthalate (MBP) (metabolite of di-butyl phthalate); mono-isobutyl phthalate (MiBP) (metabolite of diisobutyle phthalate); mono-benzyl phthalate (MBzP) (metabolite of benzyl butyl phthalate); mono-(3-carboxypropyl) phthalate (MCPP) (metabolite of di-n-octyl phthalate, as well as other low and high molecular weight phthalates); and metabolites of di-2-ethylhexyl phthalate (DEHP)–mono-2-ethylhexyl phthalate (MEHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono (2-ethyl-5-oxohexyl) phthalate (MEOHP). For the metabolites of DEHP, we calculated a summary measure (ΣDEHP) by dividing each metabolite concentration by its molecular weight and summing: [(MEHP*(1/278.34)) + (MEHHP*(1/294.34)) + (MEOHP*(1/292.33)) + (MECPP*(1/308.33))]. Urinary phthalate metabolite concentrations were measured by NSF International using Centers for Disease Control and Prevention protocols (Silva et al., 2007; Lewis et al., 2013). In order to account for urine dilution, adjustment was done for specific gravity (SG) using the following formula: $P_c = P ((1.015–1)/(SG-1))$, where P_c represents SG-adjusted concentrations and P is measured urinary concentrations. The median SG was 1.105 for the overall population. For each participant, the geometric mean for urinary phthalate metabolite concentrations was computed using measurements from all four time points across pregnancy and the composite measure was then adjusted for SG, also averaged across each of the measured time points. After adjustment for SG, mean urinary phthalate metabolite concentrations were log-transformed and analyzed in quartiles, with the highest quartile corresponding to the highest average concentrations of each urinary phthalate metabolite over the course of pregnancy.

2.3. High birth weight

Infant birth weight was measured in grams at the time of delivery. For the primary outcome, birth weight was evaluated as a continuous variable. We evaluated LGA as a secondary outcome using the U.S. national reference data to calculate large for gestational age (LGA), given that we had limited power to evaluate LGA as a primary outcome due to a small sample size. For this secondary analysis, we compared LGA infants to infants born average for gestational age and small for gestational age (Oken et al., 2003).

2.4. Maternal glucose levels

Information on maternal glucose was collected from a non-fasting 50-g glucose load test (GLT) in the second trimester as a part of standard clinical screening for GDM undertaken by all study participants. Classification of glucose levels was performed using the Carpenter-

Coustan criteria utilized by Brigham and Women's Hospital. For this, a two-step screening approach was taken for GDM diagnosis, with all women sitting for the 50-g, non-fasting glucose load test (GLT) as the first step in GDM screening. Those women with glucose levels from the GLT ≥140 mg/dL were referred for further testing with a fasting 100-g, 3-h oral glucose tolerance test (OGTT). GDM was clinically diagnosed when a woman had two abnormal values from the 3-h OGTT following the elevated glucose value from the GLT. The diagnostic thresholds for the OGTT were: > 95 mg/dL (fasting); > 180 mg/dL (1 h); > 155 mg/dL (2 h); > 140 mg/dL (3 h) (Gupta et al., 2015).

In this study, maternal glucose was assessed as both continuous and categorical variables. Based on the GLT, glucose levels were classified as < 120 mg/dL, 120– < 140 mg/dL, and ≥140 mg/dL to account for gradations of maternal glucose intolerance. Again, the latter category excluded women with diagnosed GDM. This categorization of maternal glucose intolerance has been evaluated in previous studies with respect to several adverse health outcomes (Cheng et al., 2007; American Diabetes, 2009; Figueroa et al., 2013; Subramaniam et al., 2015).

