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Urinary phthalate metabolite and bisphenol A associations with ultrasound and delivery indices of fetal growth

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Abstract

Growth of the fetus is highly sensitive to environmental perturbations, and disruption can lead to problems in pregnancy as well as later in life. This study investigates the relationship between maternal exposure to common plasticizers in pregnancy and fetal growth. Participants from a longitudinal birth cohort in Boston were recruited early in gestation and followed until delivery. Urine samples were collected at up to four time points and analyzed for concentrations of phthalate metabolites and bisphenol A (BPA). Ultrasound scans were performed at four time points during pregnancy for estimation of growth parameters, and birthweight was recorded at delivery. Growth measures were standardized to a larger population. For the present analysis we examined cross-sectional and repeated measures associations between exposure biomarkers and growth estimates in 482 non-anomalous singleton pregnancies. Cross-sectional associations between urinary phthalate metabolites or BPA and growth indices were imprecise. However, in repeated measures models, we observed significant inverse associations between di-2-ethylhexyl phthalate (DEHP) metabolites and estimated or actual fetal weight. An interquartile range increase in summed DEHP metabolites was associated with a 0.13 standard deviation decrease in estimated or actual fetal weight (95% confidence interval=−0.23, −0.03). Associations were consistent across different growth parameters (e.g., head circumference, femur length), and by fetal sex. No consistent associations were observed for other phthalate metabolites or BPA. Maternal exposure to DEHP during pregnancy was associated with decreased fetal growth, which could have repercussive effects.

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Keywords

Endocrine disruptors; fetal growth; birthweight; growth restriction; plasticizers; plastics

1. Introduction

Reduced fetal growth is a well-recognized pregnancy endpoint of concern. While definitions and origins may differ, low birthweight, small for gestational age, and intrauterine growth restriction are all associated with increased risk of neonatal mortality and morbidity and have been linked to adverse health effects later in life.^{1, 2} The process of fetal development is highly sensitive to perturbations from environmental toxicant exposures.³ Maternal behaviors such as smoking are clearly linked to reduced birthweight,⁴ and evidence also strongly suggests that some classic environmental exposures, such as lead and persistent organic pesticides, are associated with reductions in fetal growth.³ Of emerging concern is the impact of non-persistent pollutants with widespread exposure, including a variety of chemicals found in plastics. Phthalate diesters and bisphenol-A (BPA) are used widely in these and other applications, and leach or are aerosolized into adjacent matrices which make for ready human exposure through ingestion or inhalation.⁵ Additionally, phthalates and occasionally BPA found in personal care products can be absorbed dermally. Despite rapid metabolism in the human body, contact is so frequent that phthalate metabolites and BPA in urine from pregnant mothers are detected almost ubiquitously in populations worldwide.⁶⁻⁸

A number of studies have examined the relationship between biomarkers of exposure to phthalates and BPA and fetal growth, with conflicting results.⁹⁻¹⁴ However, biologic plausibility exists for an impact of these chemicals on physical development. Phthalates and BPA have been shown to cause oxidative stress, hormonal disturbances, and epigenetic modifications that all could have deleterious effects on growth.¹⁵⁻¹⁹ Inconsistencies in previous studies of phthalate or BPA exposure and fetal growth may be due to the fact that the majority model associations with birthweight or other measures at delivery only.^{3, 20-23} Longitudinal studies with repeated ultrasound measurements taken during gestation have greater power to detect effects.²⁴ Additionally, specific to these non-persistent chemicals, most studies utilize single spot urine concentrations of phthalate metabolite and BPA as indices of exposure;^{10, 20, 22, 25, 26} however, due to their short half-lives in the human body, measurements may not be representative of exposure over the course of pregnancy.²⁷ In the present analysis we investigated longitudinal associations between maternal exposure to phthalates and BPA in pregnancy and fetal growth in women from a prospective birth cohort. Notably, this study leverages a robust design including longitudinal exposure biomarker (up to 4 per subject) and growth assessments (up to 4 per subject).

