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

Rachel M. Shaffer

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Committee:
Sheela Sathyanarayana
Kelly Ferguson
Lianne Sheppard

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Abstract

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Rachel M. Shaffer

Chair of the Supervisory Committee:
Sheela Sathyanarayana
Department of Environmental and Occupational Health Sciences / Seattle Children’s Research Institute

Recent studies have linked phthalates with type 2 diabetes, but limited research exists on the potential association between phthalates and gestational diabetes (GDM), impaired glucose tolerance (IGT), and continuous glucose tolerance measures during pregnancy. We evaluated 11 urinary phthalate metabolites from the first (T1) and third (T3) trimesters of pregnancy and medical record abstraction data in 705 women from The Infant Development and Environment Study. We used logistic regression to examine the associations between log-transformed, specific gravity adjusted T1-only and average phthalate metabolite concentrations across pregnancy (average of T1 and T3) with GDM and IGT, and linear regression to examine the associations of T1 and pregnancy average phthalates with continuous glucose concentration. In sensitivity analyses, we examined interactions between exposure and race. We adjusted for maternal age, maternal body mass index, study center, race/ethnicity, and parity. We observed 60 cases of GDM, 90 cases of IGT, and an average (SD) GLT blood glucose of 113.6 (27.7) mg/dL. Average log MEP across pregnancy was associated with increased odds of GDM (OR: 1.88; 95% CI: 1.14, 3.10). Log MCOP was associated with increased blood glucose concentration (mg/dL) (T1: 6.19, 95% CI: 0.75, 11.63), T1T3: 6.98, 95% CI: 0.13, 13.82). There were suggestive associations of race-specific effects in Asians. Given the prevalence of phthalate exposures and the growing evidence of their potential metabolic effects, future studies should examine this question in larger cohorts of pregnant women, particularly in those who may be at higher risk for GDM and IGT.
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BACKGROUND

**Gestational Diabetes and Glucose Intolerance**

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that first develops during pregnancy and is not undiagnosed overt diabetes.\(^1\) The incidence of GDM has increased dramatically in the past twenty years. GDM is now detected in 8-9% percent of pregnancies in the United States, though estimates vary between certain ethnic groups and based on diagnostic criteria used.\(^2\)\(^-\)\(^7\) Known risk factors for the condition include GDM in a prior pregnancy,\(^8\)\(^-\)\(^10\) previous large for gestational age (LGA) infant,\(^11\) family history of GDM or type 2 diabetes mellitus (T2DM),\(^12\) pre-pregnancy obesity,\(^13\)\(^,\)\(^14\) nonwhite race/ethnicity (especially Asians and Hispanics),\(^7\)\(^,\)\(^12\) high gestational weight gain in early pregnancy,\(^15\) and increased maternal age.\(^4\)\(^,\)\(^16\)\(^,\)\(^17\)

GDM is associated with significant health consequences for both the mother and child. Women diagnosed with GDM are at elevated risk for preeclampsia during their pregnancy as well as cardiovascular disease and metabolic disease later in life; for example, they have a seven-fold increased risk of developing T2DM within 10 years of pregnancy.\(^4\)\(^,\)\(^18\)\(^,\)\(^19\) Potential consequences for the developing child include hyperglycemia, developmental delays, and birth complications due to LGA status.\(^4\) Additionally, children born to mothers with GDM exhibit a two-fold increased risk of childhood obesity and metabolic syndrome.\(^20\) The economic burden of these GDM-related complications is substantial. GDM was estimated to increase medical costs in the U.S. by $636 million in 2007,\(^21\) and costs are likely higher at present as prevalence has continued to rise.

Normal pregnancy is characterized by progressive insulin resistance due primarily to insulin desensitizing hormonal signals from the placenta and in small part to increased maternal adiposity.\(^22\)\(^-\)\(^24\) Maternal insulin resistance begins to rise during mid-pregnancy until the third trimester, when levels are similar to those observed in T2DM;\(^25\) this allows for decreased glucose uptake by the mother and increased uptake by the fetus.\(^26\)\(^-\)\(^28\) This insulin resistant state, which is primarily mediated by changes in insulin receptor activity and glucose transport,\(^23\) is essential for
fetal nutrition and growth. To compensate in the maternal compartment, pancreatic beta cells augment insulin secretion; there may also be increases in cell size/mass. Both of these adaptations are stimulated by pregnancy hormones, such as prolactin, estrogen, and human placental growth hormone.\textsuperscript{29} Because of these changes, there are only small deviations from normal blood glucose concentrations during a healthy pregnancy.\textsuperscript{27,30} In cases of GDM, however, there is insufficient insulin released from the beta cells and decreased skeletal muscle glucose uptake, resulting in maternal hyperglycemia.

The etiology of beta cell dysfunction and related pathological changes in GDM is not well understood. Possible contributing factors and mediators include: alterations in inflammatory signaling, particularly the tumor necrosis factor (TNF) system, which can affect the insulin receptor and glucose transporters;\textsuperscript{31-33} changes in the expression of peroxisome proliferator activated receptors (PPARs);\textsuperscript{34} and elevated oxidative stress.\textsuperscript{26,35-37} Some women (<10% GDM cases) have circulating antibodies to islet cells or key cellular enzymes, similar to those in type 1 diabetes (T1DM).\textsuperscript{38,39} An alternative theory is that GDM is actually chronic beta cell dysfunction that is only detected during pregnancy, which may be the first time that an individual’s glucose tolerance is measured.\textsuperscript{38}

The placenta plays a central role in both healthy and GDM pregnancies. As noted above, hormones released from the placenta, such as human placental growth hormone and human placental lactogen, contribute to the normal (physiological) development of insulin resistance that occurs during pregnancy.\textsuperscript{23} The placenta also synthesizes leptin, a hormone that controls energy balance.\textsuperscript{40} Its importance in the metabolic environment is additionally indicated by the high expression of insulin receptors, which demonstrate placental responsiveness to maternal and fetal insulin signaling during pregnancy. The placenta also produces numerous cytokines that exert immunomodulatory effects, such as TNF-alpha and IL-6.\textsuperscript{41,42} Its role in cytokine production may represent a key linkage between the placenta and GDM development, given that oxidative stress and inflammation are implicated in this condition (further detailed below). In recent years, studies
have documented differences in placenta tissue between GDM and healthy pregnancies, including changes in insulin receptors and glucose transporters, PPAR expression, and markers of oxidative stress in GDM, underscoring the importance of considering the role of this tissue in disease pathophysiology.

In 2014, the U.S. Preventive Services Task Force recommended universal screening for pregnant women not previously diagnosed with type 1 or type 2 diabetes. Screening and diagnosis for GDM occurs during weeks 24-28 of pregnancy. There are several testing approaches and thresholds used; evidence is not sufficient to determine one optimal strategy at this time. In the United States, the most common is the two-step approach. First, in non-fasting conditions, women receive a 50-gram oral glucose load in the (glucose load test (GLT) (also known as the glucose challenge test (GCT)); plasma glucose concentration is measured after one hour. Individuals who screen positive on this test (thresholds differ by clinic: ≥130 mg/dL, ≥135 mg/dL, ≥140 mg/dL) move to the second test: a 100-gram, three-hour oral glucose tolerance test (OGTT), with glucose concentrations measured at baseline (fasting) and at each of the three-hour timepoints. Women with two or more positive test results on the OGTT are diagnosed with GDM. As for the GLT, different thresholds for the OGTT have been proposed, and there is no clear evidence-based preference at this time. The National Diabetes Data Group (NDDG) criteria stipulate using fasting, 1-hour, 2-hour, and 3-hour plasma glucose levels of 105mg/dL, 190mg/dL, 165mg/dL, and 145mg/dL, respectively, for GDM diagnosis. The Carpenter-Coustan (CC) criteria are more inclusive with lower threshold values of 95mg/dL, 180mg/dL, 155mg/dL, and 140mg/dL.

Traditionally, GDM has been a clear marker for future disease and the focus of clinical and epidemiological work. However, recent studies suggest that elevated maternal glucose even without overt GDM diagnosis is also associated with adverse fetal and maternal health outcomes. Thus, efforts have begun to shift to better understand the physiology and
consequences of maternal hyperglycemia independent of standard clinical classifications for GDM.\textsuperscript{52}

\textbf{Phthalates}

Phthalates are a class of plasticizer chemicals utilized in numerous consumer applications. Low molecular weight (LMW) phthalates (<8 carbons in alkyl chain) are commonly added to shampoos, cosmetics, lotions, and other personal care products to preserve scent and color,\textsuperscript{53} while high molecular weight (HMW) phthalates ($\geq$ 8 carbon in alkyl chain) are used to impart flexibility in plastic products such as flooring, food wrap, and plastic tubing used in food manufacturing or medical devices.\textsuperscript{54} Because they are not bound to products, they can easily migrate from the source into air, dust, and food among other media. Exposure occurs through ingestion, inhalation, and/or dermal contact.\textsuperscript{54-57}

After exposure, metabolism of phthalates in the body occurs rapidly; the half-life of these chemicals is short (hours to days).\textsuperscript{58} Metabolism is a two-step process: hydrolysis (phase 1) followed by conjugation (phase II) (see Figure 1). During hydrolysis, catalyzed by lipase and esterase enzymes, the phthalate diester is converted to the monoester form.\textsuperscript{59} Low molecular weight phthalates are then excreted in their monoester form through urine. Higher molecular weight phthalates proceed through additional biotransformation processes, such as oxidation or hydroxylation, followed by phase II glucuronide conjugation and excretion in the urine or feces.\textsuperscript{60,61} In general, the phthalate metabolite rather than the parent is considered to be the biologically active compound.\textsuperscript{60,62}

![Figure 1: Overview of phthalate metabolism in the body\textsuperscript{63}](image-url)
Because excretion occurs primarily through urine, assessment of urinary phthalate metabolites is the most common and reliable method for quantification of short term exposure.\textsuperscript{64,65} However, care must be taken when interpreting the results of urinary exposure assessments for several reasons. First, one parent compound may be transformed into multiple metabolites;\textsuperscript{60} without accounting for all of these metabolites, accurate exposure estimates to the parent compound will not be obtained. Second, oxidative metabolites and hydrolytic metabolites have differential water solubility; the former are more water soluble and therefore detected at higher relative concentrations in the urine.\textsuperscript{66,67} And third, different metabolites may have different half-lives in the body.\textsuperscript{68} For example, di-2-ethylhexyl phthalate (DEHP) is metabolized to both hydrolytic products, such as mono-(2-ethylhexyl) phthalate (MEHP), and oxidative products, such as mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP). MEHP, MEHHP, and MEOHP have shorter half-lives than MECPP.\textsuperscript{68,69}

 Biological monitoring, including through the National Health and Nutrition Survey (NHANES), indicates that phthalates are ubiquitous across the population.\textsuperscript{70-72} Certain phthalate metabolites, such as monoethyl phthalate (MEP) and mono-benzyl phthalate (MBzP), are detected at higher concentrations in women,\textsuperscript{70,73} likely because of their prevalence in personal care products.\textsuperscript{74-76} Numerous studies have also documented the presence of these metabolites in pregnant women, specifically.\textsuperscript{72,77-81} Across these studies, MEP is most commonly detected at the highest concentrations. For example, in a representative sample of pregnant women in the United States during 2003-2004, the geometric mean (GM) (geometric standard deviation (GSD)) of MEP was found to be 226.53 (3.33) \text{ug/L}; the next highest phthalate metabolite detected was mono-n-butyl phthalate (MBP) (GM: 18.82 \text{ug/L}, GSD: 2.08).\textsuperscript{72} MEP was also found at the highest concentration among cohorts of pregnant women in the Netherlands during 2002-2006 (GM: 112.0 \text{ug/L}, GSD: 5.6),\textsuperscript{78} Canada in 2008-2011 (GM: 37.73 \text{ug/L}, GSD: 3.64),\textsuperscript{81} and Spain
in 2004-2008 (GM: 324 µg/L, Interquartile range: 519).\textsuperscript{77} Sources of diethyl phthalate (DEP), the parent compound of MEP, include personal care products and pharmaceutical coatings.\textsuperscript{82} Despite the short half-life of the compounds and their documented temporal variability during pregnancy and non-pregnancy,\textsuperscript{83-85} consistent personal behavioral patterns in relation to sources of phthalates may actually allow for fairly stable body burdens over time – and therefore more confidence in the meaning of these spot biomonitoring estimates.