2.5. Statistical analysis

For statistical analysis, we calculated descriptive statistics for maternal and infant characteristics in the overall population, as well as stratified by gradations of maternal glucose intolerance (i.e. glucose from GLT < 120 mg/dL, 120– < 140 mg/dL, ≥140 mg/dL). We used *t*-test to evaluate differences in the geometric means for urinary phthalate metabolites by gradations of glucose levels. Multivariable linear regression was used to examine the difference in birth weight over quartiles of urinary phthalate metabolites relative to the lowest quartile, along with the 95% confidence intervals. Associations were evaluated in the overall study population and stratified by maternal glucose tolerance status, as this was our main question of interest. We identified potential confounders based on the literature for factors associated with: 1) phthalate exposure and high birth weight and 2) phthalate exposure and pregnancy glucose levels. These potential confounders included: maternal age, race/ethnicity, education, smoking status, alcohol use, gestational age at delivery and infant sex in multivariable models. We assessed maternal age and gestational age at delivery as continuous variables. Race/ethnicity was evaluated as non-Hispanic white (reference), non-Hispanic black, non-Hispanic Asian, Hispanic, Other. Maternal education was evaluated as high school or less, technical school or some college, college graduate or higher (reference). Smoking status was categorized as current, past, never (reference). Alcohol use during pregnancy was categorized as yes versus no (reference). We calculated p-for-interaction to determine whether maternal glucose levels modified the association between urinary phthalate metabolite concentrations and birth weight. Maternal glucose levels and phthalate metabolite concentrations in the models evaluating interaction were continuous variables. If p-for-interaction was < 0.10, we concluded that the interaction was statistically significant.

We conducted several sensitivity analyses. First, we evaluated the association between urinary phthalate metabolite concentrations and LGA (> 90th percentile for birth weight). Second, we examined visit-specific urinary phthalate metabolite concentrations and higher birth weight for the overall population. Third, we looked at the association between phthalates and higher birth weight stratifying by pre-pregnancy BMI (categorizing as < 25 (normal weight) or ≥ 25 (overweight/obese))—another known LGA risk factor. All statistical analyses were performed using R version 3.3.2.

3. Results

Table 1 shows baseline maternal (first prenatal visit), and infant characteristics stratified by maternal glucose tolerance status. More non-Hispanic Asian and Hispanic women had glucose levels ≥140 mg/dL. Additionally, more women with higher glucose levels used alcohol and were obese (BMI > 30 kg/m^2). Over 20% of infants born to women with glucose levels ≥140 mg/dL (and without a GDM diagnosis) were born LGA.

Table 1
Maternal and infant characteristics stratified by glucose status (n = 350).

Characteristics	Overall	Glucose < 120 (mg/dL)	Glucose 120- < 140 (mg/dL)	Glucose ≥140 (mg/dL)without GDM[a]
	N = 350	n = 198	n = 47	n = 32
	Mean (+/-SD)			
Maternal age	31.9 (5.4)	31.3 (5.6)	31.6 (5.4)	33.7 (5.7)
BMI (kg/m^2)	25.9 (5.6)	25.3 (5.3)	27.0 (6.1)	27.2 (5.2)
Birth weight (g)	3397.5 (471.2)	3326.9 (459.9)	3456.6 (450.7)	3569.3 (484.7)
	N (%)			
Race				
-Non-Hispanic white	206 (59)	115 (58)	28 (60)	16 (50)
-Non-Hispanic black	55 (16)	38 (19)	7 (15)	3 (9)
-Non-Hispanic Asian	19 (5)	4 (2)	4 (8)	4 (13)
-Hispanic	50 (14)	29 (15)	6 (13)	7 (22)
-Other	20 (5)	12 (6)	2 (4)	2 (6)
Education				
< College	99 (29)	62 (32)	18 (39)	8 (27)
≥ College	241 (71)	133 (68)	29 (61)	22 (73)
Alcohol use				
- No	324 (95)	182 (93)	47 (100)	28 (88)
- Yes	19 (55)	14 (7)	0	4 (12)
Smoking				
-No	331 (95)	188 (95)	43 (91)	30 (94)
-Yes	19 (55)	10 (5)	4 (9)	2 (6)
BMI (kg/m^2)				
< 25	187 (0.5)	111 (57)	24 (52)	11 (34)
≥25- < 30	94 (0.3)	53 (27)	11 (24)	14 (44)
≥30	65 (0.2)	32 (16)	11 (24)	7 (22)
Infant sex				
-Female	156 (45)	84 (42)	21 (45)	15 (47)
-Male	194 (55)	114 (58)	26 (55)	17 (53)
LGA				
-No	315 (90)	185 (93)	42 (89)	25 (78)
-Yes	35 (10)	13 (7)	5 (11)	7 (22)

[a] Excludes 24 women with diagnosed GDM.