2. Methods

2.1. Study population

Pregnant women were recruited in Boston as part of the LIFECODES birth cohort study. Individuals were eligible for participation if they were less than 15 weeks pregnant, were carrying a singleton non-anomalous fetus, and were planning to deliver at Brigham and

Women's Hospital. At the initial study visit subjects provided informed consent and completed questionnaires detailing demographic information, personal and family health histories, and characteristics of pregnancy. Gestational age was calculated based on protocol established by the American College of Obstetricians and Gynecologists.²⁸ Spot urine samples were collected at four time points (visits 1-4) during pregnancy, at median 10, 18, 26, and 35 weeks gestation, in polypropylene cups. Approximately 65% of urine samples were obtained in the morning (8am to 1pm) and the other 35% were collected in the afternoon or evening (after 1pm). At delivery (visit 5), birthweight was recorded. We selected 130 cases of singleton preterm birth, defined as delivery prior to 37 weeks completed gestation, as well as 352 random singleton term controls from the participants recruited between 2006 and 2008 to examine the relationship between urinary phthalate metabolites and BPA and preterm birth. Institutional Review Board approval for the case-control study was obtained from the University of Michigan and from Brigham and Women's Hospital.

2.2. Fetal growth measurements

At the visit 1 ultrasound fetuses received a crown-rump length as part of the screen for aneuploidy. At visit 2 ultrasound scans were routinely performed for all study subjects for standard clinical assessments of fetal morphology. At visits 3 and 4, ultrasounds were not part of the study protocol. However, additional ultrasounds scans were also performed in cases where there was suspected abnormality of pregnancy (e.g., growth restriction, gestational diabetes, etc.) or at the patient's request. For all ultrasounds, measurements were abstracted from scans by board certified sonologists in the departments of Radiology and Maternal-Fetal Medicine. We used the following measurements for this analysis: head circumference (HC); abdominal circumference (AC); and femur length (FL). Additionally, measurements were combined using the following formula of Hadlock to create estimates of fetal weight (EFW) at visits 2-4.²⁹

In order to combine growth measurements across different time points during pregnancy for longitudinal models, we created z-scores of each ultrasound measurement. We used mean and standard deviation (SD) ultrasound measurements available on all non-anomalous singleton pregnancies with delivery at Brigham and Women's Hospital from 2006-2012 (N=18,904) as our standard.³⁰

2.3. Exposure assessment

Urine samples collected during pregnancy were analyzed for a panel of nine phthalate metabolites as well as total urinary BPA by NSF International (Ann Arbor, MI, USA).³¹ Briefly, urine samples undergo enzymatic deconjugation of glucuronidated metabolites, solid phase extraction, liquid chromatographic separation, and tandem mass spectrometry.³¹ Concentrations below the limit of detection (LOD) were kept as is if reported, and otherwise were replaced with the LOD divided by the square root of 2. Urinary specific gravity was measured using a digital handheld refractometer (Atago Company Ltd., Tokyo, Japan) as an indicator of urine dilution. In addition to individual phthalate metabolites, we also examined a molar sum of the di-2-ethyl- hexyl (DEHP) metabolites, including mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5- hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-

oxohexyl phthalate (MEOHP), and mono-2-ethyl-5-carboxypentyl phthalate (MECPP). For modeling purposes, we calculated cumulative pregnancy exposure to phthalate metabolites or BPA defined as the geometric average of urinary biomarker concentrations collected up until the time of ultrasound for visits 1-4. Cumulative exposure at visit 5 (delivery) was identical to the exposure metric from visit 4, since urine samples were not collected for analysis at birth.

2.4. Statistical analysis

All analyses were performed in R version 3.2.1. All analyses using the combined case-control sample were weighted using inverse probability weights indicative of the probability of preterm birth case and control selection from the base cohort population.³² Thus, the results do not over represent associations within cases of preterm birth. We examined distributions of demographic characteristics within the study population using these weights. We also calculated percentiles of specific gravity corrected²⁷ urinary phthalate metabolite measurements to present distributions.

To examine relationships between exposure and growth, we first used a cross-sectional approach to estimate associations between cumulative exposure at visit 5 (delivery) and birthweight alone. Crude models were adjusted for cumulative urinary specific gravity as well as gestational age at delivery. The fully adjusted model (Model 2) additionally included covariates that were associated with both exposures and outcome, and that impacted effect estimates by greater than 10%. These included maternal age, race/ethnicity (White, African American, Other), visit 1 body mass index (BMI; continuous), health insurance provider (private, public), and infant gender. Finally, we examined adjusted models stratified by infant sex as previous studies have identified sex differences in these relationships (Models 3 and 4 for males and females, respectively).¹⁴ Differences in coefficient estimates from male vs. female models were tested using a z statistic. We additionally created cross-sectional models with z-scored growth measures from visits 2-4 with the corresponding cumulative exposure metrics.

