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Maternal Urinary Phthalate Metabolites in Relation to Gestational Diabetes and Glucose Intolerance During Pregnancy

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Abstract

Background: Phthalates are common plasticizer chemicals that have been linked to glucose intolerance in the general population, but there is only limited research on their association with gestational diabetes (GDM).

Objective: We evaluated the association between 11 urinary phthalate metabolites and GDM, impaired glucose tolerance (IGT), and continuous blood glucose concentration during pregnancy in The Infant Development and Environment Study (TIDES). Based on prior study results, our primary analyses focused on monoethyl phthalate (MEP) in relation to our outcomes of interest.

Study Design: We used multi-variable logistic regression to examine the odds of GDM and IGT in relation to an interquartile-range (IQR) increase in natural log (ln)-transformed, specific gravity (SG)-adjusted first trimester (T1) and average of T1 and third trimester (T3) ("T1T3avg") phthalate metabolite concentrations. We fit linear regression models to examine the percent change in blood glucose per IQR increase in ln-transformed, SG-adjusted T1 and T1T3avg phthalates. In sensitivity analyses, we examined interactions between exposure and race. We adjusted for maternal age, maternal body mass index, study center, race/ethnicity, parity, and gestational age at glucose testing.

Results: In our sample of 705 pregnant women, we observed 60 cases of GDM, 90 cases of IGT, and an average GLT blood glucose of 113.6 ±27.7 mg/dL. In our primary analysis, T1T3avg MEP was positively associated with GDM ([OR (95% CI) per IQR increase] T1T3avg MEP: 1.61 (1.10, 2.36)). In secondary analyses, most other phthalates were not found to be associated with study outcomes, though some associations were noted. Sensitivity analyses indicated strong race-specific associations in Asians, though these results are based on a small sample size (n=35).

Conclusion: In alignment with our *a priori* selection, we documented an association between T1T3avg MEP and GDM. Additional phthalate metabolites were also found to be linked to glucose intolerance, with possible stronger associations in certain racial/ethnic subgroups. Given the prevalence of phthalate exposures and the growing evidence of associations with metabolic outcomes, future studies should continue to examine this question in diverse cohorts of pregnant women, particularly in those who may be at higher risk for GDM and IGT.

Keywords

gestational diabetes; impaired glucose intolerance; blood glucose; phthalates; endocrine disruptors; pregnancy

1. Introduction

Gestational diabetes mellitus (GDM) is glucose intolerance that develops during pregnancy (American Diabetes Association 2012). In GDM, there is insufficient insulin released from the beta cells and decreased skeletal muscle glucose uptake, resulting in maternal

hyperglycemia. Incidence of GDM in the United States has increased dramatically in the past twenty years, (Albrecht et al. 2010; Bardenheier et al. 2015; Thorpe et al. 2005) partially attributed to improved detection. GDM is now detected in 8–9% percent of pregnancies in the U.S., though estimates vary based on ethnicity and diagnostic criteria (Caughey et al. 2010; Coustan et al. 2010; DeSisto et al. 2014; Ehrlich et al. 2016; Reece 2010). Risk factors include prior GDM (Holmes et al. 2010; Kim et al. 2007), previous large for gestational age (LGA) infant (Simmons et al. 2009), family history of GDM or type 2 diabetes mellitus (T2DM) (Ben- Haroush et al. 2003), pre-pregnancy obesity (Chu et al. 2007; Torloni et al. 2009), nonwhite race/ethnicity (Berkowitz et al. 1992), high gestational weight gain in early pregnancy (Morisset et al. 2011), and increased maternal age (Lao et al. 2006; Reece 2010). GDM is associated with health consequences for the mother and child, but recent research suggests that elevated maternal blood glucose even without overt GDM diagnosis, such as in impaired glucose tolerance (IGT), is also associated with adverse fetal and maternal outcomes (The HAPO Study Cooperative Research Group 2008).

The etiology of beta cell dysfunction and related pathologies in GDM is not well understood. Possible contributing factors and mediators include: alterations in inflammatory signaling, which can affect the insulin receptor and glucose transporters (Winkler et al. 2002); changes in expression of peroxisome proliferator activated receptors (PPARs) (Catalano et al. 2002); and oxidative stress (Chen and Scholl 2005; Coughlan et al. 2004; Lappas et al. 2011). Some women (<10% of GDM cases) have circulating antibodies to islet cells or key cellular enzymes, similar to those in type 1 diabetes (T1DM) (Catalano et al. 1990). Increasing evidence suggests that chemical exposure may also play a role in metabolic dysregulation in pregnancy, perhaps through the pathways described above (Ehrlich et al. 2016).

Phthalates are chemicals utilized in numerous consumer applications, including plastics, personal care products, food packaging, and medical devices (Sathyanarayana 2008; Schettler 2006) Because they are not bound to products, phthalates can easily migrate into air, dust, and food. Exposure occurs through ingestion, inhalation, and/or dermal contact (Schettler 2006). Phthalates are known endocrine disruptors (National Research Council 2008), and growing evidence indicates a link to metabolic dysfunction, including obesity and diabetes (Hatch et al. 2008; James-Todd et al. 2012; Stahlhut et al. 2007).