Table 2 presents urinary phthalate metabolite concentrations by maternal glucose status. Average MEP concentrations were highest among women with glucose levels > 140 mg/dL, however the difference was not significant compared to the low glucose concentration group. Concentrations of all other individual urinary phthalate metabolites, as well as ΣDEHP, were comparable across all maternal glucose tolerance categories.

Table 3 shows the associations between maternal urinary phthalate metabolite concentrations and continuous infant birth weight (in grams) in the overall population, as well as stratified by maternal glucose tolerance status based on the GDM screening tests. Results of the regression analyses between quartiles of urinary phthalate metabolite concentrations and infant birth weight (g) are presented in Table 3 (adjusted for gestational age, mother's education, race, BMI, age, infant sex). In the overall population, no significant associations were seen between urinary phthalate metabolite concentrations and birth weight after adjustment for potential confounders. In fact, significant associations were seen between certain urinary phthalate metabolites and lower birth weight, as previously published in this study population (Ferguson et al., 2016). When stratifying by maternal glucose tolerance status, there was a positive association between MCPP and birth weight among women with higher glucose levels (≥140 mg/dL); however, the estimate was imprecise (Q4 v. Q1: β = 569.2 g; 95% CI: 14.1, 1178.2). Further, as MCPP is a non-specific metabolite of

Table 2
Average specific gravity-adjusted urinary phthalate metabolite concentrations stratified by pregnancy glucose status.

	Overall	Glucose < 120 (mg/dL) n = 198	Glucose 120- < 140 (mg/dL) n = 47	Glucose ≥ 140 (mg/dL) without GDM n = 32
Phthalates (μg/L)	Geometric means (95% CI)			
MEP	121.5 (106.9–138.0)	115.8 (98.9–135.6)	132.6 (88.5, 198.8)	140.9 (91.6–216.8)
MBP	15.2 (14.2–16.3)	15.7 (14.2, 17.3)	15.1 (13.0, 17.5)	14.4 (11.2–18.6)
MiBP	6.5 (6.1–7.0)	6.5 (5.9, 7.1)	7.1 (5.7, 8.9)	6.5 (4.7–8.9)
MBzP	6.0 (5.5–6.7)	6.3 (5.5, 7.3)	6.6 (5.0, 8.6)	4.9 (3.7–6.7)
MCPP	1.7 (1.6–1.9)	1.9 (1.7,2.1)	1.8 (1.6,2.2)	1.3 (1.1–1.7)
ΣDEHP	0.3 (0.2–0.3)	0.3 (0.2–0.4)	0.3 (0.2,0.4)	0.3 (0.2–0.4)

several high and low molecular weight phthalates, the association between MCPP and birth weight in the high glucose group may not clearly be attributed to one specific phthalate parent compound. No other positive associations were seen with other phthalate metabolites and birth weight, regardless of maternal glucose tolerance status. All tests for interactions by maternal glucose status were insignificant ($p \geq 0.10$). For our secondary analysis, we did not find any significant associations between urinary phthalate metabolite concentrations and LGA across categories of maternal glucose tolerance status (data not shown).

When conducting sensitivity analyses, visit-specific associations for urinary phthalate metabolites and birth weight in the overall population and stratified by maternal glucose tolerance status did not show any statistical significance (data not shown). None of the urinary phthalate metabolite concentrations were associated with higher birth weight, when stratifying by maternal BMI only (See supplemental table 1). Additional tests for interaction by maternal BMI were also insignificant. Associations were similar in sex-stratified analyses (See supplemental table 1). (No associations were seen when evaluating visit-specific urinary phthalate metabolite concentrations and infant birth weight. (See supplemental tables 2-5).

4. Discussion

In this study, we hypothesized that higher urinary phthalate metabolite concentrations during pregnancy would be associated with higher birth weight infants among women with risk factors related to LGA—specifically, elevated maternal glucose levels from the GDM screening tests conducted as a part of standard care. Contrary to our hypothesis, most associations were null for urinary phthalate metabolite concentrations and infant birth weight when stratifying by maternal glucose tolerance. Furthermore, no associations were seen for urinary phthalate metabolite concentrations and LGA based on maternal glucose levels from the GLT.