Our second modeling approach was to create linear mixed effects (LME) models of the relationship between repeated measures of cumulative exposure and each indicator of fetal growth using the R nlme package.³³ As with cross-sectional models, these were created in crude, adjusted, and sex-stratified manners. For LME models we only included fetal growth measurements taken at visits 3-5, as there was poor variation in fetal growth measures taken at visit 1 and 2 in our dataset (see Fig. 1), which is consistent with observations in other studies.^{9, 34} However, we additionally created models containing measures from visit 2 for comparison. Effect estimates for all analyses were presented as SD change in growth measures in association with an interquartile range (IQR) increase in visit 4 cumulative and specific gravity corrected phthalate metabolite or BPA concentrations.

3. Results

Demographic characteristics are presented in Table 1 for the 482 subjects in this study population. As previously reported, the participants were primarily White (59%), had private health insurance providers (81%), indicating high socioeconomic status, and many were

college graduates (41%).³⁵ With weightings, the populations had a preterm delivery rate that was similar to that observed in the general US population (12%). Concentrations of cumulative phthalate metabolite and BPA concentrations from urine samples are shown in Table 2, along with median (25th, 75th percentiles) gestational age at sample collection. DEHP metabolite concentrations, particularly MEHP, were higher in our population compared to those observed in other studies of pregnant women. This may be due to higher exposure levels in the Boston area, as noted in a previous study of phthalates in pregnancy,³⁶ or due to laboratory differences.²⁷ Concentrations of other phthalate metabolites and BPA were similar to those observed in other US studies.^{22, 36} We previously published intraclass correlation coefficients for urinary phthalate metabolites and BPA in this study population and observed similar variability over pregnancy to what has been observed in other studies.^{27, 36, 37} Namely, DEHP metabolites showed greater variability over pregnancy compared to other urinary phthalate metabolites, and BPA was much less reliable than other exposure measurements.^{27, 37}

Raw (i.e., non z-scored) distributions of HC, AC, FL, and EFW/birthweight by gestational age are displayed in Fig. 1. The number of measurements available at visits 3 (n=225) and 4 (n=246 for HC, n=249 for other metrics) were fewer than those available from visit 2 (n=427 for HC, AC, and EFW; n=428 for FL) or visit 5 (n=482).

Table 1 also shows associations between maternal or fetal characteristics and growth. We observed significantly lower birthweight z-scores for infants born to African American compared to White subjects, to mothers who had a visit 1 BMI <25 kg/m² compared to those with a BMI 25-30 kg/m² or 30+ kg/m², to mothers who used tobacco during pregnancy or who were nulliparous, and for male vs. female fetuses. Using LME to look at the association between demographics and repeated z-scores of weight at visits 3-5, effect estimates were similar in direction but generally larger in magnitude with narrower confidence intervals (CIs) compared to those from the cross-sectional analysis.

Table 3 displays cross-sectional associations between cumulative exposures (geometric averages from visits 1-4) and birthweight z-scores from the three different modeling approaches. In Model 1, associations were consistently negative but not statistically significant, with the exception of the association with mono-*n*-butyl phthalate (MBP; SD with IQR increase=-0.12, 95% CI= -0.22, -0.02). (Associations were similar in a crude model restricted to subjects with a complete set of covariates, N=466, data not shown.) In the fully adjusted model (Model 2), associations were again primarily inverse but imprecise. Finally, when adjusted models were stratified by infant sex, no associations were statistically significant but effect estimates were consistently inverse and largest in magnitude between DEHP metabolites, MBP, and BPA and birthweight z-scores in male infants. Cross sectional associations between cumulative exposure and z-scores of HC, AC, FL, and EFW from visits 2-4 are shown in Supplemental Table 1. Few associations were observed at visit 2, but associations at visits 3 and 4 were consistently negative between DEHP metabolites and growth indices.