Published studies on the relationship between phthalates and gestational glucose intolerance are limited. The only cohort study (n= 1274) to examine GDM diagnosis in relation to phthalate exposure found no evidence of increased risk (Shapiro et al. 2015). However, other studies have documented associations between phthalate exposure and both increases and decreases in blood glucose concentration and/or risk factors for GDM (Fisher et al. 2018; James-Todd et al. 2018; James-Todd et al. 2016; Robledo et al. 2015).

To further address this question, we utilized data from The Infant Development and Environment Study (TIDES) to investigate the associations of urinary phthalate metabolite concentrations with GDM, IGT, and continuous blood glucose. Based on results from prior studies (James-Todd et al. 2018; James-Todd et al. 2016), our primary analytical hypothesis was that concentrations of monoethyl phthalate (MEP) would be higher among mothers with

GDM compared to those who did not develop GDM. Secondary analyses considered additional individual phthalate metabolites and one weighted summary score of di-2-ethylhexyl phthalate (DEHP) metabolites. In sensitivity analyses, we evaluated race-specific associations and non-linear associations. Our study improves and expands upon previous related analyses by examining a large population from four distinct geographic regions, utilizing more than one urinary measure of phthalate exposure, and including subclinical measures (such as continuous glucose and IGT) based on medical records, in addition to clinical diagnosis of GDM.

2. MATERIALS AND METHODS

2.1 Study design

From 2010–2012, TIDES recruited first trimester (T1) pregnant women at the University of California San Francisco (UCSF), University of Minnesota (UMN), University of Rochester Medical Center (URMC), and Seattle Children's Hospital/University of Washington (SCH/UW). Eligibility criteria included: <13 weeks pregnant, English speaking, ≥18 years of age, no severe threat to pregnancy, and intention to deliver at a study hospital. After providing informed consent, participants completed questionnaires and provided urine samples during each trimester of pregnancy. Glucose tolerance test results and other data were abstracted by staff at each site from birth and medical records, with one in ten records undergoing double abstraction for quality control. This study was approved by the UW Institutional Review Board (IRB) (Study ID: #00002643).

The overall TIDES cohort includes 753 women, but this analysis is limited to 705 women who completed a T1 questionnaire, had T1 phthalate data, and underwent a glucose load test (GLT). Because a GLT is only administered to pregnant women without prior diabetes, our study is limited to individuals without previous diabetes diagnoses.

2.2 Exposure Assessment

Data from T1 and third trimester (T3) urine samples were available for this analysis. T3 collection occurred concurrent with or after GDM screening. Samples were collected in sterile, phthalate-free specimen cups, transferred to cryovials, and stored at −80°C until analysis. Specific gravity was measured with a handheld refractometer at the time of urine collection. Phthalate metabolite analyses were carried out at two laboratories. Most samples were analyzed at the National Center for Environmental Health, Centers for Disease Control and Prevention (CDC). This process involved enzymatic deconjugation of phthalate metabolites from glucuronidated form, automated online solid phase extraction, separation with high performance liquid chromatography (HPLC), and detection by isotope-dilution tandem mass spectrometry (Silva et al. 2007). A subset of samples were analyzed at the University of Washington (UW) with a modified version of CDC method 6306.03, which included HPLC with electrospray ionization-tandem mass spectrometry (Calafat A.M. 2010). Process and instrument blanks were included for quality assurance. The limit of detection (LOD) was between 0.2–2.0 ng/mL for UW and 0.2–0.6 ng/mL for CDC.

Eleven individual phthalate metabolites (mono-isobutyl phthalate (MIBP), MEP, mono-n-butyl phthalate (MNBP), mono-benzyl phthalate (MBZP), mono-carboxy-isononyl phthalate (MCNP), mono-carboxy-iso-octyl phthalate (MCOP), mono-(3-carboxypropyl) phthalate (MCPP), mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)) and the molar sum of DEHP metabolites(Ferguson et al. 2014b) (∑DEHP) were included. T1 MCOP and MCNP were only available for mothers of male infants, while T3 MCOP and MCNP were available for mothers of male and female infants. All urinary phthalates were corrected for dilution using specific gravity (SG) measurements with the following formula: $P_c = P[(SG_{median}-1)/SG-1]$ (P_c = SG-corrected concentration; P = measured urinary concentration; SG = specific gravity for the individual sample; SG_{median} = median SG over all samples).(Ferguson et al. 2014b) The metabolites were also natural log (ln)- transformed to approximate normal distributions. To calculate ∑DEHP, we divided each metabolite by its molecular weight and summed these totals. (Hauser et al. 2016) Correlation between SG-adjusted T1 and T3 phthalates were assessed through Spearman correlation coefficients.

We utilized two exposure metrics: 1) arithmetic mean of ln-transformed, SG-adjusted T1 and T3 urinary phthalate metabolite concentrations (“T1T3avg”), and 2) ln-transformed, SG-adjusted T1 urinary phthalate metabolite concentrations. The subject-specific T1T3avg, our primary exposure metric, was used to reduce exposure misclassification and obtain a more representative measure, given that phthalates are nonpersistent chemicals that exhibit variability over time (Fisher et al. 2015). T1 concentrations were utilized because this exposure assessment preceded glucose tolerance testing.

