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First trimester maternal exposures to endocrine disrupting chemicals and metals and fetal size in the Michigan Mother Infant Pairs study

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Abstract

Exposures to endocrine disrupting chemicals and metals are near ubiquitous worldwide, and their potential impact on children is a major public health concern. This pilot study was designed to characterize exposures to phthalates, phenols, and metals among pregnant women in the first trimester, and to examine associations with fetal biometrics and birth weight. Forty-one chemicals and elements were analyzed in urine from 56 mothers with full-term newborns from the Michigan Mother-Infant Pairs (MMIP) study. Bivariate analyses identified predictors of exposure biomarkers. Associations between birth weight, Fenton z-scores, and second trimester fetal biometrics with toxicants were examined via multivariable linear regression. An average of 30 toxicants was detected in maternal urine. Fast food consumption was associated with several phthalate metabolites, phenols and metals, and canned food consumption with bisphenol F ($p<0.05$). Mono (3-carboxypropyl) phthalate (MCPP) was significantly associated with higher birthweight and Fenton z-score while the opposite was observed for bisphenol S. Estimated femur length from ultrasonography was significantly inversely associated with arsenic, barium, and lead. While limited by sample size, this study is one of the first to evaluate birth outcomes with respect

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Conflict of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (set by the US Department of Health and Human Services) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the University of Michigan Medical School Institutional Review Board.

to emerging endocrine disrupting chemicals and to examine associations between toxicants and fetal biometrics. Exposure assessment was provided by the National Institute of Environmental Health Sciences' Children's Health Exposure Analysis Resource (NIEHS CHEAR), a resource available to children's studies with the goal of combining data across cohorts in an effort to characterize the impact of toxicants on child health from birth and beyond.

Keywords

Prenatal exposures; metals; phenols; phthalates; birth outcomes

Introduction

Endocrine disrupting chemicals including phthalates and phenols and metals are toxicant classes of global concern, especially to pregnant women and children [1–4]. In recent years, studies in the United States, Canada, and Denmark have measured dozens to hundreds of chemicals among pregnant women or women planning pregnancies and found phthalates, phenols, and metals to be among the most widely detected [1–3, 5–7]. For example, in the Canadian Maternal-Infant Research on Environmental Chemicals (MIREC) study, the phenols triclosan (TCS) and bisphenol a (BPA) as well as metabolites of di (2-ethylhexyl) phthalate (DEHP) were detected in >95% of first trimester maternal urine samples [3, 7]. While the exposure landscape varies by region, diet, occupation, and cultural practices around the globe, phenols, phthalates, and metals are near ubiquitous. Electronic waste recycling in African, South American, and Asian countries leads to community-wide exposures to toxic metals [8]. In thirty countries with available data, water supplies were found to be contaminated by phenols, reflecting widespread use of personal care products [9]. These examples suggest that endocrine disrupting chemical and metal exposures will remain a public health concern for the foreseeable future. As such it is imperative that the extent of exposure and its adverse effects on vulnerable populations (e.g., developing children) are known.

In line with the developmental origins of health and disease (DOHaD) hypothesis, prenatal exposures to endocrine disrupting chemicals and metals are associated with offspring health in animal and epidemiological studies, with effects on anthropometry, puberty, neurodevelopment, and more often observed years after the exposure [10–17]. Birth weight, a routinely collected clinical measure, is considered an indicator of future health with extremes at the low or high end correlated with cardiovascular and metabolic disease risk and other complications later in life [18–20]. Prenatal exposures to toxicants including lead, arsenic, cadmium, DEHP, and butylparaben (BuPB), are associated with lower birth weight individually or in combination [21–24]. Examining relationships between early gestational exposures with fetal biometrics from standard prenatal ultrasound screening could provide further insight into windows of susceptibility for effects on growth. Significant associations between decreased estimated fetal weight from ultrasonography and DEHP metabolites [25] were observed in a Boston birth cohort (n=482), suggesting metrics of fetal growth as a promising yet largely unexplored outcome for environmental epidemiology.

This study was designed to characterize three classes of prevalent toxicants of concern to pregnant women and developing children – phthalates, phenols, and metals – using first trimester urine samples from a subset of 56 mothers with full-term and healthy newborns from the Michigan Mother-Infant Pairs (MMIP) study. We conducted exploratory analyses to identify exposure predictors and associations of exposures with birth weight and second trimester fetal biometrics. These analyses were conducted as an initial exposome pilot study through support from the US National Institute of Environmental Health Sciences' Children's Health Exposure Analysis Resource (NIEHS CHEAR).

Methods

Study population

The MMIP project is an ongoing birth cohort study based out of the University of Michigan Von Voigtlander Women's Hospital. Women were recruited between 2010 to 2017 during their first prenatal visit and were eligible to participate if they were at least 18 years old, conceived naturally, had a singleton pregnancy, were between 8 and 14 weeks gestation, and intended to deliver at the University of Michigan hospital. Approximately 250 MMIP subjects have delivered as of 2017, and findings from a subset of these subjects were previously published [26–28]. For the analyses described herein, a subset of mothers recruited between 2012 and 2015 were selected for extensive exposure assessment of endocrine disrupting chemicals and metals and planned epigenomic and metabolomics analyses as a CHEAR pilot study. To be included in this subset of 56, inclusion criteria for the mother-infant pairs were: complete survey data, availability of all biospecimen from mother and child, and family not included in previous exposure assessment. Due to low prevalence of racial or ethnic minorities and maternal smoking, in an effort to reduce confounding factors in a relatively small sample size, only Caucasian, non-Hispanic, non-smoking mothers with full term newborns (>37 weeks gestation) were included.

Women provided informed, written consent prior to participation. The University of Michigan Medical School Institutional Review Board approved all study procedures.

Survey data and sample collection

At the first trimester study visit, women were administered a survey to collect information on demographics, smoking status, and potential exposure sources for endocrine disrupting chemicals in the past three months (fast food, canned food, haircare products, perfumes and cosmetics). Spot urine and venous blood samples were collected from MMIP mothers during the first trimester prenatal visit and upon arrival at the hospital for delivery. Urine samples were collected in polypropylene containers, transferred into glass vials, and stored at −80 °C prior to analysis.

Birth outcomes

Data were collected from the health records on gestational age, birth weight (measured at delivery), birth length, and head circumference measured the day after delivery. Gestational age was recorded as the healthcare provider's best estimate from either the last menstrual period or ultrasound, as recommended by the American Congress of Obstetricians and

Gynecologists. Fenton z-scores were calculated to standardize birth weight by completed gestational weeks and by sex using the Fenton Growth Chart updated in 2013 [29].

Fetal anthropometry

Fetal morphometrics including biparietal diameter, head circumference, abdominal circumference, and femur length were abstracted from a clinical ultrasound performed in the second trimester at the time of fetal survey. Published growth reference curves were used to standardize measurements based on gestational age [30].