Next we utilized LME models to examine associations between repeated z-scores of HC, AC, FL, and EFW (visits 3-4) or birthweight (visit 5) and cumulative exposures. Adjusted

associations are presented in Table 4. MECP and DEHP were significantly associated with decreases in each of these growth metrics with similar effect sizes. For example, for DEHP, the effect sizes were as follows for each outcome measure: HC ($SD = -0.11$, 95% $CI = -0.21, 0.001$); AC ($SD = -0.14$, 95% $CI = -0.26, -0.03$); FL ($SD = -0.13$, 95% $CI = -0.25, -0.01$); and estimated or actual fetal weight ($SD = -0.13$, 95% $CI = -0.23, -0.03$). No associations were detected between other phthalate metabolites or BPA and fetal growth parameters with the exception of mono-benzyl phthalate (MBzP), which was inversely associated with HC only. For comparison, associations utilizing visits 2-5 are displayed in Supplemental Table 2. No significant associations were observed when the second visit was included in LME models. Finally, we observed similar effect estimates in male and female fetuses in sex-stratified models (Supplemental Tables 3 and 4, respectively).

4. Discussion

When we applied a longitudinal analysis to examine the relationship between average exposure measures and growth we observed inverse associations between head and abdominal circumferences, femur length, and estimated fetal weight and DEHP metabolites. Within the DEHP metabolites, associations were strongest for MECP. An IQR increase in DEHP was associated with a 0.13 SD decrease in estimated fetal weight in reference to the standard population. No consistent associations were observed for other phthalate metabolites or for BPA. Cross-sectional associations between exposure biomarkers and ultrasound or delivery indices of weight were similar in direction but lacked precision. Additionally, we detected no differences in effect by sex of the fetus in linear mixed models, although in the cross-sectional analysis of average exposure over pregnancy in relation to birthweight effect estimates were greater in magnitude (i.e., more negative) for male compared to female infants.

A number of studies have investigated the relationship between maternal phthalate exposure during pregnancy and fetal growth, but the preponderance of this data utilizes birthweight or other measures at delivery alone.^{13, 20} Furthermore, the majority of these studies use single spot urine samples to approximate exposure,^{10, 22} or measurement in other matrices during pregnancy (e.g., maternal serum)³⁸ or at delivery (e.g., cord blood, meconium).²³ Phthalate metabolites measured in blood have even shorter half-lives compared to urinary biomarkers, and in cases where phthalate diesters (rather than metabolites) are measured in these matrices there is increased probability of sample contamination at the collection, processing, or measurement steps.^{39, 40} Additionally, the majority of these studies had sample sizes of ~200 or smaller.^{14, 20, 41-43} These previous investigations have had mixed, but largely null, results.^{10, 13, 14, 20, 23, 38, 41-46} The largest studies (n~300-400) reported null associations between phthalate metabolite measurements from spot urine samples collected during pregnancy and birthweight, length, and head circumference.^{10, 13}

Two studies utilized repeated ultrasound measures in combination with birthweight to examine the associations between phthalate exposure during pregnancy and fetal growth. One examining maternal occupational exposure via job exposure matrix found an inverse association with fetal growth (n=4680).⁴⁷ Another study in the INMA-Sabadell Spanish cohort included repeated ultrasound measures from three time points during pregnancy (12,

20, and 34 weeks gestation) as well as at delivery, in combination with repeated (2) measures of urinary phthalate metabolites during pregnancy (n=390 for phthalate analysis).⁹ Associations in that study were largely null.⁹ A notable difference between that analysis and the one presented here is that we combined z-scored growth measures to perform a repeated measures analysis, whereas the Spanish group performed cross-sectional analyses or modeled the relationship with change in SD scores between the first and second visits.⁹ Similarly, we detected few and unstable associations in our cross sectional analyses, but we observed significant associations between DEHP metabolites and decreased fetal weight in repeated measures models. Another major difference between these studies is that our primary results come from mothers who received clinically indicated ultrasounds later in pregnancy, which was not part of our study protocol. Thus, these findings may reflect relationships that are associated with the underlying clinical indications for the ordered ultrasound exams, and may not be detectable in a healthier population.

A number of studies have also investigated associations between BPA exposure and fetal growth, but again most relied solely on birthweight or other measures at delivery. The evidence here is also conflicting.^{10, 12, 13, 25, 48-50} Again, this may be due to suboptimal exposure assessment approaches. Two studies performed longitudinal analyses examining repeated urinary BPA concentrations as well as ultrasound scans to estimate the association with fetal growth.^{9, 11} In the INMA-Sabadell cohort described above, no associations between growth indices and BPA were observed.⁹ However, in the Generation R study, significant inverse associations were observed between urinary BPA measurements and fetal growth, with clearly improved power to detect effects with additional (up to three per subject) exposure estimates.¹¹ In our analysis we observed no associations between BPA and growth indices.