Previous studies have evaluated pregnancy urinary phthalate metabolite concentrations and their associations with birth weight not accounting for a major driver of fetal growth—maternal glucose levels (Huang et al., 2009; Zhang et al., 2009; Ferguson et al., 2016). Studies that have evaluated the association between urinary phthalate metabolites and birth weight have taken into account that phthalates might be potent reproductive toxicants, operating through multiple pathways, including hormonal (Johns et al., 2016) and inflammatory (Ferguson, Cantonwine et al., 2014) pathways. In addition to being reproductive toxicants, phthalates are also thought to be and metabolic disruptors, altering obesity risk and associated metabolic outcomes (Heindel et al., 2017),with implications for growth. Mechanistically, phthalates could alter obesity through a variety of pathways including their ability to bind to peroxisome proliferator-activated receptors (PPAR) (Desvergne et al., 2009; Casals-Casas and Desvergne, 2011). With this, they could upregulate adipogenesis and alter glucose metabolism and fat accretion, with implications for birth weight and growth over time.

In some studies evaluating phthalates and birth weight, certain urinary metabolites, including metabolites of DEHP, di-butyl phthalate and butyl benzyl phthalate, were found to be associated with low birth weight, this includes data previously published from the same study population (Casas et al., 2016; Ferguson et al., 2016). However, a separate study did not show any associations with urinary phthalate metabolite concentrations (Zhang et al., 2009) and one study showed higher birth weight for metabolites of di-butyl phthalate (Watkins et al., 2016). In rodents, prenatal exposure to phthalates has been shown to lead to changes in birth weight (Wolff et al., 2008). For example, rats exposed for two generations to high butyl-benzyl phthalate diet had lower birth weight. However, this finding was seen in male offspring only (Tyl et al., 2004). The present study did not find sex differences in the stratified regression analyses (Table S1). Furthermore, this previous animal study had exposure levels that were much higher than what is observed in humans (Zota et al., 2014). The present study's findings evaluated low dose exposures accounting for a major driver of fetal growth—maternal glucose levels. Yet, for the majority of urinary phthalate metabolites, we did not see any associations with birth weight, despite previous studies showing associations between pregnancy phthalate metabolite concentrations and higher maternal glucose levels (James-Todd, Meeker et al., 2016; James-Todd et al., 2018).

One possible reason for phthalate metabolites not being associated with increased birth weight in the present study could be a canceling out effect. More specifically, phthalates have been found to be associated with elevated glucose levels in pregnant and non-pregnant populations (Stahlhut et al., 2007; James-Todd et al., 2012; Shapiro et al., 2015). They have also been associated with lower birth weight in general populations, not accounting for degree of maternal glucose intolerance (Zhang et al., 2009; Casas et al., 2016; Ferguson et al., 2016). Yet in the context of mothers with higher glucose levels, which typically is associated with fetal overgrowth, this reduction in maternal glucose levels may be associated with adequate rather than excess fetal growth. In other words, higher phthalate exposure may work as a "brake" on overall fetal growth among women with elevated glucose levels in pregnancy, which could result in normal birth weights, rather than higher birth weights and LGA. Interestingly, the majority of the point estimates for this study suggest inverse associations, similar to the majority of previous findings that pregnancy phthalate exposure may be associated with reduced birth weight, including a previous study from this population (Zhang et al., 2009; Ferguson, McElrath et al., 2014; Ferguson et al., 2016). However, our findings did not reach statistical significance suggesting that the excess glucose exposures may mitigate some of the weight reducing effects of urinary phthalate metabolite concentrations in utero.

The finding for MCPP and higher infant birth weight among women with glucose levels ≥140 mg/dL on the GLT suggests that this phthalate metabolite may be affecting birth weight through the mechanism of modifying glucose levels during pregnancy. However, while we found this association, we also note that MCPP is a non-specific phthalate metabolite of several low and high molecular weight phthalates, which

Table 3
Regression coefficients (95% CIs) for associations between quartiles of urinary phthalate metabolites (ug/L) and infant birth weight (g) in overall population and stratified by maternal glucose tolerance status.