2.3 Outcome Assessment

GDM screening occurred during weeks 24–28 of pregnancy. The most common GDM screening approach, and the one utilized by all TIDES clinics, is a two-step test, comprised of a 1-hour 50-g glucose load test (GLT) followed by a 3-hour 100-g oral glucose tolerance test (OGTT) for those who screen positive in the initial GLT (American Diabetes 2014; Vandorsten et al. 2012). GDM is diagnosed in women with two or more abnormal values in the OGTT. Because of varying diagnostic thresholds (American College of Obstetricians and Gynecologists (ACOG) 2018; Carpenter and Coustan 1982; National Diabetes Data 1979), we standardized across the TIDES clinics with respect to GLT and OGTT test results. We classified a GLT result of ≥ 135 mg/dL as GLT exceedance/failure, since this was the midpoint of the threshold used across TIDES clinics. We then utilized results from the OGTT to classify women using the Carpenter-Coustan (CC) thresholds for exceedance (fasting: 95 mg/dL; 1 hour: 180 mg/dL; 2 hour: 155 mg/dL; and 3 hours: 140 mg/dL) (Carpenter and Coustan 1982). IGT was defined as a failed GLT but less than two exceedances on the OGTT. Therefore, by definition, GDM and IGT are mutually exclusive. Blood glucose concentrations from the GLT were utilized in our continuous outcome analysis. Two GLT values (x=1 & x=38 mg/dL) deemed implausible by study clinicians were dropped.

2.4 Statistical Analysis

Based on published literature and *a priori* model conceptualization, we considered the following covariates and precision variables in the analyses: maternal age (Hatch et al. 2008; Lao et al. 2006), maternal pre-pregnancy body mass index (BMI) (Torloni et al. 2009), gestational weight gain (GWG) (Hedderson et al. 2010), study center, race/ethnicity (Berkowitz et al. 1992; Caughey et al. 2010; Ferrara 2007; Savitz et al. 2008; Thorpe et al. 2005), maternal education (Bouthoorn et al. 2015), smoking (Wendland et al. 2008), alcohol use (Bouthoorn et al. 2015), infant sex, parity, and gestational age at glucose testing (Di Cianni et al. 2003). Our final model, based on statistical significance of variables in stepwise model building, adjusted for maternal age, maternal pre-pregnancy BMI, study center, race/ethnicity, parity, and gestational age at glucose testing. Ultimately, we included BMI instead of GWG, because adjustment for GWG may have led to bias because of its possible role as a mediator.

We first conducted univariate analyses of covariates and then assessed the relation between covariates and outcomes. For the primary inferential analyses, we used multivariable regression models to estimate associations between T1T3avg urinary MEP concentrations and outcomes of interest (logistic regression: odds ratio (OR) of GDM or IGT; linear regression: difference in blood glucose concentrations from the GLT). In secondary analyses, we estimated associations between: 1) T1T3avg urinary phthalate concentrations (for all other individual phthalates separately and ∑DEHP metabolites) and the outcomes; and 2) T1 urinary phthalate concentrations (for all individual phthalates separately and ∑DEHP metabolites) and the outcomes. To enhance comparability and interpretation, we present results in terms of an interquartile range (IQR) difference in phthalate metabolite concentrations.

Since most studies suggest that women with polycystic ovary syndrome (PCOS) are at increased risk for GDM (Ben- Haroush et al. 2003; Toulis et al. 2009), we conducted sensitivity analyses excluding individuals with PCOS (n=45). Additionally, because of the strong associations of race/ethnicity with phthalate exposure (Huang et al. 2014; Mitro et al. 2018) and glucose intolerance (Berkowitz et al. 1992; Caughey et al. 2010) as well as the differing associations between BMI and glucose tolerance by race (Hsu et al. 2015), we used interaction and stratification by group to assess potential racial/ethnic-specific effects. We also created phthalate exposure quartiles to evaluate possible non-linear associations.

To address potential concerns with reverse causality and/or changes in metabolism due to disease status, we conducted a sensitivity analysis of our primary aim after dropping individuals whose T3 urine samples were obtained after their prenatal visit with GLT screening (n=47). To evaluate the potential influence of between-lab differences in LODs, we included laboratory as a covariate in the models.

All analyses were performed using STATA (version 14.1, StataCorp, College Station, TX, USA) with complete case analysis.

3. RESULTS

Table 1 describes our study population for this analysis (n=705). Our cohort was predominantly non-Hispanic white (66.4%) and well educated (74.2% had college/ postgraduate education). Average maternal age was 31 years (standard deviation (SD) = 5.6 years), and average first trimester BMI was 26.1 kg/m^2 (SD = 6.2 kg/m^2).

We observed 60 cases of GDM and 90 cases of IGT in the cohort, for overall frequencies of 8.5% and 12.8% respectively. As noted above, these outcomes are mutually exclusive. The prevalence of these conditions varied by race/ethnicity (p = 0.04) (Table A1). GDM was observed in 6.6% of the non-Hispanic white population but in 16.4% of Hispanics, 15.6% of Asians, and 11.1% of Blacks. IGT was observed in 15.6% of the Asian population, compared to 13.2% in the non-Hispanic white population. The mean (SD) glucose concentration in the GLT test was 113.6 (27.7) mg/dL across the cohort; Asians had the highest mean glucose concentrations among race/ethnic subgroups (121.9 (24.8) mg/dL).

Summary statistics on phthalate metabolites and Spearman correlation coefficients are found in Table 2. Within-woman, between-trimester correlations were low, ranging from 0.11 for ∑DEHP to 0.46 for mBzP.