Phthalates are known endocrine disruptors and have been linked to several hormone-related outcomes, including male reproductive and developmental abnormalities.\textsuperscript{82,86} They have been found to exhibit diverse hormonal activity, including anti-androgenic\textsuperscript{87}, estrogenic,\textsuperscript{88-91} and anti-estrogenic\textsuperscript{92-94} behavior. Studies have also linked this class of compounds to metabolic dysfunction, such as obesity and diabetes\textsuperscript{95-98} - the subject of this research project.

\textit{Relationship between Phthalates and Glucose Metabolism: Prior Studies}

Studies of non-pregnant populations suggest a link between phthalates and Type 2 diabetes mellitus (T2DM). Among adult males (>18 years) assessed in 1999-2002 NHANES, several urinary phthalate metabolites were found to be associated with positive percent change in waist circumference (β for increase in 1 µ log phthalate/g creatinine (SE)/(N): MBzP = 1.09 (0.36) (n=1292); MEP = 0.66 (0.31) (n=1292); MEHHP = 1.65 (0.50) (n=696); MEOHP = 1.79 (0.55) (n=696), and positive percent change in HOMA (homeostatic model assessment), a measure of insulin resistance (n=622; MBzP = 0.061 (0.022); MEP = 0.044 (0.021).\textsuperscript{97} Among seniors (> 70 years) in Sweden (n=1016), monomethyl phthalate (MMP), monoisobutyl phthalate (MiBP), and MEP in serum were cross-sectionally associated with diabetes (defined based on diabetes medication or fasting plasma glucose levels) (OR (95%CI) comparing extreme quintiles: MMP = 2.54 (1.25, 5.13); MiBP = 2.00 (1.03-3.88); MEP = 2.27 (1.08-4.81)).\textsuperscript{99} In a nested case control study (n=971 pairs) using the Nurses Health Study (NHS) and the NHSII, total urinary phthalates, total DEHP metabolites, and total butyl phthalate metabolites were associated with self-reported
T2DM in NHSII but not the NHS (OR (95%CI) comparing extreme quartiles: total phthalates = 2.14 (1.19, 3.85); DEHP metabolites = 1.91 (1.04, 3.49); butyl phthalate metabolites = 3.16 (1.68, 5.95)). A cross-sectional study among women in Mexico (n=221) found suggestive associations between several urinary phthalate metabolites and self-reported diabetes: (adjusted OR (95%CI) MEP = 1.02 (0.74-1.39), MBP = 1.10 (0.75-1.61), MiBP = 1.01 (0.65-1.55), MBzP = 0.74 (0.55-1.00), MEHP = 1.01 (0.68-1.49), MEHHP = 1.40 (0.84-2.33), MECPP = 1.54 (0.92-2.55), sumDEHP = 1.64 (0.98-2.73). Finally, in a study of women (n=2,350) who participated in 2001-2008 NHANES, increased quartiles of MBzP, mono-(3-carboxypropyl) phthalate (MCPP), MBP, and the sum of three DEHP urinary metabolites were found to be associated with self-reported diabetes; non-monotonic dose-response associations were observed for the latter two (OR (95%CI) MBzP Q3 = 1.80 (1.16, 2.81); Q4 = 1.96 (1.11, 3.47); MCPP Q3 = 1.55 (0.98, 2.44); Q4 = 1.68 (1.03, 2.75); MBP Q3 = 1.71 (1.04, 2.81); Q4 = 1.06 (0.61, 1.85); sumDEHP Q3 = 1.73 (1.03, 2.91); Q4 = 1.53 (0.82, 2.87). While it is difficult to draw conclusions based on these limited data – especially from cross sectional studies, where evaluation of temporality and the direction of causality is challenging – there seems to be some consistency in the link between DEHP metabolites, and to a lesser extent MEP and MBzP, and metabolic changes in the general population.

Some in vivo and in vitro experimental studies also support a link between phthalates and abnormal glucose metabolism. DEHP is the most well studied. In rats, oral exposure to DEHP on alternating days for 14 days resulted in decreased serum insulin and liver glycogen as well as increased blood glucose. Two additional studies, also examining rats, found that oral exposure to DEHP for 30 days caused decreased expression of insulin signaling molecules and glucose transporters, reduced glucose uptake in adipose and skeletal muscle tissue, and increased blood glucose concentration. However, other experimental studies do not support these conclusions, finding instead no adverse effects of DEHP on glucose tolerance or only very transient changes with no long term implications. In vitro evidence indicates that exposure to
DEHP leads to decreased insulin receptor concentration and glucose oxidation in human liver cells\textsuperscript{107} and rat skeletal muscle cells.\textsuperscript{108}

Despite the evidence linking phthalates and abnormal glucose metabolism, there has been only limited research on the relationship between phthalates and gestational glucose tolerance. In a cohort study based in Boston (n=350) examining the relation between urinary phthalates and gestational diabetes risk factors, increased pregnancy average MEP concentration (µg/L) was associated with increased odds of excessive gestational weight gain (OR: 2.17, 95%CI: 0.98, 4.79) and increased second trimester MEP (µg/L) was associated with increased odds of impaired glucose tolerance (OR: 7.18, 95%CI:1.97, 26.15), while sum DEHP metabolite concentration (µmol/L) was inversely associated with impaired glucose tolerance (OR: 0.25, 95%CI: 0.08, 0.85).\textsuperscript{109} A cohort study based in Canada (total n=1,274; GDM n = 48) found no evidence of an increased risk of GDM diagnosis associated with elevated first trimester urinary phthalate metabolite concentrations (by quartile),\textsuperscript{110} while a third very small study (n=110) based in Oklahoma found an inverse relation between first trimester concentrations of two urinary phthalate metabolites and increased blood glucose concentration (mg/dL) (β(95%CI) comparing highest to lowest tertiles: MiBP =-18.3 (-35.4, -1.2); MBzP = -17.3(-34.1, -0.4).\textsuperscript{111} A recent nested case-control study (total n=232; GDM n =47) in England found a positive association between increased first trimester serum concentrations (µg/l) of two log-transformed phthalate metabolites and third trimester plasma glucose concentration (mmol/L) in women without GDM (β [p-value] MEHP: 0.27 [p=0.0002]; (mono(carboxyisooctyl) phthalate) MCIOP: 0.18 [p=0.01]).\textsuperscript{112} It should be noted that serum assessment, utilized in the final study noted above, is not the optimal matrix with which to assess phthalate exposure due to phthalate pharmacokinetics and analytical capability.\textsuperscript{65}
**Biological Mechanisms**

Glucose homeostasis depends on coordinated regulation from several tissues and organs in the body, including the liver, pancreas, skeletal muscle, adipose tissue, and brain.\textsuperscript{113,114} Pancreatic endocrine cells serve a central function: beta cells secrete insulin to promote glucose uptake and decrease blood glucose concentration, while alpha cells secrete glucagon to stimulate the liver to release glucose back into the bloodstream when levels drop too low.\textsuperscript{114} Among the many effects of insulin is activation of insulin receptors and glucose transporters, which mediate uptake of glucose into peripheral tissues. Current theories suggest that GDM is due primarily to inadequate insulin secretion by beta cells, resulting in maternal hyperglycemia. Decreased insulin sensitivity beyond normal physiological changes that occur pregnancy, as well as altered glucose transport and signaling, may also play a role in some or all cases.\textsuperscript{115}

There are several plausible biological mechanisms through which phthalates may affect glucose homeostasis in pregnancy:

- **Peroxisome Proliferator-Activated Receptors**

The peroxisome proliferator-activated receptors (PPARs) alpha, beta/delta, and gamma are nuclear receptors that are central to lipid and carbohydrate metabolism.\textsuperscript{116} PPARalpha is expressed in a wide range of tissues, including the liver, skeletal muscle, and adipose, and is involved in fatty acid oxidation and energy homeostasis.\textsuperscript{117} PPARbeta/delta is expressed in the liver and skeletal muscle, among many other tissues, and plays a role in lipid metabolism.\textsuperscript{118} PPARgamma is predominately expressed in adipose tissue and modulates adipocyte differentiation, insulin sensitivity, and inflammatory responses.\textsuperscript{119}

Phthalates can selectively modulate PPAR alpha, beta/delta, and gamma,\textsuperscript{120-126} activating only a subset of downstream genes. Changes in normal PPAR signaling due to phthalate binding could have numerous downstream metabolic effects, including on insulin release and adipocyte differentiation.\textsuperscript{116,122,124,127} For example, PPAR modulation is known to affect insulin secretion.\textsuperscript{116}
In fact, thiazolidinediones are common oral anti-diabetic drugs that increase insulin levels in the body through PPARgamma activation.\textsuperscript{128} However, PPAR binding by phthalates could selectively activate a different subset of downstream pathways, resulting in decreased insulin release.

Alternatively, PPAR activation by phthalates could trigger elevated insulin release in the short term but beta cell exhaustion and/or desensitization, resulting in decreased insulin release, in the long term.