The greatest strength of our study was having 4 repeated measures of urinary phthalate metabolites and BPA across pregnancy, the largest number of measures in any study of exposure and fetal growth to date. Additionally, our study benefited from repeated ultrasound measurements taken across pregnancy, the latter of which we were able to standardize to those taken from a large population of women in Boston. A particular strength of this study was our availability of repeated ultrasound measures from later (>22 weeks) in pregnancy. Other studies in this vein have noted that low variation in ultrasound measures taken early in gestation may be the root of inability to detect effects.^{9, 34, 51} Our ability to detect effects in this study may alternatively suggest that the mechanism by which DEHP metabolites impact pregnancy is specific to a susceptibility later in gestation. Future investigation of this question should be pursued in animal models and rigorous human observational studies.

Our study was limited by fewer measurements of fetal growth available from later study time points. This was due to the fact that ultrasound measurements were not planned as part of the original study. Importantly, receiving an ultrasound later in pregnancy was not associated with exposure or covariates in our data, so that this limitation would not differentially bias our findings (data not shown). However, the generalizability of our results may extend only to higher risk pregnancies in which subjects are asked by their physicians to receive additional ultrasounds. Models stratified by fetal sex were also limited in terms of

sample size, and our conclusions regarding minimal sex differences in effects should be verified in larger populations. Finally, we performed a large number of comparisons in the present analysis and some of the associations observed may have been due to chance.

5. Conclusions

We observed associations between maternal exposure to DEHP metabolites and decreased fetal growth during pregnancy. This is the first study to detect such associations in a population with repeated measures of urinary phthalate metabolite measurements as well as combined ultrasound and birth indices of growth. Due to our study design, these results may be specific to pregnancies for which ultrasound examinations are clinically indicated later in pregnancy, but this limitation in generalizability does not make the findings less impactful. Preventing causes of fetal growth retardation in this subset could make substantial contributions to preventing the negative consequences of this outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

BPA	Bisphenol A
MEHP	mono-2-ethylhexyl phthalate
EHHP	mono-2-ethyl-5-hydroxyhexyl phthalate
EOHP	mono-2-ethyl-5-oxohexyl phthalate
ECPP	mono-2-ethyl-5- carboxypentyl phthalate
MBzP	mono-benzyl phthalate
MBP	mono- <i>n</i> -butyl phthalat
MiBP	mono-iso-butyl phthalate
MEP	mono-ethyl phthalat
MCPP	mono-3-carboxypropyl phthalate
HC	head circumferen
AC	abdominal circumferen

FL	femur leng
EFW	estimated fetal weigh
SD	standard deviati
LOD	limit of detectio
BMI	body mass inde
LME	liner mixed effect
IQR	interquartile rang
CI	confidence interval

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Highlights

- Exposure to phthalates and BPA in pregnancy may impact development of the fetus.
- We measured exposure biomarkers at 4 visits during gestation on 482 women.
- We used ultrasound scans from pregnancy and birthweight to examine fetal growth.
- Urinary di-2-ethylhexyl phthalate metabolites were associated with reduced growth.
- This is the first study with a robust repeated measures design to detect this relationship.

Fig. 1.

Fetal growth parameters in association with gestational age (in weeks) at measurement as well as respective visit, shown in red (visit 2), blue (visit 3), green (visit 4), and black (visit 5 or delivery) with median (range) of gestational age at each visit shown in the legend.

Table 1

Demographic characteristics of study population and standard deviation change in z-score (95% confidence interval, CI) of birthweight or repeated measures of weight from study visits 3-5^a in demographic group compared to reference.

