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Candace A. Robledo
The University of Texas Rio Grande Valley, candace.robledo@utrgv.edu

Jennifer D. Peck

Julie A. Stoner

Antonia M. Calafat

Hélène Carabin

See next page for additional authors

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Urinary phthalate metabolite concentrations and blood glucose levels during pregnancy

Candace A. Robledo[a,*], **Jennifer D. Peck**[a], **Julie Stoner**[a], **Antonia M. Calafat**[b], **Hélène Carabin**[a], **Linda Cowan**[a,1], and **Jean R. Goodman**[c]

Candace A. Robledo: candace.robledo@unthsc.edu; Jennifer D. Peck: jennifer-peck@ouhsc.edu; Julie Stoner: julie-stoner@ouhsc.edu; Antonia M. Calafat: acalafat@cdc.gov; Hélène Carabin: helene-carabin@ouhsc.edu; Linda Cowan: linda-cowan@ouhsc.edu; Jean R. Goodman: jrgoodman@lumc.edu

[a]Department of Biostatistics & Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center, 801 NE 13th St., Room 309, Oklahoma City, OK 73104, USA

[b]Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention (CDC), 4770 Buford Hwy, Atlanta, GA 30341, USA

[c]Department of Obstetrics and Gynecology, Maternal-Fetal Medicine, Stritch School of Medicine, Loyola University Health System, 2160 South First Avenue, Building 103, Maywood, IL 60153, USA

Abstract

Purpose—To examine associations between phthalate metabolite urinary concentrations during early pregnancy and blood glucose levels obtained at the time of screening for gestational diabetes mellitus (GDM).

Methods—Upon initiation of prenatal care, women with a mean gestational age of 12.8 weeks were recruited for a study of environmental chemical exposures (n = 110) and provided a spot urinary specimen. Blood glucose concentrations (mg/dl) were obtained from the electronic medical record for those patients who did not experience a pregnancy loss and did not transfer care to another facility prior to glucose screening (n = 72). Urinary concentrations of nine phthalate metabolites and creatinine were measured at the US Centers for Disease Control and Prevention. Associations between tertiles of phthalate metabolites concentrations and blood glucose levels were estimated using linear regression.

Results—Compared to pregnant women in the lowest concentration tertile, women with the highest urinary concentrations (≥3rd tertile) of mono-iso-butyl phthalate (tertile: ≥15.3 μg/l, β = −18.3, 95% CI: −35.4, −1.2) and monobenzyl phthalate (tertile: ≥30.3 μg/l, β = −17.3, 95% CI: −34.1, −0.4) had lower blood glucose levels at the time of GDM screening after adjustment for urinary creatinine and demographic covariates.

*Corresponding author at: 3500 Camp Bowie Blvd, Fort Worth, TX 76107, USA. Tel.: +1 817 735 2619; fax: +1 817 735 2783.

[1]Deceased, December 31, 2013.

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Appendix A. Supplementary data: Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijheh.2015.01.005.

Conclusion—Because maternal glucose levels increase during pregnancy to provide adequate nutrition for fetal growth and development, these findings may have implications for fetal health. However, given the limitations of our study, findings should be interpreted cautiously.

Keywords

Phthalate; Pregnancy; Blood glucose

Introduction

Widespread exposure to endocrine disrupting chemicals such as phthalates has led to growing concerns about potential associations with adverse health effects. Phthalates, the diesters of 1,2-benzenedicarboxylic acid, are a group of synthetic chemicals that are ubiquitous in the environment because of their wide array of industrial applications (Graham, 1973). Phthalates impart plastics with flexibility and are found in many products such as cosmetics, automotive plastics and personal care products. Phthalates may also be found in food packaging materials. High molecular weight (HMW) phthalates (≥250 Da), such as di(2-ethylhexyl) phthalate (DEHP) are primarily used in the manufacture of flexible vinyl and can be found in flooring, medical devices and consumer products. Low molecular weight (LMW) phthalates (<250 Da) comprise metabolites of diethyl phthalate and dibutyl phthalates (DBP). These phthalates are commonly found in personal care products and are used in the making of lacquers, varnishes and in the coatings of medications (Graham, 1973). Dietary intake of contaminated food, dermal contact and inhalation are potential pathways of exposure to phthalates in the general population (Hauser and Calafat, 2005; Schettler, 2006). Upon exposure, phthalates undergo phase I and phase II transformations into their biologically active monoester metabolites which are excreted in urine and can be measured to estimate phthalate exposure in human populations (Frederiksen et al., 2007; Wittassek and Angerer, 2008).