Adipose tissue also plays a key role in glucose homeostasis through the release of endocrine and non-endocrine bioactive signaling molecules, such as leptin and tumor necrosis factor-α (TNF-α).\textsuperscript{129} A full review of the complex interplay between these factors is beyond the scope of this thesis, but their overall effects in relation to inflammation and metabolic dysregulation are briefly summarized in Figure 2. Increased adipocyte differentiation stimulated by phthalate-related PPARgamma activation could lead to elevated secretion of the pro-inflammatory cytokine TNF-α, which is linked to insulin resistance and changes in insulin signaling\textsuperscript{31,130-132} (further discussed below). Recent \textit{in vitro} evidence corroborates this idea, demonstrating that MEHP can trigger a pro-inflammatory state in adipocytes via changes in PPARgamma signaling.\textsuperscript{133}

![Figure 2: Overview of mechanisms linking adipose tissue to inflammation and insulin resistance. (FFA = free fatty acids).](image-url)
• Estrogen

Phthalates may also promote development of adverse metabolic outcomes through modulation of sex steroid hormones.\textsuperscript{122,123,135} Multiple studies document the estrogenic activity of phthalates,\textsuperscript{88-91,136} though there is also evidence to suggest anti-estrogenic activity of these chemicals.\textsuperscript{92-94,136} Estrogen plays a central role in metabolism, including through interaction with PPAR pathways\textsuperscript{137,138} and direct signaling via estrogen receptors in pancreatic beta cells.\textsuperscript{139,140} Evidence suggests that normal circulating levels in the body exert a protective effect against glucose dysregulation.\textsuperscript{123,141,142} For example, pre-menopausal women with regular estrogen cycles are protected against insulin resistance compared to men.\textsuperscript{142} In randomized controlled trials (RCTs), hormone therapy (unopposed estrogen or combined) has been demonstrated to improve insulin sensitivity, lower blood glucose, and reduce the risk of incident diabetes in post-menopausal women.\textsuperscript{143-146} Animal studies indicate that elimination of estrogen receptor (ER)-alpha leads to insulin resistance and glucose intolerance in rodents of both sexes.\textsuperscript{147}

Yet, the effects of estrogen are not entirely positive or straightforward. ER-beta knock-out mice exhibit improved glucose metabolism,\textsuperscript{148} indicating that ERalpha and ERbeta might have opposing effects. Animals exposed to high levels of estrogen and other ovarian hormones have been shown to exhibit decreased glucose transporter and insulin receptor expression.\textsuperscript{149-151} Some human studies also indicate that oral contraceptive use is associated with reduced insulin response and/or insulin resistance.\textsuperscript{152,153}

In summary, estrogen is inextricably linked with glucose metabolism in women, but studies report conflicting results about the direction of effects. One potential unifying theory relevant to the estrogenic activity of certain phthalates is while that physiological concentrations of estrogen appear to be protective, concentrations outside the range of normal may contribute to diabetes (see Figure 2).\textsuperscript{154} For example, estrogen-stimulated increases in secretion of insulin could lead to hyperinsulinemia, contributing to insulin resistance, or beta cell overstimulation followed by exhaustion, resulting in decreased insulin secretion.\textsuperscript{155,156}
- **Oxidative Stress & Inflammation**

*In vivo* and *in vitro* experimental studies demonstrate that phthalates can trigger oxidative stress and inflammation.\(^\text{133,157-159}\) Perhaps most well studied is the link between DEHP and elevated production of the pro-inflammatory cytokine TNF-alpha.\(^\text{157}\) Human observational studies, including those focusing on pregnant women, also indicate that phthalate exposure is associated with biomarkers of these processes in the body.\(^\text{160-162}\) Phthalate-related increases in inflammatory markers may be mediated through PPAR activation and increased adipocyte differentiation,\(^\text{133}\) though other mechanisms are also possible.

Inflammation and oxidative stress have been linked to metabolic dysfunction, including gestational diabetes.\(^\text{31,163-165}\) TNF-alpha, among other inflammatory signaling molecules, is associated with insulin resistance in pregnant and non-pregnant populations.\(^\text{130-132,166}\) TNF-alpha is hypothesized to modify cellular insulin receptors, altering their ability to induce glucose uptake from the bloodstream.\(^\text{167}\) Correspondingly, an ancillary effect of anti-TNF-alpha treatments for inflammatory diseases is improvement in insulin sensitivity.\(^\text{168,169}\) Oxidative stress and pro-inflammatory cytokines can also promote beta cell death through mitochondrial stress or other mechanisms,\(^\text{170}\) which could lead to decreased insulin secretion as occurs in GDM. Women with GDM have elevated levels of 8-isoprostane, a marker of oxidative stress, in the placenta compared to women with healthy pregnancies.\(^\text{36}\)
Further evidence of the link between these pathophysiological processes and abnormal glucose intolerance comes from experimental and intervention studies. In vivo studies indicate that disruptions to glucose homeostasis triggered by phthalate exposure can be prevented through administration of antioxidant vitamins, which suggests an oxidative stress-mediated pathway.\textsuperscript{103,104} In a recent RCT based in Spain (n=1000), adherence to a Mediterranean diet supplemented with nuts and olive oil, which may improve inflammatory profiles and antioxidant capacity, was associated with decreased incidence of GDM.\textsuperscript{171}

\textit{Study Overview}

To further address whether phthalate exposure during pregnancy is related to gestational glucose tolerance, we utilized data from The Infant Development and Environment Study (TIDES) to investigate the association between urinary phthalate concentrations and GDM or subclinical continuous measures of glucose intolerance. Because of prior related work and plausible biological mechanisms, we hypothesized that higher concentrations of phthalates during pregnancy would be associated with glucose intolerance. As further detailed below, our primary exposure of interest was pregnancy average MEP, and our primary outcome of interest was GDM. Other exposures and outcomes were evaluated as secondary analyses. Compared to other cohorts previously used to assess this question, TIDES offers advantages in that it is a large, diverse, population-based cohort comprised of individuals from four distinct geographic areas and provides measurements of phthalates at two periods during pregnancy as well as continuous glucose measures directly from the medical record. Given that phthalate exposures are ubiquitous across the population\textsuperscript{71} and certain metabolites are detected in higher concentrations in women,\textsuperscript{70,73} a possible link between these chemicals and GDM would have important public health implications that may help to guide future policy and regulations – as well as clinical guidance to women during pregnancy.
METHODS

Study design

Participants for TIDES were recruited from 2010-2102 during the first trimester of pregnancy at four clinical centers (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 for the study included: <13 weeks pregnant, singleton pregnancy, English speaking, at least 18 years of age, no severe threat to pregnancy, and intention to deliver at one of the study hospitals. After eligibility was confirmed, all participants signed a consent form for themselves and their infants. Participants completed questionnaires and provided urine samples during each trimester of pregnancy. Data from birth records and medical records were abstracted under the guidance of Dr. Kelly K. Ferguson (National Institute of Environmental Health Sciences). Two TIDES staff members worked on this process at each study site, with one person abstracting all data and the other abstracting one in ten records.

Women were included in this analysis if they had first trimester questionnaire results, first trimester phthalate levels, and glucose load test (GLT) data (N=705). Given that administration of a GLT is recommended to be administered to women without prior diabetes, our analysis can be taken as restricted only to women without medically-diagnosed pre-pregnancy diabetes.

Exposure Assessment

First trimester (T1) and third trimester (T3) urine was 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. Urine samples from mothers of girls for T1 and a subset of mothers for T3 were analyzed for phthalate metabolites at the Environmental Health Laboratory at the University of Washington (UW) with a modified
version of CDC method 6306.03. Briefly, the glucuronidated phthalate monoesters were subjected to enzymatic deconjugation, followed by online-solid phase extraction (SPE) coupled with reversed high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS). Samples from mothers of boys in T1 and a subset of T3 mothers were analyzed by the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention (CDC) with a modified method described by Silva et al, 2007. This process involved enzymatic deconjugation of phthalate metabolites from glucuronidated form, automated on-line solid phase extraction, separation with high performance liquid chromatography, and detection by isotope-dilution tandem mass spectrometry. Process and instrument blanks were included for quality assurance. The limit of detection (LOD) was between 0.2 and 2.0 ng/mL for UW and 0.2 to 0.6 ng/mL for CDC.

The phthalate metabolites of interest for this study are listed in Table 1. Eleven individual phthalates and one summary measure of di-2-ethylhexyl phthalate (DEHP) metabolites were included in the analyses. It is standard in current epidemiological analyses to include this aggregate measure of DEHP metabolites. T1 MCOP and MCNP were only assessed by CDC and therefore available for mothers of male infants only. T3 MCOP and MCNP were assessed by CDC and UW and therefore available for mothers of both male and female infants. All urinary phthalates were adjusted for dilution using specific gravity (SG) measurements with the following formula: $P_c = P \times (SG_{\text{median}}^{-1}/SG^{-1})$ ($P_c = \text{SG-adjusted concentration}; P = \text{measured urinary concentration}; \text{SG} = \text{specific gravity for the individual sample}; \text{SG}_{\text{median}} = \text{median SG over all samples}$). The metabolites were also logarithmically transformed to display normal distributions. To calculate the molar sum of diethylhexyl phthalate (DEHP) metabolites, we divided each DEHP metabolite by its molecular weight and summed these totals: $\Sigma$ DEHP metabolites = ((mono-2-ethylhexyl phthalate (MEHP)/278) + (mono-2-ethyl-5-hydroxy-hexyl phthalate (MEHHP)/294) + (mono-2-ethyl-5-oxy-hexyl phthalate (MEOHP)/292) + (mono-2-
ethyl-5-carboxypentyl phthalate (MECPP/308) nmol/mL. Correlations between first trimester and third trimester phthalates were assessed through Spearman correlation coefficients.

We utilized two exposure metrics in this study: natural log-transformed, specific-gravity adjusted TI urinary phthalate concentrations and the arithmetic mean of natural log-transformed, specific-gravity adjusted T1 and T3 urinary phthalate concentrations. Because GDM screening occurs at the beginning of T3, the T1 sample represents exposure prior to the outcome assessment. T3 phthalate assessment occurred concurrent with or after GDM screening in this study population; thus, the average of T1 and T3 was used as a rough metric of “average exposure during pregnancy” and also to reduce exposure misclassification, given that phthalates exhibit variability over time not captured by a single urine assessment.\(^\text{85}\)

**Table 1: Phthalate metabolites under investigation in this study**

<table>
<thead>
<tr>
<th>Phthalate / Phthalate Metabolite</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono-benzyl phthalate</td>
<td>MBzP</td>
</tr>
<tr>
<td>Mono-n-butyl phthalate</td>
<td>MBP</td>
</tr>
<tr>
<td>Mono-(2-ethylhexyl) phthalate</td>
<td>MEHP</td>
</tr>
<tr>
<td>Mono-(2-ethyl-5-hydroxyhexyl) phthalate</td>
<td>MEHHP</td>
</tr>
<tr>
<td>Mono-(2-ethyl-5-oxohexyl) phthalate</td>
<td>MEOHP</td>
</tr>
<tr>
<td>Mono-(2-ethyl-5-carboxypentyl) phthalate</td>
<td>MECPP</td>
</tr>
<tr>
<td>Mono-(3-carboxypropyl) phthalate</td>
<td>MCPPP</td>
</tr>
<tr>
<td>Monoethyl phthalate</td>
<td>MEP</td>
</tr>
<tr>
<td>Mono-isobutyl phthalate</td>
<td>MiBP</td>
</tr>
<tr>
<td>Mono-carboxy-iso-octyl phthalate</td>
<td>MCOP</td>
</tr>
<tr>
<td>Mono-carboxyl-nonyl phthalate</td>
<td>MCNP</td>
</tr>
<tr>
<td>Diethylhexyl phthalate metabolites (sum)</td>
<td>DEHP</td>
</tr>
</tbody>
</table>

*Outcome Assessment*

During the TIDES study period (2010-2012), routine GDM screening was not officially recommended by the U.S. Preventative Services Task Force.\(^\text{175}\) However, the American College of Obstetricians and Gynecologists had recommended screening for all pregnant women at that time.\(^\text{176}\) and data indicate that 96% of obstetricians routinely screened for GDM\(^\text{177}\) – though criteria and screening thresholds would have varied by clinic (see Background: Gestational Diabetes and Glucose Intolerance).
As described above, the most common GDM screening approach 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.\textsuperscript{178,179} GDM is diagnosed in women with two or more abnormal values in the OGTT. Because of varying diagnostic thresholds, we standardized across the TIDES clinics with respect to GLT and OGTT test results. We classified a GLT result of $\geq 135$ mg/dL as GLT exceedance/failure and then utilized results from the OGTT to consistently 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).\textsuperscript{49} Impaired glucose tolerance (IGT) was defined as a failed GLT but less than two exceedances on the OGTT. Continuous glucose concentrations from the GLT were utilized in our continuous outcome analysis. Two GLT values (x=1 & x=38 mg/dL) that were deemed implausible by obstetrics and gynecology specialists advising this study were dropped from the analyses and treated as missing for these women.