Exposure assessment: Endocrine disrupting chemicals

Panels of 12 phthalate metabolites and 12 environmental phenols were quantified in maternal urine samples collected during the first trimester study visit at the NSF International Applied Research Center Laboratory (Ann Arbor, MI, USA) via isotope dilution liquid chromatography-tandem mass spectrometry (ID LC-MS/MS). Methods were modified from our previously published work [28, 31] to include more analytes. The analytical methods are based on the Centers for Disease Control and Prevention Laboratory Procedure Manuals for phthalate metabolites and environmental phenols (method no. 6306.03 and 6306.01, respectively), and analysis was conducted on a TSQ Vantage triple quad/Transcend II instrument with Ultimate 3000 HPLC Pumps. For phthalates, the analytes included metabolites of DEHP: mono (2-ethyl-5-carboxylpentyl) phthalate (MECPP), mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono (2-ethylhexyl) phthalate (MEHP), and mono (2-ethyl-5-oxohexyl) phthalate (MEOHP) and dibutyl phthalates (DBP): mono-isobutyl phthalate (MIBP) and mono n-butyl phthalate (MnBP). Concentrations of mono-benzyl phthalate (MBzP), mono-carboxy isononyl phthalate (mCINP), mono (3-carboxypropyl) phthalate (MCPP), mono (6-COOH-2-methylheptyl) phthalate (MCOMHP), monoethyl phthalate (MEP), and mono-isononyl phthalate (mINP) were also determined. For environmental phenols, analytes were bisphenols (BPA, BPF, BPS), parabens (butyl, ethyl, methyl, and propyl paraben [BuPB, EtPB, MePB, PrPB]), 2,4 and 2,5-dichlorophenol (DCP24, DCP25), benzophenone-3 (BP3), triclocarban (TCC), and TCS.

Exposure assessment: Metals and metalloids

Metals were quantified in first trimester maternal urine samples at the NSF International Laboratory via isotope chromatography plasma tandem mass spectrometry (ICPMS) following a protocol based on CDC method 3018.3 with modifications for an expanded metal panel and a iCAP RQ instrument (Thermo Scientific). The seventeen metals analyzed were arsenic, barium, beryllium, cadmium, chromium, copper, mercury, manganese, molybedenum, nickel, lead, selenium, tin, thallium, uranium, tungsten, and zinc (As, Ba, Be, Cd, Cr, Cu, Hg, Mn, Mo, Ni, Pb, Se, Sn, Tl, U, W, and Zn). One sample with insufficient urine quality and quantity was excluded from metals analysis.

Quality control procedures during the exposure assessment of all toxicants included assessing intra- and inter-day variability and accuracy through replicates spiked at different concentrations. The laboratory also participates in external proficiency testing programs for many of the measured analytes. Concentrations below the limit of detection (LOD) were assigned a value of LOD/$\sqrt{2}$. Specific gravity of maternal urine samples were measured via a

handheld device (ATAGO Company, Ltd., Tokyo, Japan) to account for variability due to urinary dilution [32].

Statistical analysis

Descriptive statistics were computed for demographics, birth outcomes, survey responses, and toxicant concentrations. The molar sums for metabolites of DEHP (MECPP, MEHHP, MEHP, and MEOHP) and DBP (MIBP and MnBP) were calculated by summing metabolite concentrations divided by their respective molar mass. Exposure sum variables were calculated by first ranking concentrations of each toxicant into tertiles, assigning 0, 1, or 2 to the first, second, and third tertiles, respectively, followed by taking the sum of assigned integers within each class (phthalate, phenol, or metal), as well as a comprehensive sum of all chemical agents. Continuous variables failing to depict a normal distribution were transformed by the natural logarithm for further analysis.

Toxicants that were not detected in at least 30% of samples (mINP, TCC, Be, U, and W) were excluded from multivariate and bivariate single-exposure analyses. Bivariate associations were evaluated between chemical agents and birth outcomes, survey responses, and demographic factors using Spearman correlation coefficients, Wilcoxon rank-sum tests, and Kruskal-Wallis tests as appropriate. Multiple linear regression models, adjusting for specific gravity, gestational age, and infant gender (when appropriate), were used to regress chemical agents on birthweight, Fenton z-scores, and fetal biometrics. Toxicants were analyzed individually, summed within their respective class (phthalate, phenol, and metal), and all-inclusive sum of agents measured based on tertiles as described above. Phenols BPF and BPS were also described and analyzed as detect / non-detect due to a high percentage of concentrations below LOD. All statistical analyses were conducted using SAS 9.4 (Cary, N.C.).

Results

Demographics and birth outcomes

Characteristics of women and infants of the MMIP cohort subset are displayed in Table 1. The cohort is comprised of (n=56) non-Hispanic Caucasian women, with a median age of 31.5 years (IQR=6). Prior to pregnancy, women were typically within the normal BMI range (median=23.41 kg/m^2). The homogeneous group were primarily married (89%), never smokers (89%), and reported some degree of undergraduate college education or higher (92%). The majority of women currently had at least one child (parity ≥ 1). All births were full term by design and of normal birthweight (median=3,520 g). After adjusting for gestational age, infants were average in size compared to the general population (Fenton z-score median percentile = 59.7). When separated by sex, females had a median percentile of 54.4 while males were slightly larger (median percentile = 62.7; see S1 Table for sex-stratified anthropometry). Most births were vaginal (66.1%).

Exposure assessment

Distributions of phthalate, phenol, and metal concentrations from first trimester maternal urinary samples are depicted in Table 2. All phthalate metabolites except MEHP and mINP

were highly detected (> 90%) and most metabolites were moderate to highly correlated (S2 Table). Fewer phenols were above the LOD and were weakly to moderately correlated with one another (S3 Table). Most metal concentrations were highly detected (> 60%), and were significantly correlated with one another, except Hg (S4 Table).

Out of 41 toxicants analyzed, women in this cohort had an average of 30 detected, (range 17 to 38) during their first trimester of pregnancy including an average of 11 phthalate metabolites, 8 phenols, and 13 metals. Summed scores based on tertiles of exposures for each toxicant reveal a distribution across the sample ranging from mothers in the lowest tertile for nearly all the toxicants to mothers in the highest tertile for almost all analytes (S5 Table).