Certain phthalates have anti-androgenic properties and can activate peroxisome proliferator activated receptors (PPAR), properties that have led researchers to suspect that phthalate exposure can impact energy balance and metabolism (Desvergne et al., 2009; Grun and Bloomberg, 2009). Experimental studies in rats have shown that diets supplemented with DEHP can induce glucose intolerance (Martinelli et al., 2006; Mushtaq et al., 1980), decrease blood insulin and increase blood glucose levels (Gayathri et al., 2004). Although limited in number, several cross-sectional studies that include adult men (Stahlhut et al., 2007), adult women (Svensson et al., 2011), and lactating women (Hines et al., 2009) support associations between phthalate metabolite urinary concentrations, insulin resistance and diabetes mellitus. Widespread phthalate exposure and its potential for substantial public health impact have led to studies that describe exposure among vulnerable subgroups such as pregnant women and women of reproductive age (Adibi et al., 2008; Braun et al., 2013; Peck et al., 2010). While there is concern about the endocrine disrupting properties of phthalates, studies have yet to examine whether phthalate exposure during pregnancy is associated with metabolic endpoints such as blood glucose levels. Pregnancy naturally induces an insulin-resistant state in order to direct maternal metabolism to provide enough nutrition to support the growth and development of the fetus. This insulin-resistant state

results in higher circulating levels of glucose. An insufficient pancreatic insulin response to lower blood glucose into the normal range can lead to gestational diabetes mellitus (GDM) (Ryan, 2003).

Given emerging evidence that phthalates may disrupt insulin or glucose action in human populations (Hauser and Calafat, 2005), we examined whether phthalate exposure is associated with blood glucose alterations during pregnancy, a window when both maternal and fetal health are susceptible to changes in glucose action or uptake. We evaluated this hypothesis by measuring urinary concentrations of phthalate metabolites during early pregnancy and examining associations with blood glucose levels obtained at the time of prenatal GDM screening.

Materials and methods

Study population

Pregnant women (n = 110) were recruited for a pilot study of environmental chemical exposures during their first prenatal care visit at the University of Oklahoma Medical Center Women's Clinic between February and June 2008. Women were eligible to participate in the study if their first prenatal care visit occurred before the 22nd week of pregnancy, they were 18 years of age or older, and spoke either English or Spanish. Women were ineligible to participate if at the time of enrollment they presented with a medically threatened pregnancy, multiple gestation, or if they had a history of diabetes (type 1 or type 2), preeclampsia, preterm rupture of membranes, or preterm labor.

For purposes of this analysis, women were excluded if they reported having a history of gestational diabetes (n = 6). Patients were administered a one hour 50 g oral glucose challenge test as part of routine GDM screening (median gestational age at screen: 26.3 weeks; range: 10.3–35.4 weeks). Blood glucose concentrations (mg/dl) were obtained from the electronic medical record. Pregnant women with an elevated screening value of ≥135 mg/dl received further testing (oral glucose tolerance tests) for diagnosis of GDM (Carpenter and Coustan, 1982; Metzger and Coustan, 1998). Our analyses were restricted to 72 pregnant women for whom glucose challenge test results were available in the medical record. Reasons for missing glucose challenge test results included experiencing a pregnancy loss (n = 10), transferring care to another facility (n = 6) or not returning to the clinic for prenatal care (n = 16) prior to GDM screening. The demographic characteristics of women who were excluded from analyses did not statistically differ from women whose data were available (Table 1).