	Overall `N = 350		Glucose < 120 (mg/dL) n = 198	Glucose 120- < 140 (mg/dL) n = 47	Glucose≥140 without GDM (mg/dL) n = 32
Phthalates µg/L[b]	Unadjusted	Adjusted[a]	Adjusted[a]	Adjusted[a]	Adjusted[a]
	Difference in birth weight in grams				
MEP					
Q1 (< 3.9)	Ref	Ref	Ref	Ref	Ref
Q2 (3.9- < 4.7)	13.1 (-128.2, 154.4)	13.6 (-117.7, 145.0)	105.0 (−64.8, 275.0)	48.1 (−330.8, 427.1)	206.1 (−351.0, 763.3)
Q3 (4.7- < 5.5)	−117.5 (−263.4, 28.3)	−89.2 (−227.2, 48.7)	−12.7 (−197.5, 171.9)	−144.4 (−570.4, 281.5)	−58.4 (−644.9, 528.0)
Q4 (≥ 5.5)	−60.9 (−202.6, 80.7)	−57.4 (−195.2, 80.3)	−33.7 (−223.0, 155.6)	48.6 (−350.3, 447.6)	179.2 (−367.5, 726.0)
MBP					
Q1 (< 2.3)	Ref	Ref	Ref	Ref	Ref
Q2 (2.3- < 2.6)	22.9 (−123.0, 169.0)	−38.5 (−175.7, 98.7)	0.7 (−183.5, 185.0)	−163.1 (−544.8218.6)	50.8 (−392.3, 494.1)
Q3 (2.6- < 3.0)	−127.4 (−264.0, 10.5)	−93.9 (−223.7, 35.8)	−40.3 (−215.3, 134.6)	20.0 (−371.5, 411.6)	−40.7 (−458.6, 377.2)
Q4 (> 3.0)	−161.9 (−296.8, −26.9)	−93.6 (−231.1, 43.8)	−54.4 (−238.1, 129.2)	−267.9 (−673.0,137.2)	268.8 (−217.7, 755.4)
MibP					
Q1 (< 1.4)	Ref	Ref	Ref	Ref	Ref
Q2 (1.4- < 1.8)	38.9 (−110.9, 188.8)	49.2 (−87.8, 186.3)	139.0 (−48.1, 326.1)	−135.4 (−518.5, 247.6)	172.1 (−256.5, 600.7)
Q3 (1.8- < 2.2)	−54.4 (−193.3, 84.4)	−34.2 (−165.8, 97.4)	93.1 (−78.7, 265.0)	12.0 (−423.3, 447.4)	191.2 (−308.3, 690.7)
Q4 (> 2.2)	−43.3 (−182.2, 95.5)	29.0 (−110.3, 168.5)	76.9 (−108.1, 262.0)	−80.5 (−488.4, 327.3)	233.1 (−220.0, 686.2)
MBZP					
Q1 (< 1.1)	Ref	Ref	Ref	Ref	Ref
Q2 (1.1- < 1.6)	−38.3 (−187.6, 10.9)	42.7 (−93.5, 178.9)	78.0 (−102.4, 258.5)	−239.8 (−676.8, 197.1)	−258.2 (−740.5, 224.0)
Q3 (1.6- < 2.2)	−11.5 (−157.6, 134.5)	45.7 (−88.6, 180.2)	56.8 (−122.6, 236.2)	−260.0 (−678.2, 158.1)	−248.4 (-726.9, 230.0)
Q4 (> 2.2)	−57.5 (−203.3, 88.3)	46.0 (−97.2, 189.3)	108.7 (−76.1, 293.6)	−294.2 (−745.9, 157.5)	38.7 (-532.5, 609.8)
MCPP					
Q1 (< 0.04)	Ref	Ref	Ref	Ref	Ref
Q2 (0.04- < 0.45)	59.0 (−80.7, 198.9)	122.5 (−6.8, 251.8)	125.2 (−45.0, 295.4)	−7.9 (−422.1, 406.1)	146.2 (−221.2, 513.7)
Q3 (0.45- < 0.97)	−36.3 (−175.4, 102.6)	11.2 (−129.7, 126.3)	−21.7 (−195.9152.3)	−82.2 (−494.4, 329.9)	316.2 (−80.3, 712.7)
Q4 (> 0.97)	−175.1 (−314.2, −36.1)	−112.6 (−251.0, 6.1)	−89.3 (−251.0, 72.2)	−421.9 (−854.8, 10.9)	596.22 (14.1, 1178.2)
ΣDEHP					
Q1 (< -1.6)	Ref	Ref	Ref	Ref	Ref
Q2 (1.6- < -1.1)	76.1 (−64.7, 216.9)	80.6 (−50.9, 212.1)	172.6 (5.1, 340.1)	−152.2 (−526.9, 222.4)	148.54 (−470.4, 767.5)
Q3 (-1.1- < -0.6)	73.0 (−59.7205.7)	22.5 (−100.9, 146.0)	110.4 (−53.0, 274.0)	−85.6 (−460.0, 288.7)	208.03 (−218.2, 634.2)
Q4 (> -0.6)	−45.0 (−186.4, 96.2)	−63.7 (−193.9, 66.4)	−11.9 (−179.1, 155.3)	−358.8 (−726.6, 8.9)	−17.1 (−583.3, 549.0)