Predictors of exposure biomarkers

Frequency of survey responses to possible endocrine disrupting chemical sources including diet and personal care products during the first trimester can be found in Table 3. Concentrations for metabolites, mCINP (Wilcoxon rank-sum test p = 0.002), MCPP (p = 0.04), meCPP (p = 0.02), and MiBP (p = 0.01) were higher for those who ate fast food, while an inverse relationship was detected for MnBP (p=0.004; S6 Table). With phenols, 2,5-DCP, MeBP, and TCS (p = 0.03) were higher among those who consumed fast food (S7 Table). Concentrations of BPF were higher for those who not only consumed canned food (p = 0.03), but also for those who reported higher frequency of consumption per week (p=0.02; S8 Table). Few significant relationships were detected among survey responses and metals (S9 Table). However, concentrations of Se (p=0.01), Sn (p=0.02), and Zn (p=0.02) were higher in those who reported fast food consumption.

Exposures and size at birth

The associations of phthalates, phenols, and metals that were detected in at least 30% of samples with birthweight and Fenton z-scores are displayed in Table 4. Several significant associations were observed ($p<0.05$). One unit of natural log-transformed MCPP concentration was associated with a 78.48 g increase in birthweight (95% CI: 2.95, 154.01; p = 0.04) and a 0.19 increase in Fenton z-score (95% CI: 0.02, 0.35; p = 0.02). We identified a significant decrease in birthweight (β= −150.42 g, 95% CI: −294.85; −6.00; p=0.04) and Fenton z-score (β= −0.31; 95% CI: −0.62, 0.002; p = 0.05) with increasing BPS concentrations. Since BPS was only detected in 37% of samples, we examined this association with dichotomized BPS (detect vs. non-detect, see S10 Table) and the relationship with lower birth weight (p=0.04) and Fenton z-score remained (p=0.02) among mother-infant pairs with detectable BPS. No significant relationships were observed between metals or summed scores of phthalates, phenols or metals with birth weight or Fenton z-score.

Exposures and fetal size

Regression analyses for toxicants with standardized fetal anthropometry are depicted in Table 5. MEP was positively associated with abdominal circumference (β = 0.53, 95% CI: 0.05, 1.01, p = 0.03) while the metals As (β = −0.26, 95% CI: −0.46, −0.07; p = 0.01), Ba (β = −0.25, 95% CI: −0.55, −0.15; p = 0.001), and Pb (β = −0.28, 95% CI: −0.51, −0.04; p =

0.02) were all negatively associated with femur length. Relationships between fetal anthropometry measurements and summed exposures were not statistically significant.

Discussion

In the MMIP cohort, we report widespread exposure to endocrine disrupting chemicals and metals in first trimester maternal urine samples with an average of 30 toxicants detected out of 41. Some toxicants were near ubiquitous with detection in >90% of samples including all essential elements, non-essential elements (As, Ba, Tl), 10 phthalate metabolites, BP-3, MePB, PrPB, and TCS. Toxicants that are increasingly being detected in humans in recent decades, MCPP and BPS [33, 34], were significantly associated with higher and lower birth weight, respectively, among this pilot sample from MMIP. We also observed associations between decreased second trimester femur length and metals, suggesting the potential utility of fetal biometrics in understanding windows of susceptibility.

MMIP along with other recent environmental epidemiology studies is moving beyond assessment of highly studied toxicants (e.g., As, Cd, BPA) to characterize trends in the ever-changing exposome and ultimately adverse health outcomes associated with these exposures. We detected an average of 30 out of 41 endocrine disrupting chemicals and metals measured in urine with a maximum of 38 detected in an individual. Similarly, Woodruff *et al.* observed high detection levels amongst many chemical classes including phenols, phthalates, metals, and pesticides measured in biological samples from 268 pregnant women who participated in the 2003–2004 cycle of NHANES [1]. In the Canadian MIREC study, multiple classes of chemicals were detected in maternal first trimester urine samples with socio-demographic characteristics predicting concentrations of some chemicals but not all [3, 35]. For example, DEHP metabolites were detected in 98% of participants, and concentrations were independent of socio-demographic characteristics [3].

The MMIP sample in this study was comprised of a well-educated and healthy group of Caucasian women with exposure levels similar to or lower than those reported in NHANES. The toxic burden carried by pregnant women in vulnerable populations and the subsequent health effects on mother and child are likely to be greater due to region-specific, SES-related and/or environmental justice issues such as urban air pollution, access to fresh produce or clean water, proximity to industrial operations, consumer product use patterns and more. For example, in a sample of predominantly black pregnant women from New York, MePB and PrPB urinary concentrations were >4 times greater than that observed in MMIP [36]. Exposure to metals is a global concern with disproportionate burdens posed on many populations including those living near outsourced electronic waste recycling sites [8] or populations with As or Pb contaminated water supplies [37, 38].

In the MMIP study and NHANES, fast food consumption was associated with higher exposures to parent phthalates such as DEHP and DiNP [39]. We also observed associations between fast food consumption and 2,5-DCP, MePB, TCS, Se, Sn, and Zn, but the extent to which frequent consumers of fast food are exposed to these chemicals and elements is unknown. While canned food consumption and BPA were not significantly correlated, we did observe higher BPF concentrations by frequency of canned food consumption. This

reflects the changing landscape of bisphenols in consumer products with BPA being replaced by other bisphenols with endocrine-disrupting potential [34]. Overall, there is a need to characterize the recent exposome of diverse maternal populations – by global region, race, ethnicity, and socio-economic status – to better understand the relevant chemical mixtures of most concern for maternal and child health.

We observed an association between higher birth weight and first trimester MCPP, a phthalate metabolite on the rise in the US according to trends in NHANES data from 2000–2012 [33, 40]. MCPP is a metabolite of the parent di-n-octyl phthalate (DOP) and other high molecular weight phthalates. These parent chemicals are widely used as plasticizers in diverse products including flooring, vinyl gloves, adhesives, and food packaging. While few animal studies to date have modeled prenatal exposure to the primary parent compound (DOP) or to MCPP directly, epidemiological studies suggest that MCPP exposure in early pregnancy affects the mother. For example, lower free triiodothyronine (T3) and higher BMI were associated with higher urine MCPP among pregnant women [41, 42]. Lower maternal thyroid hormone levels and higher BMI increase the risk for larger offspring [43, 44]. In a different subset of MMIP participants recruited in the study's early years, we previously reported significant associations among female newborns between first trimester MCPP and increased birth length, as well as maternal urinary MCPP at delivery and higher birth weight [28]. However, in the Infant Development and the Environment Study (TIDES, n=753), no significant associations between first trimester maternal MCPP and birthweight were observed among male or female infants [45]. The association between average MCPP throughout pregnancy and birthweight was also not significant among newborns from the LIFECODES study [25]. Given the mixed evidence for MCPP's effects on fetal growth, the potential impact of MCPP on pregnant women, and the timing-specificity of this relationship, the influence of MCPP on birth outcomes requires further research.