\textit{Covariates}

The following covariates were considered \textit{a priori} when planning and conducting this study: maternal age, maternal body mass index (BMI), T1 gestational weight gain (GWG), late pregnancy GWG, study center, race/ethnicity, maternal education, smoking, alcohol use, infant sex, and parity.

- **Maternal Age** (continuous): Because of the strong association of maternal age with GDM in both our dataset and the broader scientific literature,\textsuperscript{17,96,180,181} we included maternal age (as a continuous variable) in all of our models.

- **Maternal BMI & GWG** (continuous): We considered three possible weight variables in our analyses: pre-pregnancy BMI, T1 GWG, and late pregnancy (T3) GWG. BMI was obtained from self-report, and GWG was calculated from medical record abstraction of T1 and T3 visit weights in relation to self-reported pre-pregnancy weight data. All three measures are strongly correlated with GDM in the scientific literature.\textsuperscript{13-15,182} Maternal BMI was associated with glucose intolerance in our dataset. While we also considered
GWG as a potential covariate, pre-pregnancy BMI was more strongly associated with GDM than were the GWG measures in our dataset and substitution with GWG did not meaningfully change the regression estimates; therefore, only BMI was used in the analytical models.

- **Race/ethnicity** (categorical: non-Hispanic white, non-Hispanic black, Hispanic, Asian, and other/mixed): Race/ethnicity is strongly associated with GDM risk. 6,7,12,183-186 Specific racial/ethnic groups with particularly elevated risk include Asians, Hispanics, and non-Hispanic Blacks. 185,187 This covariate was included in the *a priori*, extended, and reduced models.

- **Parity** (binary: ever/never previous live birth): We used a narrow definition of parity as ever/never previous live birth. Because it is standard to adjust for parity in perinatal and maternal epidemiology, this variable was included in the *a priori*, extended, and reduced models.

- **Smoking** (binary: any smoking during any trimester): This variable was included in our *a priori* and extended models because of its importance in perinatal and maternal epidemiology and the documented association between smoking and glycemic measures in non-pregnant populations. 188-190 However, data are limited and inconclusive about the role of cigarette smoking on gestational diabetes, specifically; 191 therefore, this variable was not included in the reduced model. Smoking was not associated with the outcome in our dataset.

- **Alcohol** (binary: any alcohol during any trimester): Alcohol is commonly examined in all perinatal analyses because of its impacts on maternal health and fetal development. 192,193 This covariate was included in the extended model but not the other models, because of the lack of association between alcohol and our exposure or outcome in the literature.

- **Study Center** (categorical): In prior TIDES analyses, study center was found to be associated with outcomes of interest, even after adjusting for race/ethnicity. Therefore, we included this variable in the *a priori*, extended, and reduced models.

- **Infant sex** (binary: male/female): Phthalate analyses were conducted in different laboratories according to infant sex, as noted above. For first trimester phthalates only, samples from mothers of boys were sent to CDC while samples from mothers of girls were sent to UW. Therefore, we included this as a potential precision variable in our extended model.

- **Maternal education** (categorical: some/all high school, some college, and college/post-graduate): This variable was included in the *a priori* and extended models because of
both its association with GDM and its possible role as a crude estimate of socioeconomic status, which has been associated with GDM. Maternal education was not associated with the outcomes in our dataset.

**Models**

The four models considered in our analysis plan are listed below:

- **Minimally adjusted model**: maternal age and maternal BMI
- **A priori model**: Maternal age, maternal BMI, study center, race/ethnicity, parity, smoking, maternal education
- **Extended model**: Maternal age, maternal BMI, study center, race/ethnicity, parity, smoking, maternal education, alcohol, infant sex
- **Reduced model**: Maternal age, maternal BMI, study center, race/ethnicity, and parity

While we considered these four models in our analysis plan, only results from the minimally adjusted, reduced, and a priori models are discussed in the paper. The additional variables in the extended model did not meaningfully change the regression parameters. Because maternal smoking and maternal education category (included in the a priori model) were not significantly associated with the outcomes of interest in the dataset and also did not meaningfully alter the regression parameters, reporting is focused on results from the reduced model only. Given that we conducted a complete case analysis and there was varying missingness for each covariate, the reduced model with fewer parameters can draw upon a larger sample of the study population.

**Statistical Analysis**

All statistical analyses were performed using STATA (version 14.1, StataCorp, College Station, TX, USA). Overall, because missingness was low across the dataset, we evaluated our study questions using complete case analysis.

- **Aim 1: GDM**

For the primary analysis, we assessed the association between pregnancy average urinary MEP concentrations and GDM. This phthalate was selected for the primary analysis because of a
previous study results suggesting associations with GDM risk factors. As a secondary analysis, we assessed the association between: 1) pregnancy average urinary phthalate concentrations (for all other individual phthalates separately and total DEHP metabolites and GDM; and 2) T1 urinary phthalate concentrations (for all individual phthalates separately and total DEHP metabolites) and GDM. We used logistic regression to evaluate four confounder models as listed above.

Model: 
\[ \text{Logit}(p)_A = \beta_0 + \beta_1 X_A + \beta_2 X_B + \beta_3 X_C \ldots \beta_K X_K \]

(where \( \text{logit}(p)_A \) is the log odds ratio for the outcome (GDM) and phthalate =A, \( \beta_A \) is the regression coefficient for the phthalate =A, \( X_A \) is the phthalate measure of interest, \( B_2 \ldots K \) are regression coefficients for the confounders in the model, and \( X_{B_2} \ldots K \) are the values of the confounders in the model).

- **Aim 2: IGT**

  For the primary analysis, we evaluated the association between pregnancy average urinary MEP concentrations and IGT as defined above. As a secondary analysis, we assessed the association between 1) pregnancy average urinary phthalate concentrations (for all other individual phthalates separately and total DEHP metabolites) and IGT; and 2) T1 urinary phthalate concentrations (for all individual phthalates separately and total DEHP metabolites) and IGT. We used logistic regression and evaluated four models with confounder adjustments as described above.

Model: 
\[ \text{Logit}(p)_A = \beta_0 + \beta_1 X_A + \beta_2 X_B + \beta_3 X_C \ldots \beta_K X_K \]

(where \( \text{logit}(p)_A \) is the log odds ratio for the outcome (IGT) and phthalate =A, \( \beta_A \) is the regression coefficient for the phthalate =A, \( X_A \) is the phthalate measure of interest, \( B_2 \ldots K \) are regression coefficients for the confounders in the model, and \( X_{B_2} \ldots K \) are the values of the confounders in the model).

- **Aim 3: continuous blood glucose concentrations from GLT**

  For the primary analysis, we evaluated the association between the pregnancy average MEP concentrations and continuous blood glucose concentrations from the GLT. As a secondary analysis, we assessed the association between 1) pregnancy average urinary phthalate concentrations (for all other individual phthalates separately and DEHP metabolites) and continuous glucose concentrations, and 2) T1 urinary phthalate concentrations (for all individual phthalates separately and DEHP metabolites) and continuous glucose concentrations. We used multiple linear regression and evaluated four confounder models as described above.
Model: $y_A = \beta_0 + \beta_1 X_A + \beta_2 X_B + \beta_3 X_C \ldots \beta_K X_K$

where $y_A$ = continuous glucose intolerance measure for phthalate=$A$, $B_i$ is the regression coefficient for the phthalate=$A$, $X_A$ is the phthalate measure of interest, $B_2\ldots K$ are regression coefficients for the confounders in the model, and $X_B\ldots K$ are the values of the confounders in the model.

- **Sensitivity Analyses**

  We conducted multiple sensitivity analyses on these data. First, to evaluate potential non-linear dose response relationships, we created phthalate quartiles and evaluated the associations between: 1) pregnancy average phthalate quartiles and GDM, and 2) pregnancy average phthalate quartiles and IGT. Significance was tested using a global Wald test. We also conducted sensitivity analyses to exclude individuals with polycystic ovary syndrome (PCOS), which is characterized by the presence of abnormal hormonal, metabolic, and inflammatory states.\(^{196}\)

  Most, but not all, studies suggest that women with PCOS are at increased risk for GDM.\(^{12,197}\) We also examined whether results were altered by removal of any individuals currently taking diabetes medication. Finally, because of the strong associations of race/ethnicity with phthalate exposure\(^{70,198,199}\) and glucose intolerance\(^{6,7}\) as well as the differing effect of BMI on risk of glucose intolerance by race,\(^{200}\) we tested for the presence of interaction of race/ethnicity with both BMI and pregnancy average phthalates using a likelihood ratio test, comparing a full model (phthalate, maternal age, BMI, race, parity, race*phthalate, and race*BMI) to a reduced model (phthalate, maternal age, BMI, race, parity; and race*BMI) for continuous glucose concentrations in the GLT only. This outcome measure was selected as the focus of the interaction testing because GLT results were available on the entire sample, allowing for a larger sample size for the analysis. Race-stratified analyses were also conducted, removing study center from the model (see Appendix).

**RESULTS**

*Study population: demographic characteristics; exposure and outcome patterns*

Table 2 describes the study population (n=705) for this analysis. The cohort was predominantly non-Hispanic white (66.38%) and well educated (74.18% had college/post-
graduate education). Average maternal age was 31 years, and average first trimester BMI was 26.12. Most of the participants in our study sample were based at URMC (28.51%), while the fewest were based at UW (18.58%).

We observed 60 cases of GDM and 90 cases of IGT in the entire cohort, for overall frequencies of 8.5% and 12.8% respectively (Table 3). The prevalence of these conditions varied by race (p =0.04). For example, GDM was found in 6.6% of the non-Hispanic white population but 16.4% of Hispanics and 15.6% of Asians. IGT was observed in 15.6% of the Asian population. The mean (SD) glucose concentration in the GLT test was 113.6 (27.7) mg/dL across the entire cohort; Asians had the highest mean glucose concentrations among race/ethnic subgroups (121.95 (24.77) mg/dL).

In table 4, we present summary statistics on phthalate metabolite concentrations during the first trimester and third trimester independently as well as their Spearman correlation coefficients. In both trimesters, MEP was present at the highest concentrations. The geometric means (GM) and geometric standard deviations (GSD) for MEP were as follows: T1 GM (GSD) =37.64 (3.79) ug/L; T3 GM (GSD) = 42.13 (4.51) ug/L. Phthalate metabolites MCNP, MCPP, and MEHP were present at the lowest concentrations during each trimester. The GMs of MBzP, MBP, and MiBP were lower in T1 compared to T3, while the GM of MCOP was higher in T1 compared to T3. Within woman, between trimester correlations were found to be low, ranging from 0.11 for the sum of DEHP metabolites to 0.46 for mBzP.

Primary & secondary analyses

The findings of the analyses of the association between phthalate metabolite concentrations and glucose intolerance outcomes are presented in tables 5-10. One ug/L increase in log pregnancy average MEP was associated with increased odds of GDM (OR: 1.88; 95% CI: 1.14, 3.10). One ug/L increase in log monocarboxyoctyl phthalate (MCOP) was associated with
increased blood glucose concentrations in the GLT (T1: 6.19, 95% CI: 0.75, 11.63), pregnancy average: 6.98, 95% CI: 0.13, 13.82).