This study was approved by the University of Oklahoma Health Sciences Center Institutional Review Board. The analysis of blinded specimens by the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

Biomarkers of phthalate exposure

Upon enrollment, women provided a urine spot sample to measure biomarkers of exposure to environmental contaminants and cotinine. Sterile urine collection containers were

provided by the CDC laboratory. Following collection, urine specimens were temporarily refrigerated in the clinic, until they could be aliquotted for storage (−20 °C) at the end of each recruitment day. After the enrollment period ended, in 2011, samples were shipped to the CDC laboratory on dry ice.

Urinary concentrations of nine phthalate metabolites and creatinine were measured. The metabolites and their respective parent diesters are listed in Appendix A. Phthalate metabolites were measured using online solid phase extraction coupled with high performance liquid chromatography isotope dilution tandem mass spectrometry as described elsewhere (Kato et al., 2005). Creatinine was measured using an enzymatic reaction on a Roche Hitachi 912 chemistry analyzer (Roche Hitachi, Basel Switzerland).

Limits of detection (LODs) ranged from 0.2 μg/l for monocarboxypropyl phthalate (MCPP) to 1.2 μg/l for mono-2-ethylhexyl phthalate (MEHP). Reported concentrations, including the LOD of monoethyl phthalate (MEP) and monobenzyl phthalate (MBzP), were multiplied by 0.66 and 0.72, respectively, to account for the purity of the analytical standards used (Centers for Disease Control and Prevention National Center for Environmental Health Divsion of Laboratory Sciences, 2012). All but three of the nine phthalate metabolites were detectable in 100% of urine specimens analyzed. MBzP and MCPP were detectable in 98% and 99% of urine specimens, respectively. MEHP, a metabolite of DEHP, was detectable in 78% of urine specimens. For statistical analysis, urinary concentrations of phthalate metabolites below the LOD were converted by dividing the LOD by the square root of two (Hornung and Reed, 1990).

Measurement of urinary cotinine

Using urine samples collected at enrollment, analysis of urinary cotinine was conducted by Lab Stat International in Canada (www.labstat.com) using high resolution capillary-column gas chromatography with split/splitless injection, a fused silica capillary column and a nitrogen-phosphorus detector. The LOD for urinary cotinine was 1.0 μg/l.

Phthalate exposure variables

Phthalate metabolite concentrations, expressed as continuous variables, were not linearly associated with blood glucose concentrations. Therefore, categorical exposure variables were created using tertiles of urinary concentrations of each phthalate metabolite (i.e., <33rd percentile, 33rd to <66th percentile, and ≥66th percentile). Values defining the 33rd and 66th percentiles are displayed in Table 2.

Additional variables were created by summing the urinary concentrations of the metabolites of DEHP (ΣDEHP), of DBP (ΣDBP), and by molecular weight of the parent compound (low: ΣLMW or high: ΣHMW). ΣHMW included MBzP, MCPP and all DEHP metabolites. ΣLMW included MEP, mono-n-butyl phthalate (MnBP) and mono-iso-butyl phthalate (MiBP).

Covariates of interest

Participants completed an enrollment interview that provided information on demographics, reproductive and medical histories and lifestyle factors. Demographic factors included age, race/ethnicity, annual household income and educational level. Self-reported pre-pregnancy height (inches) and weight (pounds) were used to calculate pre-pregnancy body mass index (BMI) in kg/m^2 using the formula weight (lb)/[height (in)]^2 × 703. Participants also reported date of last menstrual period (LMP), and parity. Gestational age at enrollment (weeks) was calculated by subtracting the date of LMP from the date of enrollment and dividing the number of days by seven. Gestational age at screening was calculated by subtracting LMP date from the date of the glucose challenge test. If a woman self-reported she was currently smoking or had urinary cotinine concentrations ≥15 μg/l, she was defined as an active smoker (Benowitz et al., 2009).

Statistical methods

Analyses were conducted using SAS version 9.1.3. Continuous and categorical characteristics of the sample (n = 72) were summarized using descriptive statistics. Geometric mean (GM) concentrations, 95% confidence intervals (CI) and distribution percentiles of unadjusted urinary phthalate metabolite concentrations were calculated.