While the pool of research on birth outcomes and phthalate or BPA exposures is growing, few studies apart from MMIP have investigated emerging chemicals of concern such as parabens and TCS with birth outcomes. Associations between parabens and decreased gestational age at birth, increased odds for preterm birth and low birth weight with increasing BuPB concentrations in cord blood plasma were observed among immigrants living in Brooklyn, New York as well as an association between TCC and decreased gestational age at birth [24]. While our study only includes term neonates by design, we observed a similar trend of lower birth weight with increasing maternal first trimester BuPB ($p=0.12$). We also observed a significant association between decreased birth weight and BPS – a replacement chemical for BPA with endocrine-disrupting potential that has recently been detected in populations from around the world [34]. Prior evidence suggests that BPS crosses the placenta in humans [46], and this is one of the first studies to our knowledge to examine associations between birth outcomes and BPS. Rodent models of perinatal BPS exposure have identified health effects manifesting later in life, including at dose levels below the recommended daily intake for humans. Health effects observed were altered maternal behavior in mice [47], overweight and metabolic complications in adult male mice [48], and altered gene expression in the prefrontal cortex of juvenile female rats [49]. Thus the short- and long-term effects of prenatal exposures to BPA replacements merit further investigation in human populations.

Second trimester fetal biometry measurements are part of standard prenatal care in the U.S. and elsewhere, and accessing this data provides an additional window of susceptibility to examine the influence of environmental exposures [50]. While work in this area is limited to date, positive associations between maternal BMI and adiposity with fetal biometrics [50, 51] as well as decreased estimated fetal weight with DEHP metabolites [25] have been reported. Metals (As, Ba, Pb) were negatively associated with femur length in this study. *In vitro,* human exposure relevant doses of arsenic inhibit osteoblast differentiation [52]. Prenatal lead exposure has previously been associated with decreased birth weight and length and higher risk of small-for-gestational-age [22, 53, 54] as well as decreased osteoblastogenesis [55]. Findings in the MMIP cohort may reflect an earlier window to detect effects on fetal growth that should be considered in future research.

This study involved extensive first trimester exposure assessment of emerging endocrine disrupting chemicals (e.g., parabens, BP-3), and we are the first to our knowledge to report associations between BPS and birth weight as well as between metals and fetal biometrics. These relationships merit future exploration in large and diverse cohorts since this pilot study had several limitations. The sample size was small, and associations would not have remained statistically significant after accounting for multiple comparisons. Low statistical power, the relatively small range of exposure levels among MMIP participants, inability to perform sex-stratified analyses, and exclusion of preterm infants may have biased our results towards the null. Urinary measures from the first trimester were available, yet blood is a better biomarker for some metals (e.g., Pb, methyl-Hg), and exposures later in pregnancy may also influence birth size [24, 28]. Due to the sample size, statistical analyses tested for linear relationships between outcomes and exposure biomarkers. We did not additionally test for non-monotonic relationships (e.g., U-shaped response with health effects observed in cases of deficiency and excess) that might occur for essential elements such as Se, Zn, or Cu [56]. We did not replicate a previously reported association from a different subset of MMIP participants between first trimester maternal BPA and lower birthweight [27]. This is likely due to a difference in biomarkers as unconjugated BPA and BPA glucuronide were measured in plasma in the previous study while total urinary BPA was measured in this set of MMIP participants. The homogenous sample is a limitation for generalizability of results but a strength for reducing confounding (e.g., from maternal smoking and race). Characterization of the MMIP exposome lays the groundwork for future in-depth exploration supported by CHEAR of biophysiological mechanisms (epigenomics, metabolomics, oxidative stress markers) by which metals, phenols, and phthalates may ultimately influence child health.

In conclusion, associations between first trimester exposure biomarkers with birth weight (increased with MCPP; decreased with BPS) and with femur length estimated during ultrasonography (decreased with As, Ba, and Pb) were observed in the MMIP cohort. While this study had several limitations, it serves as an introduction to the future of comprehensive exposure assessment in children's health research, and in particular, through the NIEHS CHEAR program. Exposure measures were provided by CHEAR, a resource that fulfills the need for sophisticated and thorough exposure assessment within multiple children's health cohorts that can ultimately be combined. The data generated from CHEAR will be made publically available and will be used to assess relationships between toxicant exposures with outcomes such as birth weight in a large and diverse sample from multiple studies. This will

allow for sufficient power to accommodate more sophisticated statistical analysis of the health impacts of exposure to mixtures in addition to individual chemicals or classes of chemicals. The CHEAR program will add not only exposure biomarker data but also measures of biological responses including metabolomics, epigenomics, endocrine function, inflammation, oxidative stress, and others in an effort to advance risk assessment and increase mechanistic understanding of toxicity in children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. Environ Health Perspect. 2011;119(6):878–85. [PubMed: 21233055]
2. Rosofsky A, Janulewicz P, Thayer KA, McClean M, Wise LA, Calafat AM, et al. Exposure to multiple chemicals in a cohort of reproductive-aged Danish women. Environ Res. 2017;154:73–85. [PubMed: 28039828]
3. Lee WC, Fisher M, Davis K, Arbuckle TE, Sinha SK. Identification of chemical mixtures to which Canadian pregnant women are exposed: The MIREC Study. Environ Int. 2017;99:321–30. [PubMed: 28040263]
4. Katsikantami I, Sifakis S, Tzatzarakis MN, Vakonaki E, Kalantzi OI, Tsatsakis AM, et al. A global assessment of phthalates burden and related links to health effects. Environ Int. 2016;97:212–36. [PubMed: 27669632]
5. Arbuckle TE, Liang CL, Morisset AS, Fisher M, Weiler H, Cirtiu CM, et al. Maternal and fetal exposure to cadmium, lead, manganese and mercury: The MIREC study. Chemosphere. 2016;163:270–82. [PubMed: 27540762]
6. Ettinger AS, Arbuckle TE, Fisher M, Liang CL, Davis K, Cirtiu CM, et al. Arsenic levels among pregnant women and newborns in Canada: Results from the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort. Environ Res. 2017;153:8–16. [PubMed: 27880879]
7. Arbuckle TE, Marro L, Davis K, Fisher M, Ayotte P, Belanger P, et al. Exposure to free and conjugated forms of bisphenol A and triclosan among pregnant women in the MIREC cohort. Environ Health Perspect. 2015;123(4):277–84. [PubMed: 25494523]
8. Chen A, Dietrich KN, Huo X, Ho S-m. Developmental Neurotoxicants in E-Waste: An Emerging Health Concern. Environmental Health Perspectives. 2011;119(4):431–8. [PubMed: 21081302]
9. Montes-Grajales D, Fennix-Agudelo M, Miranda-Castro W. Occurrence of personal care products as emerging chemicals of concern in water resources: A review. Sci Total Environ. 2017;595:601–14. [PubMed: 28399499]