		N (weighted %)	Association with weight z- score (visit 5 only) ^b			Association with weight z- score (visits 3-5) ^c		
			SD	(95% CI)	p	SD	(95% CI)	p
Race/ethnicity	White	282 (59)						
	African American	77 (16)	−0.40	(−0.66, −0.14)	<0.01	−0.49	(−0.72, −0.26)	<0.01
	Other	123 (26)	−0.06	(−0.28, 0.15)	0.58	−0.16	(−0.35, 0.04)	0.12
BMI category	< 25 kg/m ²	250 (53)						
	25-30 kg/m ²	126 (27)	0.27	(0.06, 0.49)	0.01	0.22	(0.02, 0.42)	0.03
	>30 kg/m ²	102 (20)	0.30	(0.06, 0.54)	0.02	0.27	(0.06, 0.48)	0.01
Health insurance	Private	385 (81)						
	Public	85 (19)	−0.24	(−0.48, −0.003)	0.048	−0.41	(−0.63, −0.20)	<0.01
Education	High school	68 (14)						
	Technical school	77 (16)	−0.16	(−0.50, 0.17)	0.35	0.04	(−0.25, 0.34)	0.78
	Junior/some college	139 (30)	0.17	(−0.13, 0.46)	0.28	0.25	(−0.01, 0.52)	0.06
	College graduate	187 (41)	0.17	(−0.11, 0.46)	0.23	0.32	(0.07, 0.58)	0.01
Gender	Male	214 (45)						
	Female	268 (55)	0.29	(0.10, 0.47)	<0.01	0.25	(0.09, 0.42)	<0.01
Preterm	No	352 (88)						
	Yes	130 (12)	0.14	(−0.26, 0.55)	0.49	−0.05	(−0.23, 0.13)	0.572
IVF	No	450 (94)						
	Yes	32 (6)	−0.03	(−0.41, 0.35)	0.88	−0.06	(−0.38, 0.27)	0.73
Parity	Nulliparous	215 (45)						
	Parous	267 (55)	0.38	(0.20, 0.56)	<0.01	0.26	(0.09, 0.42)	<0.01
Tobacco use	No	445 (94)						
	Yes	31 (6)	−0.42	(−0.80, −0.03)	0.03	−0.26	(−0.60, 0.08)	0.13
Alcohol use	No	452 (95)						
	Yes	20 (5)	0.17	(−0.26, 0.60)	0.44	0.25	(−0.20, 0.69)	0.28

BMI, body mass index; IVF, in vitro fertilization.

N missing (%) for each of the covariates is as follows: BMI=4 (0.8%); health insurance=12 (2.5%); education=11 (2.3%); tobacco use=6 (1.2%); and alcohol use=10 (2.1%).

^aVisits 3-4 represent ultrasound estimates of fetal weight; Visit 5 represents birthweight.

^bEstimates from linear regression model of covariate in association with birthweight z-score, adjusted for gestational age at delivery and weighted for study design.

^cEstimates from LME model of covariate in association with repeated measures of fetal weight (visits 3-5), adjusted for gestational age at ultrasound/delivery (time-varying) and weighted for study design. LME models include random intercepts for subject ID and random slopes for gestational age at ultrasound/delivery.

Medians (25th, 75th percentiles) of cumulative urinary phthalate metabolite and bisphenol-A levels (µg/L) and gestational age at sample collection^a in study population by visit (N=479 at visit 1,^b N=482 at subsequent visits). All measures standardized to urinary specific gravity.

Table 2

	Visit 1		Visit 2		Visit 3		Visit 4	
	50 th (25 th , 75 th)		50 th (25 th , 75 th)		50 th (25 th , 75 th)		50 th (25 th , 75 th)	
Gestational age (weeks)	9.71 (8.29, 11.4)		18.0 (17.0, 18.9)		26.1 (25.1, 27.0)		35.1 (34.4, 35.9)	
MEHP (µg/L)	10.1 (5.15, 24.8)		10.9 (5.67, 21.9)		11.2 (5.75, 18.9)		10.5 (6.14, 18.3)	
MEHHP (µg/L)	33.5 (17.4, 80.2)		34.2 (20.3, 67.1)		32.8 (18.6, 57.0)		34.1 (19.9, 57.4)	
MEOHP (µg/L)	16.8 (8.57, 40.3)		17.1 (10.3, 35.2)		16.7 (10.4, 31.6)		18.3 (11.1, 29.8)	
MECPP (µg/L)	40.3 (18.9, 107)		40.3 (21.5, 83.0)		40.0 (21.6, 73.1)		42.9 (23.7, 70.7)	
DEHP (µmol/L)	0.37 (0.18, 0.82)		0.36 (0.22, 0.74)		0.35 (0.22, 0.63)		0.39 (0.22, 0.62)	
MBzP (µg/L)	6.22 (3.36, 13.6)		6.29 (3.62, 12.8)		6.19 (3.61, 12.0)		6.37 (3.70, 11.9)	
MBP (µg/L)	16.1 (10.8, 26.8)		16.1 (10.8, 26.1)		16.5 (11.1, 24.0)		16.7 (11.7, 25.0)	
MtBP (µg/L)	7.14 (4.50, 11.1)		7.10 (4.61, 11.1)		7.13 (4.75, 11.0)		7.66 (5.03, 10.9)	
MEP (µg/L)	122 (48.8, 357)		133 (56.2, 335)		136 (59.4, 300)		130 (62.4, 312)	
MCPP (µg/L)	1.69 (1.06, 3.41)		1.84 (1.16, 3.10)		1.88 (1.18, 3.23)		1.88 (1.20, 3.02)	
BPA (µg/L)	1.28 (0.75, 2.08)		1.33 (0.81, 1.99)		1.33 (0.92, 1.92)		1.32 (0.94, 1.87)	