3.1 Primary & secondary analyses

Regression results are presented Figures 1–2 and Table 3, and IQRs are presented in Table A2. Because regression results for individual DEHP metabolites were similar, results are presented for ∑DEHP only. Our primary analysis indicated that T1T3avg MEP was associated with increased odds of GDM (OR (95% CI) per IQR increase: 1.61 (1.10, 2.36)). In secondary analyses, other T1T3avg phthalate metabolites were generally found to have slight positive associations; however, the confidence intervals were wide and overlapped the null, suggesting no overall effect. Most T1 metabolites were estimated to have negative associations; yet with the exception of MCPP ([OR (95% CI) per IQR increase]: (0.64 (0.43, 0.96)), these confidence intervals were also consistent with no effect. Analyses of both exposure metrics of phthalate metabolites with IGT generally suggested slight positive associations; most of these confidence intervals overlapped the null, indicating no effect, with the exception of T1T3avg MNBP ([OR (95% CI) per IQR increase]: 1.32 (1.00, 1.75)). Finally, our analyses suggested positive associations between phthalate metabolites and blood glucose difference for both exposure metrics. However, only the confidence intervals for MCOP excluded the null ((blood glucose difference (95%CI) per IQR increase) T1: 1.91 (0.25, 3.55), T1T3avg: 1.50 (0.02, 2.98)).

3.2 Sensitivity analyses

Sensitivity analyses excluding individuals with PCOS did not alter results. Race/ethnicity-stratified analyses adjusting for maternal age, maternal BMI, and parity suggested associations between several phthalates on blood glucose among Asians only (Table A3). Quartile analyses did not indicate any non-linear associations (results not shown). Sensitivity analyses excluding women whose T3 urine samples occurred after GLT (n=47) and adjusting for laboratory did not change our estimates (results not shown).

4. DISCUSSION

Our primary finding that T1T3avg MEP is significantly associated with increased odds of GDM (OR (95%CI): 1.61 (1.10, 2.36)) supports our *a priori* primary analytical hypothesis and previous studies suggesting associations with GDM risk factors and blood glucose. (James-Todd et al. 2018; James-Todd et al. 2016) In secondary analyses, most other phthalates were not found to be associated with study outcomes; however, we did detect a positive association between T1T3avg MNBP and IGT, and between both T1T3avg and T1 MCOP and blood glucose. By contrast, T1 MCPP was found to be inversely associated with GDM.

Previously, five studies had evaluated the association between phthalate exposure and outcomes related to gestational glucose intolerance. It is challenging to draw overall conclusions from this body of work, given their disparate results. Yet, of relevance, MEP has been positively associated with both IGT (James-Todd et al. 2016) and blood glucose (James-Todd et al. 2018), though two other studies observed no association (Fisher et al. 2018; Robledo et al. 2015). Other phthalate metabolites have been estimated to have both negative and positive associations with gestational glucose tolerance outcomes, though many of these estimates had wide confidence intervals overlapping the null (Fisher et al. 2018; James-Todd et al. 2018; James-Todd et al. 2016; Robledo et al. 2015; Shapiro et al. 2015). In the only previous study to assess GDM in relation to phthalates (Shapiro et al. 2015), wide confidence intervals for all metabolites precluded any meaningful conclusions; though some metabolites were associated with increased risk while others were associated with decreased risk (Shapiro et al. 2015). Shapiro et al. evaluated phthalates using only T1 urine samples, which may not capture the relevant exposure period given their short half-life (Fromme et al. 2007). Furthermore, they utilized different criteria for OGTT results, based on Canadian guidelines (Berger et al. 2002) that are less conservative than the classifications we used. These less stringent diagnostic criteria may partially account for their null findings.

The overall prevalence of GDM in our population was 8.5%, consistent with national estimates of 8–9% (DeSisto et al. 2014). The prevalence of GDM was highest in Asians and Hispanic subgroups (15.8% and 16.4%, respectively) (Table A1); national estimates and previous studies have also documented high burdens of metabolic conditions in these subgroups (Ferrara 2007; Thorpe et al. 2005). Concentrations of phthalate metabolites detected in our cohort of pregnant women (Table 2) were similar to those found in nationally representative data from the general population in the 2011–2012 National Health and Nutrition Examination Survey (NHANES) (Centers for Disease Control and Prevention 2018) and for the full TIDES cohort (Swan et al. 2015). We found that within woman, between trimester correlations of SG-adjusted phthalate metabolite concentrations were moderately low, ranging from 0.11 for ∑DEHP metabolites to 0.46 for MBzP (Table 2). Our findings are consistent with previous studies of pregnant populations that have documented low to moderate correlations between phthalates at different timepoints (Adibi et al. 2008; Ferguson et al. 2014a; Valvi et al. 2015), which helped to inform our decision to use T1T3avg phthalates as the primary exposure variable.