10. Ferguson KK, Peterson KE, Lee JM, Mercado-Garcia A, Blank-Goldenberg C, Tellez-Rojo MM, et al. Prenatal and peripubertal phthalates and bisphenol A in relation to sex hormones and puberty in boys. Reprod Toxicol. 2014;47:70–6. [PubMed: 24945889]
11. Rajesh P, Balasubramanian K. Phthalate exposure in utero causes epigenetic changes and impairs insulin signalling. The Journal of endocrinology. 2014;223(1):47–66. [PubMed: 25232145]
12. Tellez-Rojo MM, Cantoral A, Cantonwine DE, Schnaas L, Peterson K, Hu H, et al. Prenatal urinary phthalate metabolites levels and neurodevelopment in children at two and three years of age. Sci Total Environ. 2013;461–462:386–90.
13. Yang TC, Peterson KE, Meeker JD, Sánchez BN, Zhang Z, Cantoral A, et al. Bisphenol A and phthalates in utero and in childhood: association with child BMI z-score and adiposity. Environmental Research. 2017;156:326–33. [PubMed: 28390300]
14. Onishchenko N, Tamm C, Vahter M, Hokfelt T, Johnson JA, Johnson DA, et al. Developmental exposure to methylmercury alters learning and induces depression-like behavior in male mice. Toxicol Sci. 2007;97(2):428–37. Epub 2007 Jan 4. [PubMed: 17204583]
15. Faulk C, Barks A, Sanchez BN, Zhang Z, Anderson OS, Peterson KE, et al. Perinatal lead (Pb) exposure results in sex-specific effects on food intake, fat, weight, and insulin response across the murine life-course. PLoS One. 2014;9(8):e104273. [PubMed: 25105421]
16. Weinhouse C, Anderson OS, Bergin IL, Vandenbergh DJ, Gyekis JP, Dingman MA, et al. Dose-dependent incidence of hepatic tumors in adult mice following perinatal exposure to bisphenol A. Environ Health Perspect. 2014;122(5):485–91. [PubMed: 24487385]
17. Harley KG, Aguilar Schall R, Chevrier J, Tyler K, Aguirre H, Bradman A, et al. Prenatal and postnatal bisphenol A exposure and body mass index in childhood in the CHAMACOS cohort. Environ Health Perspect. 2013;121(4):514–20. [PubMed: 23416456]
18. Barker DJ. The origins of the developmental origins theory. J Intern Med. 2007;261(5):412–7. [PubMed: 17444880]
19. Oken E, Gillman MW. Fetal origins of obesity. Obesity research. 2003;11(4):496–506. [PubMed: 12690076]
20. Johnsson IW, Haglund B, Ahlsson F, Gustafsson J. A high birth weight is associated with increased risk of type 2 diabetes and obesity. Pediatric obesity. 2015;10(2):77–83. [PubMed: 24916852]
21. Govarts E, Remy S, Bruckers L, Den Hond E, Sioen I, Nelen V, et al. Combined Effects of Prenatal Exposures to Environmental Chemicals on Birth Weight. Int J Environ Res Public Health. 2016;13(5).
22. Gonzalez-Cossio T, Peterson KE, Sanin LH, Fishbein E, Palazuelos E, Aro A, et al. Decrease in birth weight in relation to maternal bone-lead burden. Pediatrics. 1997;100(5):856–62. [PubMed: 9346987]
23. Laine JE, Bailey KA, Rubio-Andrade M, Olshan AF, Smeester L, Drobna Z, et al. Maternal arsenic exposure, arsenic methylation efficiency, and birth outcomes in the Biomarkers of Exposure to ARsenic (BEAR) pregnancy cohort in Mexico. Environ Health Perspect. 2015;123(2):186–92. [PubMed: 25325819]
24. Geer LA, Pycke BF, Waxenbaum J, Sherer DM, Abulafia O, Halden RU. Association of birth outcomes with fetal exposure to parabens, triclosan and triclocarban in an immigrant population in Brooklyn, New York. Journal of hazardous materials. 2017;323(Pt A):177–83. [PubMed: 27156397]
25. Ferguson KK, Meeker JD, Cantonwine DE, Chen YH, Mukherjee B, McElrath TF. Urinary phthalate metabolite and bisphenol A associations with ultrasound and delivery indices of fetal growth. Environ Int. 2016.
26. Marchlewicz EH, Dolinoy DC, Tang L, Milewski S, Jones TR, Goodrich JM, et al. Lipid metabolism is associated with developmental epigenetic programming. Sci Rep. 2016;6:34857. [PubMed: 27713555]
27. Veiga-Lopez A, Kannan K, Liao C, Ye W, Domino SE, Padmanabhan V. Gender-Specific Effects on Gestational Length and Birth Weight by Early Pregnancy BPA Exposure. J Clin Endrocrinol Metab. 2015;100(11):E1394–403.