Multiple linear regression was used to assess the association between tertiles of urinary concentrations of phthalate metabolites (μg/L) and blood glucose levels (mg/dl), while controlling for potential confounders. We included creatinine concentrations as an independent factor in all models to adjust for urinary dilution (Barr et al., 2005). We refer to models adjusted only for urinary creatinine concentrations as crude models.

We examined confounding by comparing estimates of the crude and adjusted model parameters (linear coefficients) for each exposure of interest. Each potential confounding variable was added to the model until all possible combinations of confounding factors were explored. Covariates were retained in the final models if controlling for the factor(s) produced a >10% change in adjusted estimates for phthalate metabolites. Variables evaluated as confounders included Hispanic race/ethnicity, having greater than a High School degree, reporting an annual household income greater than or equal to $20,000, being nulliparous or a current smoker as well as age, pre-pregnancy BMI, gestational age at enrollment and glucose screening. Final models evaluating MiBP were adjusted for race/ethnicity. Models evaluating ΣLMW were adjusted for race/ethnicity and BMI. All other models were adjusted for race/ethnicity and gestational age at enrollment.

Results

The women retained in our analytic cohort were similar in demographic and clinical characteristics when compared to those that were excluded from analyses (Table 1). The majority of pregnant women (n = 72) were younger than 25 years of age, non-Hispanic, had a pre-pregnancy BMI classified as overweight or obese and had less than or equal to a High School education. Lastly, 29% of women were active smokers (Table 1). The highest and lowest urinary metabolite concentrations observed were for MEP (GM = 216.4 μg/L, 95%

CI: 161.9, 289.4) and for MEHP (GM = 3.2 μg/L, 95% CI: 2.5, 4.1) and MCPP (GM = 3.7, 95% CI: 3.1, 4.6), respectively. The GM and distribution percentiles for phthalate urinary concentrations are reported in Table 2.

We present crude and adjusted linear regression models of the association between blood glucose levels and urinary phthalate metabolite concentrations in the 2nd and 3rd tertiles as compared with the 1st tertile in Table 3. Pregnant women with urinary concentrations of MiBP (β = −18.30 95% CI, −35.41 to −1.19) and MBzP (β = −17.26 95% CI, −34.12 to −0.40) in the highest concentration tertile had mean blood glucose levels approximately 18 mg/dl lower when compared to those in the 1st tertile after adjustment for urinary creatinine, race/ethnicity, and gestational age at enrollment (for MBzP).

Discussion

Certain phthalates can activate PPARs (Desvergne et al., 2009; Grun and Bloomberg, 2009; Hurst and Waxman, 2003), receptors known to influence lipid and glucose homeostasis. However, our findings showing inverse associations between urinary concentrations of MiBP and MBzP and blood glucose levels during pregnancy do not suggest that phthalate exposure is associated with insulin resistance and subsequently higher blood glucose levels. Although not statistically significant, associations with blood glucose levels were in the same direction for all but two of the remaining urinary metabolites examined.

Our findings for MBzP are consistent with a cross-sectional study examining the relationship between phthalate exposure and the prevalence of diabetes in 255 non-pregnant women living in the northern states of Mexico (Baja California Norte, Chihuahua, Coahuila, Durango, Nuevo León, Sonora, and Tamaulipas) (Svensson et al., 2011). In that study, the odds of self-reported diabetes (type 1 or 2) were lower for each 1-standard deviation (SD) unit increase in log creatinine-adjusted urinary concentrations of MBzP (OR = 0.73, 95% CI 0.55, 0.97), but not for MiBP (OR = 0.94, 95% CI 0.62, 1.43). In contrast to our findings, the odds of self-reported diabetes were higher with increasing levels of urinary concentrations for individual DEHP metabolites (except MEHP) and for ΣDEHP (OR = 1.66 (1.01–2.73). These discrepencies may be due to differences in characteristics between source populations.