Phthalates may alter glucose metabolism through several mechanisms. They can selectively modulate PPARs, altering lipid processing and glucose homeostasis (Desvergne et al. 2009; Grun and Blumberg 2007; Liu and Sun 2016; Sarath Josh et al. 2014; Tordjman et al. 2002). Phthalates are also known endocrine disruptors, linked to changes in sex steroid hormones and related outcomes (Diamanti-Kandarakis et al. 2009), and several phthalates have been found to have estrogenic activity specifically (Harris et al. 1997; Jobling et al. 1995; Sathyanarayana et al. 2017). Substantial evidence indicates that alterations in estrogens are linked to insulin resistance, changes in adipocytes, and related metabolic disruptions in females (Chen et al. 2009; Ding et al. 2007; Liu and Sun 2016; Livingstone and Collison 2002; Louet et al. 2004; Pallottini et al. 2008). In the short term, phthalate-driven elevations in estrogen could lead to increased insulin signaling through an estrogen receptor alpha (ERalpha)-mediated pathway. However, over time, prolonged activation could result in excess insulin release, beta cell exhaustion, and peripheral insulin resistance (Aston-Mourney et al. 2008; Nadal et al. 2009). Some but not all experimental studies support a link between phthalates and abnormal glucose metabolism, including changes in insulin signaling molecules, glucose transporters, glucose uptake, and blood glucose concentrations after exposure (Rajesh et al. 2013; Rengarajan et al. 2007; Srinivasan et al. 2011; Viswanathan et al. 2017). MEP, the *a priori* focus of our study, may act by estrogenic and/or PPAR-related pathways (Guven et al. 2016).

Certain racial/ethnic groups, particularly Asians, have higher risk of GDM and other metabolic disorders (Ferrara 2007; Thorpe et al. 2005). Sensitivity analyses to evaluate our study question using race-stratification suggested elevated risk among Asians from numerous phthalate metabolites (Table A3). This exploratory finding is interesting given that, while Asians are at highest risk for GDM and other metabolic diseases, they have low rates of obesity, one of the strongest risk factors (Hedderson et al. 2012). Genetic factors may play a role in the observed susceptibility among Asians. The PPARgamma2 polymorphism Pro12Ala is associated with decreased risk of diabetes (Stumvoll and Haring 2002). Due to reduced binding of this variant to PPARgamma-responsive DNA elements, there is altered production and release of adipose factors, including reductions in free fatty acids, TNF-alpha, and resistin –all of which reduce insulin sensitivity –and increases in adiponectin – which improves insulin sensitivity (Stumvoll and Haring 2002). Given that PPARgamma is one possible mode of action of phthalates on insulin resistance, individuals with this variant would be less susceptible to phthalate-mediated insulin resistance. The prevalence of this polymorphism varies by race, with the highest frequencies among Caucasians (~12%) and the lowest among certain Asian groups [e.g. Japanese (~4%), Chinese (%1)] and African Americans (~3%)] (Mori et al. 2001; Stumvoll and Haring 2002; Vigouroux et al. 1998). The low frequency of this protective variant among Asians may confer greater vulnerability to the effects of exposure. Ethnic and cultural differences in diet, particularly with respect to high glycemic foods, also likely play a role (Hiza et al. 2013; Zhang and Ning 2011).

Our research has several limitations. Phthalate metabolites were only measured in two samples per woman, but phthalate concentrations during pregnancy can change considerably from day-to-day (Fisher et al. 2015). Furthermore, MCOP and MCNP were only available on a subset of the population, which reduced our sample size for these analyses. We were

unable to adjust for several confounders, including prior GDM in pregnancy, prior T2DM, or family history of T2DM (Kim et al. 2007); diet (Serrano et al. 2014; Zhang and Ning 2011); and/or other exogenous compounds with similar exposure sources also linked to diabetes and metabolic dysfunction, such as bisphenol-A (Song et al. 2015). Additionally, we were underpowered to thoroughly evaluate racial/ethnic subpopulations and did not have detailed information on the different sub-groups within this category, suggesting that a very cautious interpretation of our intriguing findings from sensitivity analyses is warranted. Finally given the uncertainty regarding the critical windows of exposure for GDM, we cannot be certain that exposure assessment preceded initiation of the disease process. Future research to elucidate disease progression can inform the design of epidemiological studies that can more accurately assess exposure during critical windows.

Despite these limitations, our study had important strengths. The TIDES cohort is derived from four centers across the country, providing geographic diversity not present in some prior studies. Furthermore, our study is unique in utilizing phthalate measures from two timepoints during pregnancy. The low within-woman correlation between T1 and T3 phthalates underscores the importance of utilizing multiple exposure measurements. Finally, we also had access to continuous measures of glucose intolerance. These data allowed us to investigate not only the clinical outcome of GDM but also subclinical measures of glucose intolerance linked to adverse pregnancy outcomes (The HAPO Study Cooperative Research Group 2008), but not as thoroughly investigated.

5. CONCLUSION

Overall, this study adds to growing literature on the association between phthalates and gestational glucose intolerance, and in particular provides additional data to support the link between MEP and GDM. There are several mechanisms by which phthalates may affect metabolic function and, given the significant maternal and fetal consequences of hyperglycemia during pregnancy, research should continue to address this subject – especially in susceptible populations.