While consistent with no increased risk, trends for all T1 phthalates except MEP suggested decreased odds of GDM. Trends were more mixed for pregnancy average phthalates and GDM. Most T1 and pregnancy average phthalate measures showed trends towards increasing OR for IGT (Tables 7 and 8). Of particular note is that pregnancy average MCOP and MBP had increased OR of IGT with a lower 95% CI bound near one, which provides more confidence in the interpretation of these results: 1.86 (0.92, 3.76) and 1.99 (0.97, 4.11), respectively. Trends for T1 phthalates and continuous glucose concentrations in the GLT were also mixed, while most but not all measures of pregnancy average phthalates trended towards a positive association with continuous glucose concentrations. However, overall, it is difficult to draw conclusions about the size of the odds (~risk) in these analyses, given that the 95% CI overlaps with the null effect value.

_Sensitivity analyses_

Figure 4 illustrates the results of analyses by phthalate quartiles. Based on the global Wald test, individuals in Q3 for pregnancy average MCPP exhibited significantly reduced odds of GDM compared to those in Q1 (0.22 (95% CI: 0.07, 0.64)). There were suggestive nonlinear dose response trends for some other phthalates and GDM or IGT.

Sensitivity analyses to exclude individuals with PCOS did not alter the results; therefore, these individuals were retained in the dataset. Because only one individual within the study sample was recorded as currently taking diabetes medication, we did not expect this to alter results and kept this individual in the dataset.

Likelihood ratio testing for the presence of interaction between phthalates with race and BMI (separately) suggested a significant interaction for pregnancy average MiBP (p=0.04) only. As noted above, this analysis was only conducted for the GLT data. In this model, the coefficient
for the interaction term for Asians was 45.46 (16.97, 73.95), while the main effect for Asians was -41.37 (-107.70, 24.95). Race-stratified analyses adjusting for maternal age, maternal BMI, and parity indicated significant effects for most phthalates on continuous glucose concentrations among Asians (see Appendix).

DISCUSSION

Study Population Characteristics & Exposure Measures

The overall prevalence of GDM in our population was approximately 8.5%, which is within the range of national estimates of 8-9%. The prevalence of GDM was highest in Asians and Hispanic subgroups (15.8% and 16.4%, respectively) (see Table 3). This finding is in agreement with national estimates and previous studies that have documented high burden in these subgroups. The frequency of IGT also varied by racial/ethnic subgroup, with the lowest frequency in Hispanics (9.1%) and the highest in Asians (15.8%). Asians also exhibited the highest mean (SD) glucose concentrations in the GLT, 121.95 (24.77). Race-specific considerations are further discussed below.

In both trimesters, among the individual phthalate measures evaluated, MEP was present at the highest concentrations across the overall study population (Table 4). Sources of diethyl phthalate (DEP), the parent compound of MEP, include personal care products and pharmaceutical coatings. Among subgroups, non-Hispanic blacks had the highest mean DEHP metabolite concentrations, while other/mixed and non-Hispanic blacks had the highest mean MEP levels (data not shown). Other studies also indicate that phthalate metabolite concentrations during pregnancy differ by race/ethnicity. For example, James-Todd et al. 2017 report that non-Hispanic blacks and/or Hispanic women in their Boston-based cohort (n=350) had the highest concentrations of each of the phthalate metabolites examined, compared to other non-Hispanic whites. Subgroup-specific differences in DEHP exposure are likely due to differences in dietary habits, particularly fast food consumption. Subgroup-specific differences in MEP and other
phthalates found in personal care products may be due to differences in product use; several studies have found women in certain racial/ethnic groups may be more likely to use personal care products with phthalates and other chemicals of concern. 203-205

Urinary phthalate concentrations and patterns in our study were within the range of those reported in some prior studies of gestational glucose intolerance. For example, in accordance with our findings, Shapiro et al. detected MEP at the highest concentrations, with a range of 34.5-38.8 ug/L across disease categories.110 James-Todd et al. and Robledo et al. also detected MEP at the highest concentrations, with a GM ranging from 112.4 – 319.2 ug/L across age groups and 216.42 ug/L across the study population, respectively;109,111 however, these values are much higher than those in our TIDES sample. Our TIDES study sample also had lower GM concentrations of sum DEHP metabolites compared to those reported by Robledo et al. (GM: 216.42).111 Concentrations of phthalate metabolites detected in our cohort of pregnant women were similar to those found in nationally representative data from the general population in the 2011-2012 National Health and Nutrition Examination Survey (NHANES) (selected creatinine-corrected GM (CI) examples: MBzP = 5.15 (4.80-5.52); MBP = 8.66 (7.79-9.62); MiBP = 6.83 (6.30-7.40); MEP = 43.2 (38.5-48.5).206

Within women, between trimester correlations of phthalate metabolite concentrations were found to be moderately low, ranging from 0.11 for the sum of DEHP metabolites to 0.46 for MBzP. Our findings are aligned with previous studies of pregnant (as well as non-pregnant) populations that have documented low to moderate correlations between phthalate measures at different timepoints. 83,174,207 Valvi et al. 2015 reported Pearson correlation coefficients between 0.06 (MEOHP) and 0.26 (MEP) for T1 and T3 urinary phthalate concentrations.207 In comparison, both of these metabolites exhibited similar but higher between trimester correlations in our study, with Spearman correlation coefficients of 0.13 and 0.41, respectively. As in our study, Ferguson et al. 2014 also reported that sum of DEHP metabolites had the lowest correlation between early and late pregnancy timepoints (Spearman correlation coefficients between 0.21-0.26). These
authors also document higher correlations among MBzP compared to other phthalate metabolites, with Spearman correlation coefficients between 0.52-0.59; MBzP had the highest correlations in our data as well. Overall, these low within-woman correlations and the short half-life of phthalate metabolites in the body emphasize the importance of utilizing multiple assessments of exposure to reduce misclassification in future epidemiological analyses. However, it should also be noted that while within woman correlations were low, the cohort-wide GMs of T1 and T3 concentrations were fairly similar, indicating that overall population exposures were stable across time.

**Primary & Secondary Analyses and Mechanistic Context**

Prior to this work, only four studies had evaluated the association between phthalate exposure and gestational glucose tolerance. However, each of these studies had limitations, such as small sample size and/or only one phthalate assessment during pregnancy. Of these studies, the only previous one that assessed urinary phthalate metabolite quartiles and GDM risk, specifically, found no associations (adjusted OR (95%CI) MEP Q2 = 0.7 (0.3-1.8), Q3 = 0.8 (0.3-2.1), Q4 = 0.5 (0.2-1.4); MBP Q2 =1.7 (0.6-4.4), Q3 = 1.0 (0.3-3.2), Q4 = 0.6 (0.1-2.2); MBzP Q2 = 0.7 (0.2-2.2); Q3 = 1.5 (0.6-4.2); Q4 = 1.5 (0.5-4.7); MCPP Q2 = 1.2 (0.5-2.9), Q3 = 0.6 (0.2-1.8), Q4 = 0.6 (0.2-1.9); sumDEHP Q2 = 1.0 (0.4-2.5), Q3 = 0.4 (0.1-1.5), Q4 = 0.9 (0.3-2.9). Yet, this study evaluated phthalates at only one timepoint, which may not capture the relevant exposure period given the short biological half-life of the chemicals. Furthermore, this Canadian-based study utilized different classification criteria for OGTT results, based on Canadian guidelines that are similar to the higher thresholds in the NDDG rather than the more conservative classifications from Carpenter and Coustan that we utilized in our work. These distinct diagnostic criteria may partially account for their null findings.

Our primary analysis finding that pregnancy average MEP is significantly associated with increased odds of GDM (OR: 1.88; CI: 1.14, 3.10) is in alignment with our a priori hypothesis.
and with a previous study that documented an association of pregnancy average MEP with excessive gestational weight gain and second trimester MEP with impaired glucose tolerance (based on a GLT $\geq 140$ mg/dL).\textsuperscript{109} We developed this \textit{a priori} hypothesis based on that particular study because of the robust methodology used by the authors and its focus on subclinical GDM risk factors, which provide a more sensitive way to evaluate the role of phthalates. Prior animal and cellular research suggesting pro-diabetic mechanisms of MEP also informed our decision to focus on this phthalate. While the exact mechanisms by which MEP may act to promote glucose intolerance remain to be fully elucidated, hormone mediation and PPAR modulation are plausible. Animal studies indicate that the parent compound of MEP, DEP, may be estrogenic.\textsuperscript{210} Recent \textit{in vitro} work also suggests that low dose MEP has both estrogenic and PPARgamma agonist activity,\textsuperscript{211} both of which are plausible mechanisms.

Our secondary analyses indicate that MCOP is associated with increased blood glucose concentrations (T1: 6.19, CI: 0.75, 11.63), T1T3 mean: 6.98, CI: 0.13, 13.82). However, these results should be interpreted with caution, given that measurement of MCOP was restricted to a subset of mothers in our dataset. Further studies should evaluate whether this association remains in a larger sample. A recent analysis using data from a nested case-control study of endocrine disrupting chemicals and cryptorchidism documented a positive association between increased first trimester levels of MEHP and MCiOP ($\mu$g/L) and T3 plasma glucose (mmol/l) concentration in women without GDM.\textsuperscript{112} In comparison, in our dataset, pregnancy average MEHP was also positively associated with blood glucose concentration (mg/dL), though we are unable to draw definitive conclusions about the role of MEHP given that the 95\% CI indicate that our results could be compatible with either positive or negative associations (1.20 (95\%CI: -5.36, 7.76) . MEHP has be found to activate PPARgamma,\textsuperscript{125} which may explain this positive association with glucose intolerance.

Overall, as described above, there are several possible mechanisms by which phthalates may increase the risk of diabetes. First, they can bind to PPARs and act as selective
modulators. PPAR alpha plays an important role in lipid processing and beta cell activity, and PPAR gamma regulates adipocytes and energy homeostasis. Findings from experimental studies indicate that PPAR alpha activation can alter insulin secretion and induce beta cell dysfunction and that PPAR gamma activation can induce adipocyte differentiation. These two pathways are thought to be responsible for many of the phthalate-related metabolic changes in the body; yet, no studies have specifically examined these mechanisms during pregnancy and how they may interact with physiological changes in metabolism that occur during this period. One potential hypothesis, however is that chronic PPAR agonism – stimulated by phthalate exposure or other environmental agonists - could lead to beta cell exhaustion and dysfunction. Another possibility is that, through selective modulation of PPAR, phthalates could trigger expression of a certain subset downstream genes that would result in metabolic disruption.

Second, phthalates are known endocrine disruptors, linked to changes in sex steroid hormones and related outcomes. Substantial evidence indicates that alterations in estrogens are linked to insulin resistance, changes in adipocytes, and related metabolic disruptions in females. Several phthalates have been found to have estrogenic activity, among other hormonal behavior. 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.