There are several methodological considerations that need to be taken into account when interpreting our results. The pilot and exploratory nature of this study did not allow us to explore the associations between maternal urinary phthalate levels and health and/or developmental outcomes. While the majority of participants were screened between 24 and 28 weeks gestation as is typically recommended in the US, eight (11%) and 23 women (32%) women were screened at gestational ages before 24 weeks and after 28 weeks, respectively. Pregnant women are naturally insulin resistant, which inherently affects glucose levels (Ryan, 2003) and hence, limits the generalizability of our findings. Also, since metabolic changes increase glucose levels during pregnancy to support fetal growth, our findings may have more implications for fetal health as opposed to maternal health. We assessed phthalate exposure approximately 15 weeks (range: 3.4–25.1 weeks) before blood glucose levels were obtained. It is possible that phthalate exposure at that time was outside

the etiologically relevant window for exposure during pregnancy. Alternatively, the variability in phthalate metabolite concentrations may have hindered our ability to accurately examine the associations of interest. In addition, while their characteristics did not statistically differ from our study sample, data for a large proportion of women were unavailable (n = 38 or 34%). Our small sample size (n = 72) limited precision, statistical power and our ability to assess confounding. We also tested a large number of associations and our statistically significant findings could be attributed to chance. However, the fact that associations between blood glucose levels and phthalate metabolites were in the same (inverse) direction (except for MEHP and MEP), suggests that our results are fairly robust.

Phthalate exposure in this study was categorized from a single spot urine sample collected approximately 15 weeks before the screening test. Thus, exposure misclassification is a concern given that phthalates are metabolized quickly in humans, with half-lives less than 24 h (Frederiksen et al., 2007), and exposures are most likely episodic. Evidence from studies examining the temporal variability of phthalate metabolites suggests that measurements obtained from a single urine sample are relatively predictive of exposure over a limited period of time (1–3 months) (Adibi et al., 2008; Cantonwine et al., 2014; Hauser and Calafat, 2005; Hoppin et al., 2002; Irvin et al., 2010; Peck et al., 2010). This is attributed to the fact that exposure to phthalates via consumer products, such as through the use of personal care products, may be recurrent. In a study of phthalate variability during pregnancy (Braun et al., 2012), Braun et al. reported the top tertile of trimester-specific MBP, MBzP and MEP concentrations had moderate sensitivity (0.62–0.81) and specificity (0.80–0.90) for classifying the highest exposure tertile based on an average of three samples collected throughout pregnancy. However, Braun et al. also demonstrated that variability was biomarker specific. The authors suggest that a single spot urine sample may be adequate to classify MBP and MEP concentrations during pregnancy but more than one spot urine sample may be necessary for MBzP and the metabolites of DEHP. While we learn a great deal regarding the variability of phthalate metabolite concentrations during pregnancy from Braun et al., the study population was of higher socioeconomic status, recruited before pregnancy as they sought infertility treatment and were told that the study was examining the health effects of phthalates and other environmental chemicals. The authors note that these factors may have hindered the generalizability of their results and impacted participants' behavior before and during pregnancy; accounting for some of the variability in phthalate metabolite concentrations observed.

Another study showed better reproducibility for urinary MBzP concentrations measured in 2–3 urine samples over a 6–8 week period among minority women living in New York City than for other metabolites (mean interclass correlation coefficient = 0.64) (Adibi et al., 2008). Of further relevance to categorical measures, when studies of phthalate variability defined exposure tertiles using a single urine measurement and then calculated the geometric mean concentrations of repeated samples (3–4 urine samples) from the individuals within each tertile, the geometric mean values were consistently lowest for those in the bottom tertile and highest for those in the top tertile (Peck et al., 2010; Teitelbaum et al., 2008). Thus, the use of a single urine sample to assess exposure in this cohort is expected to

provide a reasonable indication of low, medium or high average phthalate exposure, but the measure is not without error.