28. Watkins DJ, Milewski S, Domino SE, Meeker JD, Padmanabhan V. Maternal phthalate exposure during early pregnancy and at delivery in relation to gestational age and size at birth: A preliminary analysis. Reprod Toxicol. 2016;65:59–66. [PubMed: 27352641]
29. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13:59. [PubMed: 23601190]
30. Verburg BO, Steegers EA, De Ridder M, Snijders RJ, Smith E, Hofman A, et al. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2008;31(4):388–96.
31. Perng W, Watkins DJ, Cantoral A, Mercado-Garcia A, Meeker JD, Tellez-Rojo MM, et al. Exposure to phthalates is associated with lipid profile in peripubertal Mexican youth. Environ Res. 2017;154:311–7. [PubMed: 28152472]
32. Pearson MA, Lu C, Schmotzer BJ, Waller LA, Riederer AM. Evaluation of physiological measures for correcting variation in urinary output: Implications for assessing environmental chemical exposure in children. J Expos Sci Environ Epidemiol. 2008;19(3):336–42.
33. Zota AR, Calafat AM, Woodruff TJ. Temporal trends in phthalate exposures: findings from the National Health and Nutrition Examination Survey, 2001–2010. Environmental health perspectives. 2014;122(3):235–41. [PubMed: 24425099]
34. Chen D, Kannan K, Tan H, Zheng Z, Feng YL, Wu Y, et al. Bisphenol Analogues Other Than BPA: Environmental Occurrence, Human Exposure, and Toxicity-A Review. Environ Sci Technol. 2016;50(11):5438–53. [PubMed: 27143250]
35. Lewin A, Arbuckle TE, Fisher M, Liang CL, Marro L, Davis K, et al. Univariate predictors of maternal concentrations of environmental chemicals: The MIREC study. Int J Hyg Environ Health. 2017.
36. Pycke BF, Geer LA, Dalloul M, Abulafia O, Halden RU. Maternal and fetal exposure to parabens in a multiethnic urban U.S. population. Environ Int. 2015;84:193–200. [PubMed: 26364793]
37. Hanna-Attisha M, LaChance J, Sadler RC, Champney Schnepp A. Elevated Blood Lead Levels in Children Associated With the Flint Drinking Water Crisis: A Spatial Analysis of Risk and Public Health Response. American journal of public health. 2016;106(2):283–90. [PubMed: 26691115]
38. Hopenhayn C, Huang B, Christian J, Peralta C, Ferreccio C, Atallah R, et al. Profile of urinary arsenic metabolites during pregnancy. Environ Health Perspect. 2003;111(16):1888–91. [PubMed: 14644662]
39. Zota AR, Phillips CA, Mitro SD. Recent Fast Food Consumption and Bisphenol A and Phthalates Exposures among the U.S. Population in NHANES, 2003–2010. Environ Health Perspect. 2016;124(10):1521–8. [PubMed: 27072648]
40. Prevention CfDCa. Fourth Report on Human Exposure to Environmental Chemicals, Updated Tables (January 2017).. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, 2017.
41. Johns LE, Ferguson KK, Soldin OP, Cantonwine DE, Rivera-Gonzalez LO, Del Toro LV, et al. Urinary phthalate metabolites in relation to maternal serum thyroid and sex hormone levels during pregnancy: a longitudinal analysis. Reproductive biology and endocrinology : RB&E. 2015;13:4. [PubMed: 25596636]
42. Bellavia A, Hauser R, Seely EW, Meeker JD, Ferguson KK, McElrath TF, et al. Urinary phthalate metabolite concentrations and maternal weight during early pregnancy. Int J Hyg Environ Health. 2017;220(8):1347–55. [PubMed: 28939183]
43. Vrijkotte TGM, Hrudey EJ, Twickler MB. Early Maternal Thyroid Function During Gestation Is Associated With Fetal Growth, Particularly in Male Newborns. The Journal of Clinical Endocrinology & Metabolism. 2017;102(3):1059–66. [PubMed: 28359096]
44. Kim SY, Sharma AJ, Sappenfield W, Wilson HG, Salihu HM. Association of maternal body mass index, excessive weight gain, and gestational diabetes mellitus with large-for-gestational-age births. Obstetrics and gynecology. 2014;123(4):737–44. [PubMed: 24785599]
45. Sathyanarayana S, Barrett E, Nguyen R, Redmon B, Haaland W, Swan SH. First Trimester Phthalate Exposure and Infant Birth Weight in the Infant Development and Environment Study. Int J Environ Res Public Health. 2016; 13(10).

46. Liu J, Li J, Wu Y, Zhao Y, Luo F, Li S, et al. Bisphenol A Metabolites and Bisphenol S in Paired Maternal and Cord Serum. Environ Sci Technol. 2017;51(4):2456–63. [PubMed: 28110528]
47. Catanese MC, Vandenberg LN. Bisphenol S (BPS) Alters Maternal Behavior and Brain in Mice Exposed During Pregnancy/Lactation and Their Daughters. Endocrinology.2017; 158(3):516–30. [PubMed: 28005399]
48. Ivry Del Moral L, Le Corre L, Poirier H, Niot I, Truntzer T, Merlin JF, et al. Obesogen effects after perinatal exposure of 4,4'-sulfonyldiphenol (Bisphenol S) in C57BL/6 mice. Toxicology. 2016;357–358:11–20.
49. Castro B, Sanchez P, Torres JM, Ortega E. Bisphenol A, bisphenol F and bisphenol S affect differently 5alpha-reductase expression and dopamine-serotonin systems in the prefrontal cortex of juvenile female rats. Environ Res. 2015;142:281–7. [PubMed: 26186136]
50. Cantonwine DE, Ferguson KK, Mukherjee B, Chen YH, Smith NA, Robinson JN, et al. Utilizing Longitudinal Measures of Fetal Growth to Create a Standard Method to Assess the Impacts of Maternal Disease and Environmental Exposure. PLoS One. 2016;11(1):e0146532. [PubMed: 26731406]
51. Lopes KRM, Souza ASR, Figueiroa JN, Alves JGB. Correlation between pre-pregnancy body mass index and maternal visceral adiposity with fetal biometry during the second trimester. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2017;138(2):133–7.
52. Wu CT, Lu TY, Chan DC, Tsai KS, Yang RS, Liu SH. Effects of arsenic on osteoblast differentiation in vitro and on bone mineral density and microstructure in rats. Environ Health Perspect. 2014;122(6):559–65. [PubMed: 24531206]
53. Taylor CM, Golding J, Emond AM. Adverse effects of maternal lead levels on birth outcomes in the ALSPAC study: a prospective birth cohort study. Bjog. 2015;122(3):322–8. [PubMed: 24824048]
54. Wang H, Li J, Hao JH, Chen YH, Liu L, Yu Z, et al. High serum lead concentration in the first trimester is associated with an elevated risk of small-for-gestational-age infants. Toxicol Appl Pharmacol. 2017;332:75–80. [PubMed: 28755861]
55. Beier EE, Maher JR, Sheu T-J, Cory-Slechta DA, Berger AJ, Zuscik MJ, et al. Heavy Metal Lead Exposure, Osteoporotic-like Phenotype in an Animal Model, and Depression of Wnt Signaling. Environmental Health Perspectives. 2013;121(1):97–104. [PubMed: 23086611]
56. Mattson M P, Calabrese E Hormesis: What it is and Why it Matters2009. 1–13 p.

Table 1.

Demographic Characteristics of the Michigan Mother Infant Pairs (MMIP) Study (n=56)

	Median or N (%)	Range (Min – Max)
Mother		
Age	31.5	(26 – 40)
Pre-pregnancy BMI [a]	23.41	(19.24 – 48.41)
Parity		
0	14 (25.0)	
1	21 (37.5)	
2	14 (25.0)	
3	5 (8.9)	
4	2 (3.6)	
Smoking status		
Never	49 (89.1)	
Past smoker	6 (10.9)	
Education		
High School	4 (7.1)	
Some college	34 (60.7)	
≥ Bachelor's	18 (32.1)	
Marital status		
Married	50 (89.3)	
Single	6 (10.7)	
Infant		
Gestational age (weeks)	39.9	(37.6 – 41.7)
Infant gender		
Female	29 (51.8)	
Male	27 (48.2)	
Route of delivery		
Cesarean	19 (33.9)	
Vaginal	37 (66.1)	
Birthweight (g)	3520	(2805 – 4685)
Fenton z-score % tile	59.65	(6.58 – 95.14)
Fetal Anthropometry [b]		
Abdominal circ.	138.7	(111 – 242)
Biparietal diameter	43.85	(36 – 70)
Femur length	29.5	(23 – 51)
Head circ. [c]	162.25	(135 – 265)

[a] n=53

[b] Units= mm

[c] Circ: circumference

Table 2.