Overall, we documented mixed associations between phthalates and the outcomes that we examined in this study. The lack of consistent and/or strong associations could be explained by a “tipping point” idea. Phthalate exposure may initially lead to increased levels of insulin through either PPAR- or endocrine-related mechanisms, but then, in the longer term, trigger beta-cell exhaustion and reductions in insulin secretion. Inter-individual variability in exposure history and physiological resilience could result in differential manifestation and timing of the above effects
in a population. Additionally, of course, the role of phthalates should be considered within the context of the multiple other well-established risk factors for GDM and subclinical measures of glucose intolerance, such as maternal BMI. We hypothesize that phthalates alone would likely contribute to only slight shifts in individual risk for glucose intolerance, but the collection of multiple exposures in concert with well-established risk factors could perhaps change the pattern of this condition across the population.

We also found inconsistent patterns in the relationship between phthalates and the outcomes, which represent varying severities of glucose intolerance. If the outcomes were part of a progression of glucose dysregulation, we would perhaps expect that trends for the same phthalates would be similar for GDM, IGT, and continuous blood glucose and that the effects would be able to be detected more clearly with the more sensitive, subclinical assessments of IGT and continuous blood glucose. However, there was limited evidence that these conditions represent related spectrums. For example, in comparison with the primary MEP-GDM finding, increased log pregnancy MEP (µg/L) was not associated with increased odds of IGT (OR = 0.99 (95% CI: 0.64, 1.52) or continuous blood glucose concentrations (mg/dL) in the GLT (beta: 2.83 (95% CI: -1.05, 6.72). In comparison with our secondary finding of MCOP linked to blood glucose concentrations, increased log pregnancy average MCOP (µg/L) was not associated with increased odds of GDM (OR = 0.90 (95% CI: 0.36, 2.26) or IGT (OR = 1.86 (95% CI: 0.92, 3.76). These discordances suggest non-overlapping characteristics of the conditions. In other words, while GDM, IGT, and increased blood glucose concentrations share similar characteristics of glucose dysregulation, there may also be distinct aspects of the conditions such that they are differentially impacted by phthalate exposure.

**Race-specific associations**

It is well known that specific racial/ethnic groups, particularly Asians, have higher risk of GDM and other metabolic disorders. Differential phthalate exposure by race/ethnicity and
country of origin has also been documented.\textsuperscript{70,199,225} As noted above, these differences in exposure may be due to differential use of personal care products and/or differences in dietary patterns.\textsuperscript{202,203} Due to our small sample size, our study was underpowered to thoroughly evaluate race-specific associations. Sensitivity analyses suggested potential interaction between pregnancy average MiBP exposure and race in relation to continuous glucose concentrations in the GLT (p=0.04), with a significant interaction term between phthalate and Asian race only. These results should be interpreted with caution, however, given the heterogeneity within these broad racial/ethnicity categories, the limited sample size, the post-hoc nature of these analyses – and especially the opposing direction of coefficient for the main effect for Asians. Results from the race-stratified analysis are provided in the appendix, which provide evidence of elevated risk among Asians from numerous phthalate metabolites.

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, which is one of the strongest risk factors for these conditions.\textsuperscript{226} The reasons for these disparate trends are not clear, yet several theories have been presented. One reason may be that, for women at a specific BMI, Asians tend to have a higher percentage of body fat and visceral (central) adipose tissue compared to other subpopulations.\textsuperscript{227-229} Visceral adipose tissue is a known risk factor for insulin resistance, partially due to the secretion of bioactive molecules such as TNF-alpha and other inflammatory factors.\textsuperscript{230-232} Thus, for Asians, standard BMI categories may not adequately capture the actual physiological factors (ie: visceral adipose tissue) that most directly affect metabolic disease.\textsuperscript{200} Genetic risk factors may also play a role, as has been suggested for other related conditions.\textsuperscript{233,234} The PPARgamma2 polymorphism Pro12Ala is associated with decreased risk of diabetes.\textsuperscript{235,236} 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.\textsuperscript{235} The prevalence of this polymorphism varies by race, with
the highest frequencies among Caucasians (~12%) and the lowest among certain Asian groups (Japanese (~4%), Chinese (~1%) and African Americans (~3%). One of the possible modes of action of phthalates on insulin resistance is via PPARgamma, and therefore it is plausible that this polymorphism could partially explain the differences in risk across racial/ethnic groups. Individuals with this variant would be less susceptible to phthalate-mediated insulin resistance, but the frequency of this protective variant is least common among Asians – perhaps making them more vulnerable to the effects of exposure. Future, larger studies should further address the potential role of phthalates in mediating increased susceptibility among this racial/ethnic group, particularly given their risk for higher exposures.

*Non-monotonic Dose-Response (NMDR)*

The presence of NMDR in endocrine disruption has been well documented, including in prior studies evaluating endocrine-related metabolic outcomes specifically. There are several potential mechanisms that could explain these patterns, including receptor downregulation/de-sensitization at higher exposures, cytotoxicity at higher exposures, differential receptor selectivity at different levels of exposure, and internal negative feedback loops, among other processes.

Prior research on metabolic outcomes and phthalates in particular has also suggested the presence of non-monotonic dose response relationships. For example, non-monotonic associations for MBP and sum of DEHP metabolites with prevalent diabetes were reported previously. However, these patterns are not reflected consistently across the literature, and non-monotonic associations between phthalate quartiles and gestational glucose tolerance were not documented in a prior study of pregnant women.

In our study, based on a global Wald test, individuals in Q3 for pregnancy average MCPP exhibited significantly reduced odds of GDM compared to those in Q1. There were suggestive but non-significant NMDR associations for other exposures and outcomes. Overall, given that
these analyses were conducted as sensitivity analyses and that there was inconsistency in the observed patterns across different phthalates, these findings should be interpreted with caution. Future studies of gestational glucose tolerance should incorporate assessment of phthalate exposure by quartiles to better understand the potential for NMDR in these outcomes.

Limitations:

Our research has several limitations. First, we only evaluated two urinary phthalate measurements, one from the T1 and one from T3. Phthalate concentrations during pregnancy can change considerably from day-to-day. If these measurements are not representative of phthalate levels during all of pregnancy, our results could be biased from exposure misclassification. To partially address this issue, we classified exposure not only by a single trimester measurement but also by the average of T1 and T3 phthalate levels. However, there may still be residual misclassification given the short half-life of phthalates in the body. Additionally, measures of MCOP and MCNP were only available on a subset of the study population, which reduced our sample size for all analyses of these phthalates.

We were unable to adjust for several confounders in these analyses. We did not have access to medical record data on prior GDM in pregnancy or prior diagnosis of and/or family history of T2DM. Prior GDM and family history of metabolic disease are associated with increased risk of GDM; thus, our results may be biased without adjustments for these factors. Additionally, we used the presence of a GLT in the medical record as an indication that the individual did not have diabetes; if this assumption was overly simplistic, we could have misclassified individuals with diabetes incorrectly as having GDM. We also did have access to data to adjust for diet in these analyses, which may be associated with both the exposure (phthalates, primarily DEHP) and the outcome (GDM and glucose intolerance). However, results from prior studies in non-pregnant populations were not meaningfully altered by
adjustment for diet, which somewhat mitigates our concern about the omission by this variable. Nevertheless, future studies evaluating this question should include adjustment for diet.

Additionally, our study was not able to evaluate the association between phthalate exposure and GWG, an important risk factor for GDM and a metabolic outcome that has been explored in previous research (including the study that informed our a priori hypothesis). This limitation was due to lower confidence in the quality of the GWG information across the different study centers, such as variations in how or when these data were collected.

While our results are suggestive of a potential interaction between pregnancy average MiBP and race/ethnicity, our small sample size precludes a thorough evaluation of potential race-specific effects. Further studies, with a larger number of diverse participants, should pursue this question further.

Our study did not consider exposure to other exogenous compounds that have been linked diabetes and metabolic dysfunction and that may also have similar exposure sources as phthalates, such as bisphenol-A; this omission may have resulted in unmeasured confounding in our analyses.

Finally, while our study was designed as a prospective cohort study, the short follow-up time and the uncertainty regarding the critical windows of exposure for GDM development necessitates caution in interpretation of these findings. More specifically, given that the susceptible period for the development of GDM remains to be determined, we cannot be certain that our exposure assessment preceded initiation of the disease process. Additional basic research to elucidate the details of disease progression can inform the design of epidemiological studies that can more accurately assess exposure during critical windows.

Strengths:

Our study had several important strengths. The TIDES cohort is derived from four research centers across different parts of the country (NY, WA, MN, and CA), which provides
geographic population diversity not present in prior analogous studies. Furthermore, despite the limitations noted above regarding potential exposure misclassification, our study is unique in utilizing phthalate measures from two timepoints during pregnancy rather than only one. The low within-woman correlation between T1 and T3 phthalates in our dataset underscores the importance of utilizing multiple exposure measurements when addressing this question in future studies. Finally, we also had access to the continuous measures of glucose intolerance that were abstracted from the medical record. This extensive data allowed us to investigate not only the clinical outcome of GDM but also subclinical measures of glucose intolerance, which have also been linked to adverse pregnancy outcomes but have not been thoroughly investigated in the epidemiological literature.

CONCLUSION

This study adds to a small but growing body of literature on the association between phthalates and gestational glucose tolerance. Given that there are several possible mechanisms by which phthalates may affect metabolic function and the significant maternal and fetal consequences of hyperglycemia during pregnancy, future research should continue to address this subject—especially in populations that may be particularly susceptible.
TABLES & FIGURES:

Table 2: Demographic characteristics of 705 mothers included in analyses of phthalates and gestational glucose intolerance

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>Study Center</td>
<td></td>
</tr>
<tr>
<td>UCSF</td>
<td>165 (23.40)</td>
</tr>
<tr>
<td>UMN</td>
<td>192 (27.23)</td>
</tr>
<tr>
<td>URMC</td>
<td>201 (28.51)</td>
</tr>
<tr>
<td>UW</td>
<td>131 (18.58)</td>
</tr>
<tr>
<td>missing</td>
<td>16 (2.27)</td>
</tr>
<tr>
<td>Maternal Age (years)</td>
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</tr>
<tr>
<td>&lt;=20</td>
<td>21 (2.98)</td>
</tr>
<tr>
<td>21-30</td>
<td>262 (37.16)</td>
</tr>
<tr>
<td>31-40</td>
<td>393 (55.74)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>29 (4.11)</td>
</tr>
<tr>
<td>missing</td>
<td>0</td>
</tr>
<tr>
<td>First Trimester Body Mass Index (BMI)</td>
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</tr>
<tr>
<td>&lt;=24.9</td>
<td>379 (53.76)</td>
</tr>
<tr>
<td>25-29.9</td>
<td>155 (21.99)</td>
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<tr>
<td>&gt;=30</td>
<td>159 (22.55)</td>
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<td>missing</td>
<td>12 (1.70)</td>
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<tr>
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</tr>
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<td>Non-Hispanic White</td>
<td>468 (66.38)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>81 (11.49)</td>
</tr>
<tr>
<td>Non-Hispanic Asian</td>
<td>38 (5.39)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>55 (7.80)</td>
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<tr>
<td>Other/Mixed</td>
<td>49 (6.95)</td>
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<td>14 (1.99)</td>
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<tr>
<td>Highest Education Attended</td>
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<tr>
<td>Some/all High School</td>
<td>97 (13.76)</td>
</tr>
<tr>
<td>Some College</td>
<td>85 (12.06)</td>
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<td>College/post-graduate</td>
<td>523 (74.18)</td>
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<tr>
<td>Any Smoking During Pregnancy</td>
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<tr>
<td>Yes</td>
<td>47 (6.67)</td>
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<tr>
<td>No</td>
<td>591 (83.83)</td>
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<td>missing</td>
<td>67 (9.50)</td>
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<td>Any Alcohol During Pregnancy</td>
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<td>Yes</td>
<td>91 (12.91)</td>
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<tr>
<td>No</td>
<td>546 (77.45)</td>
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<tr>
<td>missing</td>
<td>68 (9.65)</td>
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Table 3: Race-specific and overall frequencies of glucose intolerance outcomes in study population