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APPENDIX:

A1:: Race-specific and overall frequencies of glucose intolerance outcomes in study population1

Race/Ethnicity	n	GDM (n (%))	IGT (n (%))	GLT (mean (SD)(mg/dL))
Non-Hispanic White	468	31 (6.6)	62 (13.2)	112.9 (27.1)
Non-Hispanic Black	81	9 (11.1)	8 (9.9)	108.3 (31.0)
Non-Hispanic Asian	38	6 (15.8)	6 (15.8)	121.9 (24.8)
Hispanic	55	9 (16.4)	5 (9.1)	114.6 (29.9)
Other/Mixed	49	5 (10.2)	6 (12.2)	119.0 (25.7)
Missing	14	0 (0)	3 (21.4)	118.9 (25.0)
Total	705	60 (8.5)	90 (12.8)	113.6 (27.7)

[1]GDM = Gestational diabetes; IGT = impaired glucose tolerance; GLT = glucose load test; SD = standard deviation

A2:: Interquartile range (IQR) for ln-transformed phthalate metabolites

Phthalate	T1 IQR	T1 T3avg IQR
MIBP	1.1	0.9
MEP	1.8	1.8
MNBP	1.1	0.9
MBZP	1.4	1.3
MCNP	1.3	1.2
MCOP	1.7	1.6
MCPP	1.6	1.5
MEHP	1.1	0.8
MEHHP	1.0	0.9
MEOHP	1.0	0.8
MECPP	1.0	0.8
∑DEHP	0.9	0.9

A3:: Race-stratified adjusted mean difference in glucose concentration (mg/dL) in the glucose load test (GLT) associated with one IQR increase in T1T3avg phthalate1

Phthalate	White (n=413; MCOP/MCNP n=249)	Black (n=68; MCOP/MCNP n=38)	Asian (n=35; MCOP/MCNP n=21)	Hispanic (n=45; MCOP/MCNP n=33)
MIBP	−0.78 (−2.49, 0.93)	0.56 (−3.77, 7.03)	10.73* (5.29, 14.59)	0.41 (−5.42, 6.33)
MEP	0.38 (−.62, 1.38)	−0.14 (−2.70, 2.41)	4.80* (1.39, 8.21)	0.25 (−2.75, 3.26)
MNBP	0.14 (−1.29, 1.58)	0.46 (−3.81, 4.73)	4.60* (0.85, 8.36)	−0.10 (−5.10, 4.90)

Phthalate	White (n=413; MCOP/MCNP n=249)	Black (n=68; MCOP/MCNP n=38)	Asian (n=35; MCOP/MCNP n=21)	Hispanic (n=45; MCOP/MCNP n=33)
MBZP	−0.23 (−2.74, 2.28)	−1.79 (−5.37, 1.78)	10.65 (−0.46, 21.78)	0.34 (−7.53, 8.22)
MCNP	−2.66 (−7.33, 1.99)	.4.41 (−24.54, 15.72)	1.49 (−11.34, 14.33)	−5.85 (−17.92, 6.21)
MCOP	1.36 (−0.53, 3.24)	3.96 (−0.80, 8.72)	0.98 (−5.41, 7.36)	−2.36 (−7.72, 3.00)
MCPP	−0.27 (−4.11, 3.56)	0.17 (−8.34, 8.67)	11.53 (−9.40, 32.43)	0.18 (−9.70, 10.05)
MEHP	−0.25 (−4.07, 3.56)	0.35 (−8.45, 9.16)	7.74 (−6.24, 21.71)	2.69 (−11.02, 16.42)
MEHHP	−0.30 (−1.65, 1.04)	1.07 (−2.29, 4.43)	4.24* (0.81, 7.67)	−1.48 (−6.95, 3.98)
MEOHP	−0.29 (−1.82, 1.25)	0.32 (−3.75, 4.39)	5.26* (0.79, 9.74)	−0.96 (−6.86, 4.95)
MECPP	−0.29 (−1.48, 0.90)	0.73 (−2.48, 3.94)	3.74* (0.81, 6.67)	−1.51 (−6.87, 3.86)
∑DEHP	−0.004 (−0.69, 0.68)	0.14 (−2.03, 2.31)	2.59* (0.41, 4.76)	−0.41 (−2.77, 1.95)

[1]Model adjusted for maternal age, maternal BMI, and parity. Star denotes statistical significance at the 0.05 alpha level.

IQR = interquartile range.

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Highlights

- Growing evidence suggests an association between certain phthalates and diabetes, but few studies have focused on gestational diabetes or impaired glucose tolerance
- In agreement with prior studies, we observed an association between elevated mono-ethyl phthalate (MEP) and gestational diabetes
- Secondary and sensitivity analyses indicated that some other common phthalates were linked to glucose intolerance, with possible stronger associations in certain racial/ethnic groups