Phthalate, Phenol, and Metal Concentrations in First Trimester Maternal Urine Samples (n=56)

						Percentiles							
Exposure	**LOD**	**N< LOD**	**% < LOD**	**GM**	**95% CI**	**Min**	**10th**	**25th**	**50th**	**75th**	**95th**	**99th**	**Max**
Phthalates (μg/L)													
MnBP	0.20	0	0	6.87	(5.11, 9.23)	0.43	1.39	4.10	6.70	14.29	41.46	54.37	54.37
MBzP	0.50	2	3.6	4.20	(2.91, 6.06)	<LOD	0.75	1.60	4.33	9.63	31.07	351.85	351.85
MCOMHP	0.20	0	0	4.18	(2.89, 6.04)	<LOD	0.35	0.72	1.47	2.60	6.34	14.53	14.53
mCINP	0.20	4	7.2	1.29	(0.98, 1.71)	0.29	0.75	1.60	4.33	9.63	31.07	351.85	351.85
MCPP	0.10	5	8.9	1.38	(0.90, 2.11)	<LOD	0.17	0.49	1.40	4.13	24.70	55.34	55.34
MeCPP	0.20	0	0	5.14	(3.79, 6.97)	0.32	1.16	2.26	4.79	12.83	29.50	40.91	40.91
MEHHP	0.10	0	0	5.30	(3.92, 7.16)	0.47	1.14	2.45	5.47	11.63	31.08	40.93	40.93
MEHP	1.00	20	35.7	1.93	(1.51, 2.47)	<LOD	<LOD	<LOD	2.04	4.24	9.83	11.85	11.85
MEOHP	0.10	0	0	2.76	(2.03, 3.76)	0.25	0.61	1.21	2.67	6.08	18.00	20.47	20.47
MEP	1.00	0	0	18.04	(12.20, 26.67)	1.49	3.97	5.85	15.16	46.85	300.06	1598.01	1598.01
MiBP	0.10	1	1.8	3.34	(2.37, 4.70)	<LOD	0.57	1.97	4.02	7.45	27.04	40.80	40.80
mINP	0.50	55	98.2	0.36	(0.34, 0.39)	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	1.90	1.90
ΣDEHP[a]	-	-	-	15.50	(11.65, 20.62)	1.77	3.60	6.88	14.23	34.52	82.15	103.60	103.60
ΣDBP [a]	-	-	-	10.74	(7.98, 14.45)	0.51	1.92	6.33	11.10	24.06	59.57	68.50	68.50
Phenols (μg/L)													
2,4-DCP	0.20	20	35.7	0.40	(0.29, 0.54)	<LOD	<LOD	<LOD	0.28	0.99	3.17	13.10	13.10
2,5-DCP	0.20	21	35.7	0.42	(0.28, 0.63)	<LOD	<LOD	<LOD	0.26	0.72	11.51	298.49	298.49
BP-3	0.20	0	0	58.35	(34.52, 98.61)	1.08	4.74	17.85	51.24	141.83	1678.11	13235.78	13235.78
BPA	0.20	13	23.2	0.71	(0.52, 0.98)	<LOD	<LOD	0.26	0.72	2.05	4.58	4.76	4.76
BPF	0.20	37	66.1	0.26	(0.20, 0.36)	<LOD	<LOD	<LOD	<LOD	0.41	2.61	29.73	29.73
BPS	0.20	35	62.5	0.21	(0.18, 0.26)	<LOD	<LOD	<LOD	<LOD	0.26	1.13	1.55	1.55
BuPB	0.20	39	69.6	0.27	(0.20, 0.37)	<LOD	<LOD	<LOD	<LOD	0.37	6.02	10.55	10.55
EtPB	0.20	21	37.5	1.07	(0.57, 2.00)	<LOD	<LOD	<LOD	0.52	3.33	220.34	769.09	769.09
MePB	0.20	0	0	53.08	(32.20, 87.49)	0.78	5.36	14.94	60.44	233.00	1225.90	1441.48	1441.48
PrPB	0.20	3	5.4	8.21	(4.67, 14.42)	<LOD	0.66	1.13	11.50	61.72	115.80	316.57	316.57

Exposure	LOD	N< LOD	% < LOD	GM	95% CI	Percentiles							
						Min	10th	25th	50th	75th	95th	99th	Max
TCC	0.20	50	89.3	0.17	(0.14, 0.21)	<LOD	<LOD	<LOD	<LOD	<LOD	1.04	5.45	5.45
TCS	0.20	4	7.1	14.50	(8.28, 25.40)	<LOD	0.74	5.60	15.39	73.33	368.89	1007.81	1007.81
Metals (μ/L)													
As	0.30	0	0	4.30	(3.07, 6.00)	0.50	0.93	1.69	3.80	8.58	43.00	270.00	270.00
Ba	0.10	0	0	5.00	(3.88, 6.44)	0.53	1.65	2.68	4.60	10.19	23.93	31.88	31.88
Be	0.04	45	81.8	0.04	(0.03, 0.04)	0.03	0.03	0.03	0.03	0.03	0.21	0.36	0.36
Cd	0.06	30	54.6	0.08	(0.07, 0.11)	<LOD	<LOD	<LOD	<LOD	0.15	0.47	0.77	0.77
Cr	0.40	7	12.7	0.69	(0.60, 0.80)	0.28	0.28	0.45	0.71	1.02	1.98	2.48	2.48
Cu	2.50	3	5.5	8.10	(6.64, 9.89)	<LOD	2.95	4.55	9.13	14.73	23.16	26.86	26.86
Hg	0.05	26	47.3	0.07	(0.06, 0.09)	0.04	0.04	0.04	0.06	0.13	0.37	0.75	0.75
Mn	0.08	0	0	1.44	(1.20,1.73)	0.33	0.8	1.04	1.54	2.13	6.45	6.95	6.95
Mo	0.30	0	0	49.20	(38.31,63.19)	6.13	15.67	26.08	48.02	95.44	220.94	344.48	344.48
Ni	0.80	1	1.8	3.77	(3.06,4.64)	0.57	1.31	1.93	3.98	6.55	12.02	17.67	17.67
Pb	0.10	13	23.6	0.22	(0.17,0.28)	<LOD	<LOD	0.11	0.21	0.46	0.91	2.86	2.86
Se	0.70	0	0	41.63	(33.23,52,15)	8.17	14.25	21.01	45.34	69.70	157.16	191.80	191.80
Sn	0.10	11	20.0	0.31	(0.23,0.43)	<LOD	<LOD	0.12	0.32	0.61	1.87	4.90	4.90
Tl	0.02	1	1.8	0.16	(0.13,0.20)	<LOD	0.06	0.90	0.18	0.27	0.52	0.65	0.65
U	0.01	46	83.6	0.01	(0.01,0.01)	0.01	0.01	0.01	0.01	0.01	0.02	0.04	0.04
W	0.20	48	87.3	0.16	(0.14,0.17)	<LOD	<LOD	<LOD	<LOD	<LOD	0.34	0.49	0.49
Zn	2.00	0	0	169.87	(129.09,223.54)	8.35	43.47	78.40	195.43	378.07	740.06	1003.10	1003.10
ΣExposure													
Phthalates	-	-	87.1[b]	10.40	(10.13,10.68)	8	9	10	11	11	11	12	12
Phenols	-	-	63.8[b]	7.34	(6.75,7.99)	2	5	6	8	9	11	11	11
Metals[bc]	-	-	75.3[b]	12.63	(12.07,13.22)	8	10	12	13	14	15	17	17
Total[bc]	-	-	74.8[b]	30.28	(28.94,31.68)	17	25	29	31	34	36	38	38