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>N</th>
<th>GDM (N%)</th>
<th>IGT (N%)</th>
<th>GLT (mg/dL) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>468</td>
<td>31 (6.6)</td>
<td>62 (13.2)</td>
<td>112.9 (27.1)</td>
</tr>
<tr>
<td>Black</td>
<td>81</td>
<td>9 (11.1)</td>
<td>8 (9.9)</td>
<td>108.3 (31.0)</td>
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<tr>
<td>Asian</td>
<td>38</td>
<td>6 (15.8)</td>
<td>6 (15.8)</td>
<td>121.9 (24.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>55</td>
<td>9 (16.4)</td>
<td>5 (9.1)</td>
<td>114.6 (29.9)</td>
</tr>
<tr>
<td>Other/Mixed</td>
<td>49</td>
<td>5 (10.2)</td>
<td>6 (12.2)</td>
<td>119.0 (25.7)</td>
</tr>
<tr>
<td>Missing</td>
<td>14</td>
<td>0 (0)</td>
<td>3 (21.4)</td>
<td>118.9 (25.0)</td>
</tr>
</tbody>
</table>

Table 4: Summary statistics on T1 & T3 phthalates* in overall study population

<table>
<thead>
<tr>
<th>Phthalate Metabolite</th>
<th>N</th>
<th>%&gt;LOD</th>
<th>Geo. Mean (GSD)</th>
<th>Min</th>
<th>Max</th>
<th>T1 N</th>
<th>%&gt;LOD</th>
<th>Geo. Mean (GSD)</th>
<th>Min</th>
<th>Max</th>
<th>T3 N</th>
<th>%&gt;LOD</th>
<th>Geo. Mean (GSD)</th>
<th>Min</th>
<th>Max</th>
<th>Spearman Corr.</th>
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<tr>
<td>MBP</td>
<td>668</td>
<td>99</td>
<td>5.24 (2.39)</td>
<td>0.21</td>
<td>59</td>
<td>679</td>
<td>95</td>
<td>7.19 (2.62)</td>
<td>0.4</td>
<td>400.8</td>
<td>0.4</td>
<td>43633.32</td>
<td>0.41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEP</td>
<td>668</td>
<td>100</td>
<td>37.64 (3.79)</td>
<td>0.79</td>
<td>4293.04</td>
<td>679</td>
<td>98</td>
<td>42.13 (4.51)</td>
<td>1.6</td>
<td>3373.33</td>
<td>0.27</td>
<td></td>
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<tr>
<td>MBP</td>
<td>668</td>
<td>95</td>
<td>8.32 (2.44)</td>
<td>0.43</td>
<td>432.1</td>
<td>679</td>
<td>98</td>
<td>9.66 (2.69)</td>
<td>0.51</td>
<td>3373.33</td>
<td>0.27</td>
<td></td>
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<td></td>
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<tr>
<td>MBZP</td>
<td>668</td>
<td>95</td>
<td>4.30 (2.87)</td>
<td>0.32</td>
<td>318.55</td>
<td>679</td>
<td>95</td>
<td>4.75 (3.24)</td>
<td>0.22</td>
<td>711.67</td>
<td>0.46</td>
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<tr>
<td>MCNP</td>
<td>406</td>
<td>96</td>
<td>2.72 (2.76)</td>
<td>0.34</td>
<td>320.93</td>
<td>679</td>
<td>98</td>
<td>2.79 (2.72)</td>
<td>0.23</td>
<td>282.75</td>
<td>0.15</td>
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<tr>
<td>MCOP</td>
<td>406</td>
<td>100</td>
<td>19.26 (3.49)</td>
<td>1.16</td>
<td>514.4</td>
<td>679</td>
<td>100</td>
<td>16.03 (3.29)</td>
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<td>550.97</td>
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<td>MCPP</td>
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<td>94</td>
<td>2.54 (3.61)</td>
<td>0.06</td>
<td>802.94</td>
<td>679</td>
<td>87</td>
<td>2.43 (3.68)</td>
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<td>595.00</td>
<td>0.20</td>
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<tr>
<td>MEHP</td>
<td>668</td>
<td>70</td>
<td>2.52 (2.52)</td>
<td>0.16</td>
<td>352.83</td>
<td>679</td>
<td>76</td>
<td>2.07 (2.42)</td>
<td>0.24</td>
<td>100.94</td>
<td>0.14</td>
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<td>0.23</td>
<td>1077.46</td>
<td>679</td>
<td>99</td>
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<td>MEOPH</td>
<td>668</td>
<td>99</td>
<td>5.52 (2.49)</td>
<td>0.23</td>
<td>679.27</td>
<td>679</td>
<td>100</td>
<td>5.31 (2.47)</td>
<td>0.14</td>
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<td>0.13</td>
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<tr>
<td>MECPP</td>
<td>668</td>
<td>100</td>
<td>10.58 (2.36)</td>
<td>0.82</td>
<td>635.77</td>
<td>679</td>
<td>100</td>
<td>12.23 (2.25)</td>
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<td>555.8</td>
<td>0.20</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>sumDEHP</td>
<td>668</td>
<td>N/A</td>
<td>9.43 (2.30)</td>
<td>8.84</td>
<td>9162.65</td>
<td>679</td>
<td>N/A</td>
<td>47.74 (2.39)</td>
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<td>2442.95</td>
<td>0.11</td>
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</tr>
</tbody>
</table>

* T1 and T3 phthalate summaries are specific-gravity adjusted but not log transformed; GM, min and max units = µg/L for all individual phthalates; nmol/ml for sumDEHP measure.
### Table 5: Adjusted odds ratio for association between one unit increase in log T1 phthalates and GDM (odds ratio (OR) & 95% confidence interval (CI)). Units = µg/L for individual phthalates; nmol/mL for sumDEHP.

<table>
<thead>
<tr>
<th>T1 Phthalate</th>
<th>Minimal OR</th>
<th>95%CI</th>
<th>A Priori OR</th>
<th>95%CI</th>
<th>Reduced OR</th>
<th>95%CI</th>
</tr>
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<tbody>
<tr>
<td>MIBP</td>
<td>1.00</td>
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<td>2.09</td>
<td>0.76</td>
<td>0.32</td>
<td>1.79</td>
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<tr>
<td>MEP</td>
<td>1.45</td>
<td>0.92</td>
<td>2.27</td>
<td>1.36</td>
<td>0.81</td>
<td>2.27</td>
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<td>MBP</td>
<td>1.02</td>
<td>0.50</td>
<td>2.08</td>
<td>0.80</td>
<td>0.35</td>
<td>1.81</td>
</tr>
<tr>
<td>MBZP</td>
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<td>1.53</td>
<td>0.72</td>
<td>0.35</td>
<td>1.49</td>
</tr>
<tr>
<td>MCNP</td>
<td>0.62</td>
<td>0.26</td>
<td>1.46</td>
<td>0.46</td>
<td>0.17</td>
<td>1.26</td>
</tr>
<tr>
<td>MCOP</td>
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<td>0.38</td>
<td>1.47</td>
<td>0.67</td>
<td>0.30</td>
<td>1.49</td>
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<td>1.10</td>
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<td>1.02</td>
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<td>1.30</td>
<td>0.41</td>
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<td>0.24</td>
<td>1.28</td>
<td>0.33</td>
<td>0.12</td>
<td>0.88</td>
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Minimally Adjusted Model = maternal age, maternal BMI
A Priori Model = maternal age, maternal BMI, race/ethnicity, study center, parity, education, smoking status
Reduced Model = maternal age, maternal BMI, race/ethnicity, study center, parity

### Table 6: Adjusted odds ratio for association between one unit increase in log pregnancy average phthalates and GDM (OR & 95% CI). Units = µg/L for individual phthalates; nmol/mL for sumDEHP.

<table>
<thead>
<tr>
<th>Preg. Avg. Phthalate</th>
<th>Minimal OR</th>
<th>95%CI</th>
<th>A Priori OR</th>
<th>95%CI</th>
<th>Reduced OR</th>
<th>95%CI</th>
</tr>
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<tbody>
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<td>MIBP</td>
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<td>1.43</td>
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<td>3.56</td>
</tr>
<tr>
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<td>1.18</td>
<td>2.90</td>
<td>1.96</td>
<td>1.17</td>
<td>3.27</td>
</tr>
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<td>1.11</td>
<td>0.45</td>
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</tr>
<tr>
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<td>1.93</td>
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<td>0.64</td>
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</tr>
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<td>0.65</td>
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</tr>
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<td>1.73</td>
</tr>
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<td>0.83</td>
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<tr>
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<td>2.30</td>
<td>0.71</td>
<td>0.27</td>
<td>1.87</td>
</tr>
</tbody>
</table>

Minimally Adjusted Model = maternal age, maternal BMI
A Priori Model = maternal age, maternal BMI, race/ethnicity, study center, parity, education, smoking status
Reduced Model = maternal age, maternal BMI, race/ethnicity, study center, parity
Table 7: Adjusted odds ratio for association between one unit increase in log T1 phthalates and IGT (OR & 95% CI). Units = µg/L for individual phthalates; nmol/mL for sumDEHP.

<table>
<thead>
<tr>
<th>T1 Phthalate</th>
<th>Minimal OR</th>
<th>95%CI</th>
<th>Minimal OR</th>
<th>95%CI</th>
<th>Reduced OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIBP</td>
<td>1.41</td>
<td>0.76</td>
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<td>2.57</td>
</tr>
<tr>
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<td>0.98</td>
<td>0.65</td>
<td>1.46</td>
<td>0.93</td>
<td>0.59</td>
<td>1.46</td>
</tr>
<tr>
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<td>0.83</td>
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</tr>
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<td>0.80</td>
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<td>0.73</td>
<td>0.40</td>
<td>1.33</td>
</tr>
<tr>
<td>MCNP</td>
<td>1.34</td>
<td>0.73</td>
<td>2.48</td>
<td>1.63</td>
<td>0.83</td>
<td>3.20</td>
</tr>
<tr>
<td>MCOP</td>
<td>1.62</td>
<td>0.96</td>
<td>2.74</td>
<td>1.67</td>
<td>0.94</td>
<td>2.96</td>
</tr>
<tr>
<td>MCP</td>
<td>1.11</td>
<td>0.74</td>
<td>1.67</td>
<td>1.27</td>
<td>0.83</td>
<td>1.96</td>
</tr>
<tr>
<td>MEHP</td>
<td>1.11</td>
<td>0.63</td>
<td>1.97</td>
<td>1.04</td>
<td>0.55</td>
<td>1.97</td>
</tr>
<tr>
<td>MEHHP</td>
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<td>1.85</td>
<td>1.06</td>
<td>0.57</td>
<td>1.98</td>
</tr>
<tr>
<td>MEOHP</td>
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<td>0.54</td>
<td>1.75</td>
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<td>0.49</td>
<td>1.80</td>
</tr>
<tr>
<td>MECPP</td>
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<td>0.60</td>
<td>2.06</td>
<td>1.09</td>
<td>0.55</td>
<td>2.16</td>
</tr>
<tr>
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<td>0.56</td>
<td>2.01</td>
<td>1.03</td>
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<td>2.10</td>
</tr>
</tbody>
</table>

Minimally Adjusted Model = maternal age, maternal BMI
A Priori Model = maternal age, maternal BMI, race/ethnicity, study center, parity
Reduced Model = maternal age, maternal BMI, race/ethnicity, study center, parity

Table 8: Adjusted odds ratio for association between one unit increase in log pregnancy average urinary phthalates and IGT (OR & 95% CI). Units = µg/L for individual phthalates; nmol/mL for sumDEHP.