[a] Adjusted for gestational age, mother's education, race, BMI, age, infant sex.
[b] SG-adjusted, log transformed quartiles for phthalate metabolites.

implies that this association may not be attributed to any one specific parent compound. Further, it needs to be interpreted with caution owing to the wide confidence intervals, which could be attributed to the small number of women with high glucose levels in the highest quartile of MCPP (n = 3). Thus, we have limited power to examine this association and the present finding could be due to chance. That said, larger studies are needed to further evaluate this question.

This study has several limitations. First, spot urine samples were used to assess this non-persistent chemical exposure with potential implications for exposure misclassification due to intra-person variability, given the short half-life of these chemicals (Frederiksen et al., 2013). However, we used multiple urine samples averaged across up to four time points in pregnancy to improve reliability and assessment of urinary phthalate metabolite concentrations. Second, due to small sample size, we were unable to evaluate LGA or macrosomia as primary outcomes and instead used continuous birth weight in grams. More extreme birth weight measures may have yielded different results. However, in a secondary data analysis of LGA defined as > 90th percentile, we found directionally similar associations to those using continuous birth weight. Third, we were unable to adjust for diet and physical activity, which are lifestyle factors known to be associated with higher birth weight. However, we were able to adjust for other maternal lifestyle and infant characteristics, such as smoking, alcohol use, and infant sex. Finally, our sample size was somewhat limited for assessing effect modification by maternal glucose tolerance status. While this may have limited the power to detect associations, noted most by the wide confidence intervals, we did find statistically significant positive associations in the stratified analyses for MCPP metabolites with higher birth weight. However, as MCPP is a non-specific metabolite for several high and low molecular weight phthalates, the association between MCPP and birth weight in the high glucose group may not clearly attributed to one certain phthalate.

Despite these limitations, this study had several strengths. First, to our knowledge this is the first study to evaluate a sequela of non-diabetic glucose intolerance in pregnancy on infant birth weight as it relates to urinary phthalate metabolite concentrations. A number of papers have shown associations between phthalates and other endocrine disrupting chemicals (EDCs) as it relates to pregnancy glucose levels (James-Todd, Meeker et al., 2016; Chiu et al., 2017; Bellavia et al., 2018). As such, infant birth weight may be an important downstream outcome to consider. Second, we accounted for the low to moderate reliability of urinary phthalate metabolite concentrations by averaging urinary phthalate metabolites across multiple time points during. Third, we were able to adjust for a number of known risk factors for higher birth weight, including maternal obesity status.

5. Conclusion

Counter to our original hypothesis, we did not find associations between urinary phthalate metabolites and higher birth weight among women at higher risk of LGA—those with elevated glucose levels in pregnancy. While previous studies have found associations between phthalates and elevated maternal glucose, the present findings suggest that infants born to mothers with higher glucose levels in pregnancy may not be at increased risk of higher birth weight. Larger prospective studies are needed to further investigate this research question. If true, phthalates may alter fetal growth in women with glucose intolerance in pregnancy by mitigating some of the impact of excess glucose exposure and fetal overgrowth that traditionally impacts risk of higher birth weight and LGA.

Conflicts of interest

All authors declare that they have no competing financial interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2018.12.005.

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