Despite these limitations, this study was the first to examine the association between blood glucose levels and phthalate exposure in a sample of pregnant women. Large prospective studies collecting several spot urine samples during pregnancy would provide useful information to examine repeated measures of phthalate metabolite concentrations throughout pregnancy in relation to metabolic endpoints, as well as the effect of various lag times. Indeed, by investigating the etiologically relevant window of exposure before or during pregnancy and taking intra-individual variability into account, such studies would contribute to improved approaches for exposure assessment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Abbreviations

BzBP	benzylbutyl phthalate
DEHP	di-2-ethylhexyl phthalate
DBP	dibutyl phthalates
DOP	di-n-octyl phthalate
GDM	gestational diabetes mellitus
MBzP	monobenzyl phthalate
MCPP	mono-3-carboxypropyl phthalate
MECPP	mono-2-ethyl-5-carboxypentyl phthalate
MEHP	mono-2-ethylhexyl phthalate
MEHHP	mono-2-ethyl-5-hydroxyhexyl phthalate
MEOHP	mono-2-ethyl-5-oxohexyl phthalate
MiBP	mono-iso-butyl phthalate
MEP	monoethyl phthalate
MnBP	mono-n-butyl phthalate
NHANES	National Health and Nutrition Examination Survey

Table 1

Demographic and clinical characteristics of obstetric cohort by inclusion status, Oklahoma, 2008.

Characteristic	Analytic cohort (n = 72)		Excluded[b] (n=38)	
	n	%	*n*	%
Maternal race/ethnicity				
Hispanic	17	24	5	13
Non-Hispanic White	21	29	13	34
Non-Hispanic Black	27	37	16	42
Other	7	10	4	11
Education level				
≤High school	47	65	19	50
>High school	25	35	19	50
Annual household income				
≤ 19,999	53	74	29	76
≥$20,000	19	26	9	24
Parity				
Nulliparous	19	26	8	21
Multiparous	53	74	30	79
Current smoker				
Yes	21	29	12	32
No	51	71	26	68
Elevated GDM screen				
Yes (≥135mg/dl)	15	21	-	-
	Median (range)			
Maternal age (years)	22 (18,38)		24	(18,38)
Prepregnancy body mass index (kg/m^2)	26 (16, 47)		26	(16, 43)
Gestational age (weeks)				
Enrollment	12.8 (4.6, 22.0)		9.0	(4.0, 22.0)
At GDM[a] screen	26.3 (10.3,35.4)		-	-
Weeks from enrollment to GDM[a] screen	14.8 (3.4, 25.1)		-	-

[a] GDM, gestational diabetes mellitus.

[b] Characteristics between excluded study participants and those retained in the analytical cohort did not differ statistically. *P*-values for chi-square (categorical) or Wilcoxon rank sum tests (continuous) were not <0.05.

Table 2

Geometric means (GM), 95% confidence intervals (CI) and percentiles of phthalate metabolite urinary concentrations (μg/l) for the study population, Oklahoma, 2008 (*n* = 72).

Phthalate metabolite	Percentile						
	GM	95% CI	25th	33rd	50th	66th	75th
MnBP	30.38	24.36–37.89	16.35	22.20	29.25	43.30	56.55
MiBP	11.22	9.04–13.93	6.65	8.70	11.30	15.30	18.15
MEHP	3.24	2.54–4.13	1.40	2.00	3.55	5.20	7.75
MEHHP	19.88	14.80–26.71	10.35	12.60	18.70	29.60	40.85
MEOHP	13.97	10.57–18.47	7.70	8.80	12.90	20.40	24.20
MECPP	33.28	25.02–44.27	16.90	20.90	31.70	47.10	54.20
MCPP	3.73	3.06–4.55	2.35	2.90	3.80	5.70	6.60
MEP	216.42	161.86–289.37	92.07	112.20	205.92	343.20	525.36
MBzP	18.23	13.24–25.10	8.50	10.01	16.34	30.31	36.79
ΣDEHP	188.07	78.89–298.89	36.82	45.70	65.95	101.30	126.00
ΣDBP	63.53	49.06–78.01	23.05	30.60	43.10	63.70	76.65
ΣLMW	589.07	278.12–900.01	148.18	166.70	245.75	433.26	614.06
ΣHMW	251.69	132.83–370.56	59.48	65.14	95.21	138.30	174.32

Table 3

Linear regression models assessing the association between blood glucose levels (mg/dl) and tertiles of urinary concentrations of phthalate metabolites (μg/L), Oklahoma, 2008 (n = 72).