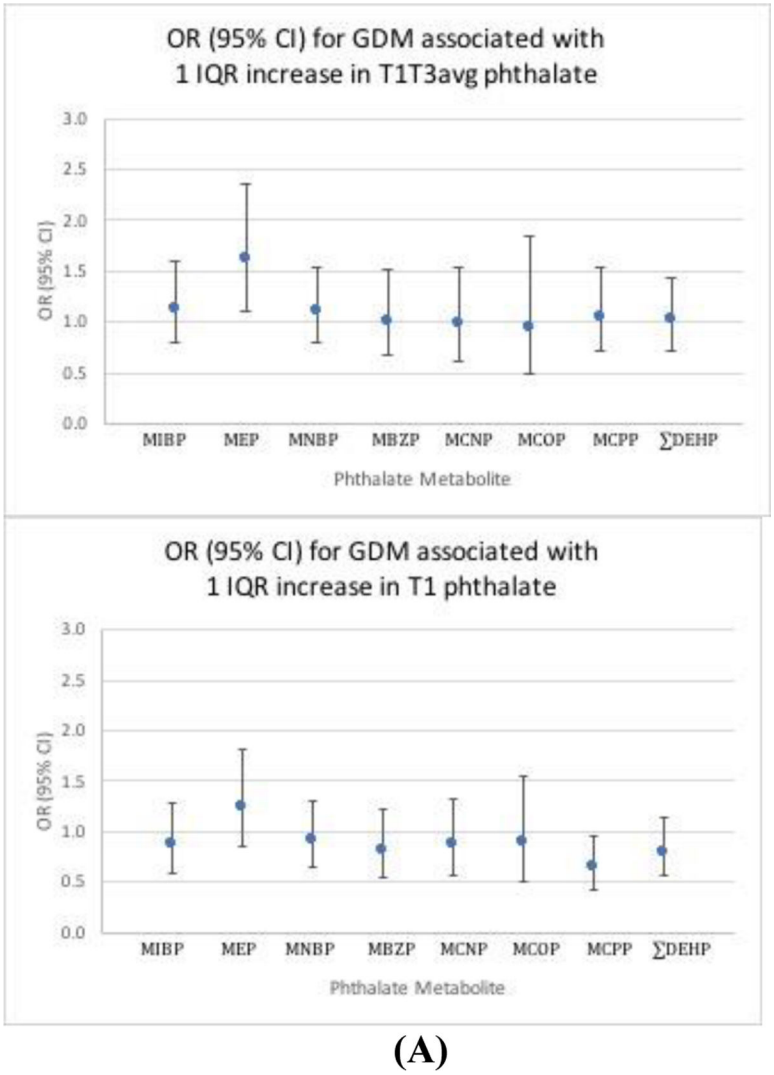
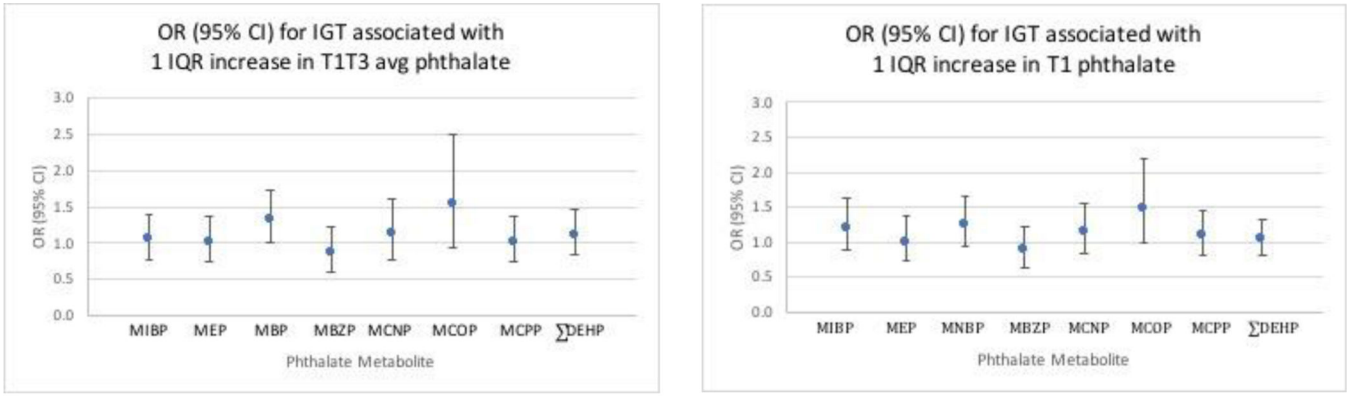


Figure 1: Phthalates in association with GDM.

Adjusted odds ratio (OR) and 95% confidence interval (95% CI) for the association between one interquartile range (IQR) increase in urinary phthalate metabolite and gestational diabetes mellitus (GDM).[1] A) T1T3avg phthalate metabolite; B) T1 phthalate metabolite

[1] Model adjusted for maternal age, maternal BMI, study center, race/ethnicity, parity, and gestational age at glucose testing.



(A) **(B)**

Figure 2: Phthalates in association with IGT.

Adjusted odds ratio (OR) and 95% confidence interval (95% CI) for the association between one interquartile range (IQR) increase in phthalate and IGT.[1] A) T1T3avg phthalate metabolite; B) T1 phthalate metabolite

1 Model adjusted for maternal age, maternal BMI, study center, race/ethnicity, parity, and gestational age at glucose testing

Table 1:

Demographic characteristics of mothers included in analyses[1]