MEHP, mono-2-ethylhexyl phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; MEOHP, mono-2-ethyl-5-oxohexyl phthalate; MECPP, mono-2-ethyl-5-carboxypentyl phthalate; <<DEHP, summed di-2-ethylhexyl phthalate metabolites; MBzP, mono-benzyl phthalate; MBP, mono-<<-butyl phthalate; MtBP, mono-iso-butyl phthalate; MEP, mono-ethyl phthalate; MCP, mono-carboxypropyl phthalate; BPA, bisphenol-A.

^a Gestational age at sample collection indicates gestational age of specific visit. Cumulative exposure metrics at each visit represent geometric average of all measures taken for each individual prior to and including that visit (e.g., visit 2 represents the geometric average of levels from visit 1 and visit 2).

^b N=479 for all urinary phthalate metabolite measurements at visit 1, however N=481 for urinary BPA measurements at visit 1.

Standard deviation change in z-score (95% confidence intervals) for birth weight in association with an interquartile range increase in cumulative urinary phthalate metabolite or bisphenol-A concentrations.^a

Table 3

	Model 1 (N=482) Crude			Model 2 (N=466) Adjusted			Model 3 (N=209) Male infants only			Model 4 (N=257) Female infants only			p for <i>b</i> difference
	SD	(95% CI)	p	SD	(95% CI)	p	SD	(95% CI)	p	SD	(95% CI)	p	
MEHP	-0.03	(-0.14, 0.09)	0.66	-0.04	(-0.16, 0.07)	0.45	-0.13	(-0.30, 0.03)	0.12	0.02	(-0.14, 0.18)	0.81	0.20
MEHHP	-0.02	(-0.14, 0.10)	0.77	-0.05	(-0.17, 0.07)	0.39	-0.11	(-0.28, 0.06)	0.21	0.01	(-0.16, 0.18)	0.92	0.33
MEOHP	-0.03	(-0.15, 0.09)	0.60	-0.07	(-0.18, 0.05)	0.24	-0.13	(-0.29, 0.04)	0.13	-0.01	(-0.17, 0.16)	0.91	0.32
MECPP	-0.04	(-0.16, 0.07)	0.47	-0.08	(-0.2, 0.03)	0.16	-0.11	(-0.27, 0.05)	0.19	-0.05	(-0.22, 0.12)	0.54	0.65
DEHP	-0.05	(-0.17, 0.08)	0.45	-0.09	(-0.21, 0.03)	0.14	-0.13	(-0.30, 0.04)	0.13	-0.04	(-0.22, 0.13)	0.62	0.49
MBzP	-0.03	(-0.14, 0.09)	0.63	0.05	(-0.08, 0.17)	0.45	-0.05	(-0.22, 0.13)	0.60	0.13	(-0.06, 0.31)	0.18	0.18
MBP	-0.12	(-0.22, -0.02)	0.02	-0.08	(-0.19, 0.02)	0.11	-0.12	(-0.27, 0.04)	0.16	-0.07	(-0.21, 0.07)	0.33	0.67
MtBP	-0.05	(-0.15, 0.06)	0.39	0.03	(-0.08, 0.14)	0.63	0.05	(-0.11, 0.21)	0.54	0.01	(-0.15, 0.17)	0.90	0.73
MEP	-0.10	(-0.22, 0.03)	0.13	-0.05	(-0.18, 0.08)	0.46	-0.06	(-0.24, 0.11)	0.48	-0.03	(-0.22, 0.16)	0.76	0.80
MCP	-0.06	(-0.16, 0.04)	0.23	-0.08	(-0.18, 0.03)	0.14	-0.05	(-0.19, 0.08)	0.45	-0.10	(-0.25, 0.06)	0.21	0.67
BPA	-0.08	(-0.20, 0.04)	0.20	-0.04	(-0.17, 0.09)	0.56	-0.10	(-0.27, 0.08)	0.27	0.03	(-0.17, 0.22)	0.79	0.35

Note: Model 1: Adjusted for cumulative urinary specific gravity and gestational age at delivery. Model 2: Additionally adjusted for maternal age, race/ethnicity, visit 1 body mass index, health insurance provider, and infant gender. Model 3: Fully adjusted model of male infants only. Model 4: Fully adjusted model of female infants only.