Phthalate metabolite	Model											
	Crude[b]						Adjusted[c]					
	Tertile 2[a]			Tertile 3[a]			Tertile 2[a]			Tertile 3[a]		
	β	95% CI	*P*-value	β	95% CI	*P*-value	β	95% CI	*P*-value	β	95% CI	*P*-value
DBP												
MnBP	1.06	(−14.33, 16.45)	0.89	−13.11	(−31.15, 4.94)	0.15	0.11	(−14.71, 14.93)	0.99	−15.61	(−32.99, 1.76)	0.08
MiBP	2.80	(−11.79, 17.38)	0.70	−14.40	(−32.27, 3.47)	0.11	−2.01	(−16.18, 12.17)	0.78	−18.30	(−35.41, −1.19)	0.04
DEHP												
MEHP	2.17	(−12.94, 17.28)	0.78	1.23	(−14.02, 16.47)	0.87	7.73	(−6.97, 22.43)	0.30	9.07	(−6.30, 24.45)	0.24
MEOHP	1.83	(−12.52, 16.17)	0.80	−8.94	(−25.71, 7.83)	0.29	2.59	(−11.28, 16.46)	0.71	−9.65	(−27.19, 7.89)	0.28
MEHHP	12.32	(−1.45, 26.10)	0.08	−5.47	(−21.25, 10.31)	0.49	11.06	(−2.35, 24.47)	0.10	−5.55	(−21.77, 10.66)	0.50
MECPP	−2.59	(−17.56, 12.38)	0.73	−4.30	(−20.33, 11.74)	0.59	−2.95	(−18.06, 12.17)	0.70	−3.26	(−20.38, 13.86)	0.70
MEP	−0.17	(−14.28, 13.94)	0.98	−6.25	(−21.08, 8.58)	0.40	4.45	(−9.30, 18.19)	0.52	0.18	(−14.57, 14.94)	0.98
MBzP	−1.48	(−16.18, 13.21)	0.84	−9.84	(−27.47, 7.79)	0.27	−0.82	(−14.37, 12.73)	0.90	−17.26	(−34.12, −0.40)	0.04
MCPP	3.16	(−11.35, 17.67)	0.67	0.17	(−16.31, 16.65)	0.98	0.72	(−13.23, 14.68)	0.92	−1.19	(−17.09, 14.72)	0.88
Sum variables												
ΣDEHP	3.82	(−10.34, 17.98)	0.59	−10.49	(−26.79, 5.81)	0.20	3.82	(−10.22, 17.86)	0.59	−9.97	(−27.11, 7.17)	0.25
ΣDBP	−5.65	(−21.01, 9.70)	0.47	−8.54	(−26.09, 9.01)	0.33	−7.88	(−22.52, 6.76)	0.29	−11.73	(−28.57, 5.12)	0.17
ΣLMW	−1.39	(−15.61, 12.83)	0.85	−6.40	(−22.06, 9.26)	0.42	−0.90	(−14.58, 12.79)	0.90	−3.29	(−19.34, 12.77)	0.68
ΣHMW	1.76	(−12.15, 15.66)	0.80	−12.98	(−29.42, 3.45)	0.12	−0.27	(−13.64, 13.11)	0.97	−14.23	(−30.71, 2.25)	0.09

[a] The referent group is the 1st tertile.

[b] Models adjusted for urinary creatinine.

[c] All models were adjusted for urinary creatinine. MnBP, MEHP, MEOHP, MEHHP, MECPP, MEP, MBzP, MCPP, ΣDEHP, ΣDBP and ΣHMW models were adjusted for gestational age at enrollment and race/ethnicity. MiBP model was only adjusted for race/ethnicity. ΣLMW model adjusted for race/ethnicity and BMI.