Characteristic	Total (n=705) n (%)	GDM (n=60) n (%)	IGT (n=90) n (%)
Study Center			
University of California, San Francisco (UCSF)	165 (23.4)	20 (33.3)	21 (23.3)
University of Minnesota (UMN)	192 (27.2)	8 (13.3)	31 (34.4)
University of Rochester Medical Center (URMC)	201 (28.5)	15 (25)	25 (27.8)
University of Washington (UW)	131 (18.6)	17 (28.3)	11 (12.2)
Maternal Age (years)			
<=20	21 (2.9)	1 (1.7)	2 (2.2)
21–30	262 (37.2)	20 (33.3)	31 (34.4)
31–40	393 (55.7)	31 (51.7)	54 (60.0)
>40	29 (4.1)	8 (13.3)	3 (3.3)
Pre-pregnancy Body Mass Index (BMI) (kg/m^2)			
<=24.9	379 (53.8)	23 (38.3)	42 (46.7)
25–29.9	155 (22.0)	11 (18.3)	27 (30.0)
>=30	159 (22.6)	24 (40.0)	21 (23.3)
Race/Ethnicity Category			
Non-Hispanic White	468 (66.4)	31 (51.7)	62 (68.9)
Non-Hispanic Black	81 (11.5)	9 (15.0)	8 (8.9)
Non-Hispanic Asian	38 (5.4)	6 (10.0)	6 (6.7)
Hispanic	55 (7.8)	9 (15.0)	5 (5.6)
Other/Mixed	49 (6.9)	5 (8.3)	6 (6.7)
Highest Education Attended			
High School or less	97 (13.8)	8 (13.3)	11 (12.2)
Some College	85 (12.1)	7 (11.7)	13 (14.4)
College/post-graduate	523 (74.2)	45 (75.0)	66 (73.3)
Any Smoking During Pregnancy			
Yes	47 (6.7)	4 (6.7)	7 (7.8)
No	591 (83.4)	50 (83.3)	75 (83.3)
Any Alcohol During Pregnancy			
Yes	91 (12.9)	7 (11.7)	10 (11.1)
No	546 (77.4)	48 (80.0)	71 (78.9)
Infant Sex			
Boy	323 (45.8)	33 (55.0)	44 (48.9)
Girl	345 (48.9)	27 (45.0)	41 (45.6)
Previous Live Birth			
Yes	296 (42.0)	22 (36.7)	44 (48.9)
No	367 (52.0)	35 (58.3)	43 (47.8)

[1] Summaries provided for entire cohort (total) and also stratified by diagnosis (gestational diabetes (GDM) or impaired glucose tolerance (IGT))

Table 2:

Descriptive data for phthalate metabolites

Phthalate Metabolite	T1[1]			T3[2]			T1 T3 Spearman Correlation[7]
	N	%>LOD[3]	GM[4] (GSD)[5,6]	N	%>LOD	GM (GSD)	
Mono-isobutyl phthalate (MIBP)	668	99	5.2 (2.4)	679	95	7.2 (2.6)	0.40
Monoethy 1 phthalate (MEP)	668	100	37.6 (3.8)	679	98	42.1 (4.5)	0.40
Mono-n-butyl phthalate (MNBP)	668	95	8.3 (2.4)	679	98	9.7 (2.7)	0.27
Mono-benzyl phthalate (MBZP)	668	95	4.3 (2.9)	679	95	4.8 (3.2)	0.46
Mono-carboxy-iso-nonyl phthalate (MCNP)	406	96	2.7 (2.8)	679	98	2.8 (2.7)	0.15
Mono-carboxy-iso-octyl phthalate (MCOP)	406	100	19.3 (3.5)	679	100	16.0 (3.3)	0.27
Mono-(3-carboxypr opyl) phthalate (MCPP)	668	94	2.5 (3.6)	679	87	2.4 (3.7)	0.20
Mono-(2-ethylhexyl) phthalate (MEHP)	668	70	2.5 (2.5)	679	76	2.1 (2.4)	0.14
Mono-(2-ethyl-5-hydroxyh exyl) phthalate (MEHHP)	668	100	7.9 (2.6)	679	99	6.7 (2.5)	0.12
Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)	668	99	5.5 (2.5)	679	100	5.3 (2.5)	0.13
Mono-(2-ethyl-5-carboxype ntyl) phthalate (MECPP)	668	100	10.6 (2.4)	679	100	12.2 (2.3)	0.20
∑Di-2-ethylhexyl phthalate (DEHP)	668	N/A	93.4 (2.3)	679	N/A	47.7 (2.4)	0.11

[1] T1 = First trimester

[2] T3 = Third trimester

[3] LOD = Limit of detection

[4] GM = Geometric mean

[5] GSD = Geometric standard deviation

[6] Units are μg/Lfor all individual phthalates; nmol/mL for ∑DEHP

[7] Within-woman, between-trimester correlations on SG-adjusted phthalates

Table 3:

Adjusted mean difference in glucose concentration (mg/dL) and 95% CI measured during glucose load test associated with one IQR increase in urinary phthalate metabolites.[1]

Phthalate	T1 Estimates	T1 T3avg Estimates
MIBP	−0.03 (−1.84, 1.79)	0.19 (−1.26, 1.63)
MEP	0.11 (−1.05, 1.28)	0.60 (−0.25, 1.44)
MNBP	0.60 (−1.17, 2.37)	0.88 (−0.62, 2.36)
MBZP	−0.19 (−1.74, 1.35)	0.01 (−1.20, 1.21)
MCNP	−0.52 (−2.47, 1.44)	−0.70 (−2.30, 0.91)
MCOP	1.91 (0.25, 3.55)	1.50 (0.02, 2.98)
MCPP	−0.13 (−1.31, 1.05)	0.09 (−0.85, 1.01)
∑DEHP	0.29 (−1.51, 2.08)	0.56 (−0.91, 2.02)

[1]Model adjusted for maternal age, maternal BMI, study center, race/ethnicity, parity, and gestational age at glucose testing. IQR = interquartile range.