<table>
<thead>
<tr>
<th>Preg. Avg. Phthalate</th>
<th>Minimal OR</th>
<th>95%CI</th>
<th>Minimal OR</th>
<th>95%CI</th>
<th>Reduced OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIBP</td>
<td>1.29</td>
<td>0.65</td>
<td>2.54</td>
<td>1.00</td>
<td>0.46</td>
<td>2.15</td>
</tr>
<tr>
<td>MEP</td>
<td>0.98</td>
<td>0.64</td>
<td>1.48</td>
<td>0.90</td>
<td>0.57</td>
<td>1.41</td>
</tr>
<tr>
<td>MBP</td>
<td>2.05</td>
<td>1.03</td>
<td>4.09</td>
<td>1.67</td>
<td>0.79</td>
<td>3.52</td>
</tr>
<tr>
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<td>0.70</td>
<td>0.37</td>
<td>1.34</td>
</tr>
<tr>
<td>MCNP</td>
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<td>1.48</td>
<td>0.71</td>
<td>3.09</td>
</tr>
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<td>3.77</td>
<td>2.00</td>
<td>0.96</td>
<td>4.15</td>
</tr>
<tr>
<td>MCP</td>
<td>1.00</td>
<td>0.64</td>
<td>1.58</td>
<td>1.13</td>
<td>0.69</td>
<td>1.83</td>
</tr>
<tr>
<td>MEHP</td>
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<td>2.32</td>
</tr>
<tr>
<td>MEOHP</td>
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<td>0.98</td>
<td>0.46</td>
<td>2.12</td>
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<tr>
<td>MECPP</td>
<td>1.13</td>
<td>0.54</td>
<td>2.35</td>
<td>1.06</td>
<td>0.47</td>
<td>2.41</td>
</tr>
<tr>
<td>sumDEHP</td>
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<td>0.58</td>
<td>2.44</td>
<td>1.12</td>
<td>0.51</td>
<td>2.48</td>
</tr>
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</table>

Minimally Adjusted Model = maternal age, maternal BMI
A Priori Model = maternal age, maternal BMI, race/ethnicity, study center, parity
Reduced Model = maternal age, maternal BMI, race/ethnicity, study center, parity
Table 9: Adjusted mean change in glucose concentration (mg/dL) measured during GLT associated with one unit increase in log T1 phthalate (beta, 95% CI). Units = µg/L for individual phthalates; nmol/mL for sumDEHP.

<table>
<thead>
<tr>
<th>T1 Phthalate</th>
<th>Minimal</th>
<th></th>
<th></th>
<th>A Priori</th>
<th></th>
<th></th>
<th>Reduced</th>
<th></th>
<th></th>
</tr>
</thead>
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<td></td>
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<td>95% CI</td>
<td>beta</td>
<td>95% CI</td>
<td>beta</td>
<td>95% CI</td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>-0.81</td>
<td>-6.99</td>
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<td>-0.03</td>
<td>-6.00</td>
<td>5.93</td>
</tr>
<tr>
<td>MEP</td>
<td>0.37</td>
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<td>4.02</td>
<td>0.12</td>
<td>-3.83</td>
<td>4.06</td>
<td>0.43</td>
<td>-3.41</td>
<td>4.27</td>
</tr>
<tr>
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<td>1.11</td>
<td>-4.45</td>
<td>6.67</td>
<td>0.17</td>
<td>-5.85</td>
<td>6.18</td>
<td>1.72</td>
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</tr>
<tr>
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<td>-5.00</td>
<td>4.73</td>
<td>-1.12</td>
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<td>4.11</td>
<td>-0.91</td>
<td>-6.00</td>
<td>4.18</td>
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<td>10.6</td>
<td>5.64</td>
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</tr>
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<td>-1.90</td>
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<td>5.52</td>
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<td>3.00</td>
<td>-0.19</td>
<td>-5.60</td>
<td>5.23</td>
</tr>
<tr>
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<tr>
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<td>-8.61</td>
<td>3.67</td>
<td>0.27</td>
<td>-5.65</td>
<td>6.18</td>
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</table>

Minimally Adjusted Model = maternal age, maternal BMI
A Priori Model = maternal age, maternal BMI, race/ethnicity, study center, parity, education, smoking status
Reduced Model = maternal age, maternal BMI, race/ethnicity, study center, parity

Table 10: Adjusted mean change in glucose concentration (mg/dL) measured during GLT associated with one unit increase in log pregnancy average phthalates (beta, 95% CI). Units = µg/L for individual phthalates; nmol/mL for sumDEHP.

<table>
<thead>
<tr>
<th>Preg. Avg. Phthalate</th>
<th>Minimal</th>
<th></th>
<th></th>
<th>A Priori</th>
<th></th>
<th></th>
<th>Reduced</th>
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<th></th>
</tr>
</thead>
<tbody>
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<td></td>
<td>beta</td>
<td>95% CI</td>
<td></td>
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</tr>
<tr>
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<td>0.11</td>
<td>-6.83</td>
<td>7.05</td>
<td>1.21</td>
<td>-5.46</td>
<td>7.87</td>
</tr>
<tr>
<td>MEP</td>
<td>2.93</td>
<td>-0.81</td>
<td>6.68</td>
<td>2.51</td>
<td>-1.45</td>
<td>6.47</td>
<td>2.83</td>
<td>-1.05</td>
<td>6.72</td>
</tr>
<tr>
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<td>-3.26</td>
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<td>1.14</td>
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<td>8.19</td>
<td>3.73</td>
<td>-3.15</td>
<td>10.61</td>
</tr>
<tr>
<td>MBZP</td>
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<td>5.65</td>
<td>-0.98</td>
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<td>-0.18</td>
<td>-5.73</td>
<td>5.37</td>
</tr>
<tr>
<td>MCNP</td>
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<td>-11.60</td>
<td>2.74</td>
<td>-4.70</td>
<td>-12.28</td>
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<td>-3.46</td>
<td>-10.86</td>
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<tr>
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<td>1.20</td>
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<td>7.76</td>
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<td>4.98</td>
<td>0.91</td>
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<tr>
<td>MEOPH</td>
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<td>-5.41</td>
<td>7.32</td>
<td>-1.66</td>
<td>-8.30</td>
<td>4.98</td>
<td>0.81</td>
<td>-5.66</td>
<td>7.27</td>
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<tr>
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<td>-1.02</td>
<td>-8.11</td>
<td>6.06</td>
<td>1.91</td>
<td>-4.93</td>
<td>8.76</td>
</tr>
<tr>
<td>sumDEHP</td>
<td>1.75</td>
<td>-4.87</td>
<td>8.38</td>
<td>-1.22</td>
<td>-8.15</td>
<td>5.70</td>
<td>1.74</td>
<td>-4.99</td>
<td>8.47</td>
</tr>
</tbody>
</table>

Minimally Adjusted Model = maternal age, maternal BMI
A Priori Model = maternal age, maternal BMI, race/ethnicity, study center, parity, education, smoking status
Reduced Model = maternal age, maternal BMI, race/ethnicity, study center, parity
**Figure 4:** Analysis of phthalates by quartile with GDM & IGT
APPENDIX: Race-stratified adjusted mean change in glucose concentration (mg/dL) measured during GLT associated with one unit increase in log pregnancy average phthalate exposure. Model adjusted for maternal age, maternal BMI, and parity. (Units = μg/L for individual phthalates, nmol/mL for sumDEHP)

<table>
<thead>
<tr>
<th>Pregnancy Avg Phthalate</th>
<th>White (N=413, MCOP/MCNP n=249)</th>
<th>Black (N=68, MCOP/MNCP n=38)</th>
<th>Asian (N=35, MCOP/MCNP n=21)</th>
<th>Hispanic (N=45, MCOP/MCNP n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIBP</td>
<td>-3.5 (-11.15, 4.16)</td>
<td>3.63 (-24.27, 31.53)</td>
<td>43.36 (21.36, 65.36)</td>
<td>1.87 (-24.63, 28.36)</td>
</tr>
<tr>
<td>MEP</td>
<td>1.74 (-2.82, 6.3)</td>
<td>-0.91 (-17.08, 15.26)</td>
<td>22.01 (6.35, 37.68)</td>
<td>1.32 (-14.23, 16.87)</td>
</tr>
<tr>
<td>MBP</td>
<td>0.8 (-7.35, 8.96)</td>
<td>3.00 (-24.80, 30.80)</td>
<td>26.89 (4.95, 48.84)</td>
<td>-0.51 (-26.51, 25.48)</td>
</tr>
<tr>
<td>MBZP</td>
<td>-0.59 (-7.2, 6.02)</td>
<td>-9.08 (-27.20, 9.03)</td>
<td>18.52 (-0.81, 37.84)</td>
<td>1.05 (-22.76, 24.85)</td>
</tr>
<tr>
<td>MCNP</td>
<td>-5.19 (-14.27, 3.9)</td>
<td>-7.39 (-41.12, 26.33)</td>
<td>3.11 (-23.63, 29.86)</td>
<td>-13.79 (-42.23, 14.65)</td>
</tr>
<tr>
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<td>5.77 (-2.24, 13.77)</td>
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<td>5.01 (-27.80, 37.83)</td>
<td>-10.73 (-35.15, 13.69)</td>
</tr>
<tr>
<td>MCPP</td>
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<td>0.24 (-11.60, 12.08)</td>
<td>10.35 (-8.45, 29.15)</td>
<td>0.34 (-18.50, 19.19)</td>
</tr>
<tr>
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<td>-0.51 (-8.14, 7.12)</td>
<td>0.84 (-20.41, 22.10)</td>
<td>15.91 (-12.84, 44.65)</td>
<td>6.78 (-27.70, 41.26)</td>
</tr>
<tr>
<td>MEOHP</td>
<td>-1.64 (-8.97, 5.69)</td>
<td>6.81 (-14.62, 28.23)</td>
<td>30.27 (5.80, 54.74)</td>
<td>-8.50 (-39.80, 22.80)</td>
</tr>
<tr>
<td>MECPP</td>
<td>-1.42 (-8.94, 6.1)</td>
<td>1.78 (-20.95, 24.50)</td>
<td>29.56 (4.42, 54.70)</td>
<td>-5.03 (-36.13, 26.07)</td>
</tr>
<tr>
<td>sumDEHP</td>
<td>-0.04 (-8.00, 7.92)</td>
<td>1.44 (-20.79, 23.67)</td>
<td>28.48 (4.56, 52.41)</td>
<td>-5.39 (-36.72, 25.93)</td>
</tr>
</tbody>
</table>
References


Auwerx J. PPARgamma, the ultimate thrifty gene. *Diabetologia* 1999; 42(9):1033-49.