^aCumulative exposure concentration represented by geometric average of urinary concentrations available from visits 1-4.

^bp-value calculated from Z-statistic for comparison of beta coefficients and standard errors for male and female models.

Standard deviation change in z-score (95% confidence intervals) for ultrasound and/or delivery measures of growth (visits 3-5) in association with an interquartile range increase in cumulative urinary phthalate metabolite or bisphenol-A concentrations.^a Results from adjusted^b linear mixed effects models with random intercepts for subject ID and random slopes for gestational age at ultrasound.

Table 4

	Head circumference (visits 3-4; N=459)			Abdominal circumference (visits 3-4; N=462)			Femur length (visits 3-4; N=462)			Weight (visits 3-5; N=928)		
	SD	(95% CI)	P	SD	(95% CI)	P	SD	(95% CI)	P	SD	(95% CI)	P
MEHP	-0.09 (-0.20, 0.01)	0.09	0.09	-0.10 (-0.22, 0.01)	0.08	0.08	-0.11 (-0.22, 0.01)	0.08	0.08	-0.08 (-0.18, 0.01)	0.09	0.09
MEHHP	-0.04 (-0.15, 0.07)	0.45	0.45	-0.07 (-0.19, 0.04)	0.22	0.22	-0.09 (-0.21, 0.03)	0.14	0.14	-0.08 (-0.18, 0.02)	0.10	0.10
MEOHHP	-0.08 (-0.18, 0.03)	0.14	0.14	-0.10 (-0.21, 0.004)	0.06	0.06	-0.11 (-0.22, 0.01)	0.07	0.07	-0.10 (-0.20, -0.01)	0.03	0.03
MECPP	-0.11 (-0.21, -0.01)	0.03	0.03	-0.12 (-0.23, -0.02)	0.02	0.02	-0.12 (-0.23, -0.01)	0.03	0.03	-0.13 (-0.22, -0.03)	<0.01	<0.01
DEHP	-0.11 (-0.21, 0.001)	0.05	0.05	-0.14 (-0.26, -0.03)	0.02	0.02	-0.13 (-0.25, -0.01)	0.03	0.03	-0.13 (-0.23, -0.03)	<0.01	<0.01
MBzP	-0.13 (-0.25, -0.01)	0.04	0.04	-0.05 (-0.18, 0.08)	0.47	0.47	-0.01 (-0.15, 0.12)	0.83	0.83	0.005 (-0.10, 0.11)	0.93	0.93
MBP	-0.004 (-0.08, 0.07)	0.91	0.91	-0.05 (-0.13, 0.03)	0.21	0.21	-0.03 (-0.12, 0.05)	0.41	0.41	-0.05 (-0.13, 0.02)	0.16	0.16
MBP	-0.03 (-0.14, 0.07)	0.52	0.52	-0.07 (-0.18, 0.04)	0.23	0.23	0.01 (-0.10, 0.13)	0.81	0.81	0.003 (-0.09, 0.10)	0.95	0.95
MEP	-0.10 (-0.22, 0.03)	0.13	0.13	-0.04 (-0.18, 0.09)	0.56	0.56	-0.09 (-0.22, 0.05)	0.22	0.22	-0.07 (-0.18, 0.04)	0.22	0.22
MCP	-0.005 (-0.09, 0.08)	0.91	0.91	0.00 (-0.10, 0.10)	1.00	1.00	-0.05 (-0.15, 0.05)	0.35	0.35	-0.03 (-0.12, 0.05)	0.41	0.41
BPA	-0.02 (-0.14, 0.10)	0.73	0.73	-0.06 (-0.19, 0.07)	0.36	0.36	-0.09 (-0.22, 0.04)	0.18	0.18	-0.07 (-0.17, 0.04)	0.20	0.20

^a Cumulative exposure concentration represented by geometric average of urinary concentrations available from visits 1-4.

^b Models adjusted for cumulative urinary specific gravity, gestational age at ultrasound, maternal age, race/ethnicity, visit 1 body mass index, health insurance provider, and infant gender.