[a] Units:μg/L

[b] PercentofchemicalsaboveLOD

[c] n=55women

GM:Geometricmean

ΣExposurereflectsthenumberofchemicalsaboveLODineachclass(phthalate,phenol,andmetal)andall-inclusivesum(total);ΣPhthalates:MnBP,MBzP,MCOMHP,mCINP,MCPP,meCPP,MEHHP,MEHP,MEOHP,MEP,MiBP,mINP;ΣPhenols:2,4-DCP,2,5-DCP,BP-3,BPA,BPF,BPS,BuPB,MePB,PrPB,TCC,TCS;ΣMetals:As,Ba,Be,Cd,Cr,Cu,Hg,Mn,Mo,Ni,Pb,Se,Sn,Tl,U,W,Zn;Total:ΣPhthalates,ΣPhenols,ΣMetals

Table 3.

Maternal Self-Reported Product Use, Fast Food and Vegetable Consumption

	N (%)
Uses perfume & cosmetics	
No	13 (23.2)
Yes	43 (76.8)
Uses haircare products	
No	13 (23.2)
Yes	43 (76.8)
Canned food consumption	
None	25 (44.6)
Yes	31 (55.4)
Canned food frequency	
None	25 (44.6)
1 serving or less per day	30 (53.6)
2–3 servings per day	1 (1.8)
4 servings or more per day	0 (0)
Fast food consumption	
None	36 (64.3)
Yes	20 (35.7)
Fast food frequency	
None	36 (64.3)
Once per week	15 (26.8)
2–3 times per week	3 (5.4)
4 or more times per week	2 (3.6)
Fresh vegetable consumption	
None	2 (3.6)
Yes	54 (96.4)
Fresh vegetable frequency	
None	2 (3.7)
1–3 servings per day	38 (70.4)
4–5 servings per day	13 (24.1)
6 or more servings per day	1 (1.9)

Table 4.

Associations between Exposure Biomarkers (μg/L) and Birth Outcomes (n=56)

	Birth-weight (g) [a]			*Fenton z score* [b]		
Exposure [c]	**β**	**(95% CI)**	**p-value**	**β**	**(95% CI)**	**p-value**
Phthalates						
MnBP	39.25	(−78.24, 156.73)	0.51	0.12	(−0.13, 0.37)	0.34
MBzP	11.02	(−75.68, 97.72)	0.80	0.06	(−0.12, 0.24)	0.52
MCOMHP	11.57	(−74.68, 97.82)	0.79	0.06	(−0.12, 0.24)	0.51
mCINP	92.52	(−22.70, 207.73)	0.11	0.21	−0.03, 0.46)	0.08
MCPP	**78.48**	**(2.95, 154.01)**	**0.04**	**0.19**	**(0.02, 0.35)**	**0.02**
meCPP	22.62	(−88.83, 134.08)	0.69	0.05	(−0.19, 0.29)	0.68
MEHHP	−3.38	(−119.37, 112.61)	0.96	−0.02	(−0.27, 0.23)	0.86
MEHP	66.05	(−70.10, 202.19)	0.33	0.04	(−0.25, 0.34)	0.76
MEOHP	6.30	(−108.48, 121.07)	0.91	−0.01	(−0.25, 0.24)	0.95
MEP	3.80	(−72.02, 79.62)	0.92	0.02	(−0.14, 0.18)	0.82
MiBP	31.42	(−65.96, 128.80)	0.52	0.04	(−0.17, 0.25)	0.69
ΣDEHP [d]	17.77	(−106.54, 142.08)	0.78	0.02	(−0.25, 0.28)	0.91
ΣDBP [e]	38.37	(−81.32, 158.07)	0.52	0.10	(−0.15, 0.36)	0.43
Phenols						
2,4-DCP	−52.80	(−159.59, 53.99)	0.32	−0.10	(−0.32, 0.14)	0.44
2,5-DCP	7.26	(−65.24, 79.75)	0.84	0.01	(−0.15, 0.16)	0.93
BP-3	15.11	(−38.41, 68.64)	0.57	0.02	(−0.10, 0.13)	0.75
BPA	13.18	(−88.64, 115.00)	0.80	0.01	(−0.21, 0.23)	0.94
BPF	54.14	(−47.73, 156.00)	0.29	0.02	(−0.20, 0.23)	0.87
BPS	**−150.42**	**(−294.85, −6.00)**	**0.04**	**−0.31**	**(−0.62, 0.002)**	**0.05**
BuPB	−62.66	(−142.67,17.35)	0.12	−0.12	(−0.29, 0.05)	0.16
EtPB	12.29	(−34.25, 58.83)	0.60	0.01	(−0.09, 0.10)	0.91
MePB	−31.87	(−90.54, 26.80)	0.28	−0.05	(−0.17, 0.07)	0.43
PrPB	−16.60	(−64.77, 31.56)	0.49	−0.03	(−0.13, 0.07)	0.51
TCS	−4.01	(−60.50, 52.48)	0.89	0.04	(−0.06, 0.16)	0.39
Metals [f]						
As	9.03	(−92.34, 110.39)	0.86	−0.002	(−0.22, 0.21)	0.98
Ba	26.31	(−81.92, 134.54)	0.63	−0.08	(−0.16, 0.31)	0.52
Cd	45.91	(−111.43, 203.26)	0.56	−0.07	(−0.38, 0.24)	0.65
Cr	80.83	(−131.60, 293.26)	0.76	0.10	(−0.36, 0.55)	0.67
Cu	20.83	(−146.22, 187.89)	0.80	−0.05	(−0.40, 0.30)	0.79
Hg	−46.59	(−165.60,72.43)	0.44	−0.08	(−0.34, 0.17)	0.51
Mn	−36.68	(−231.23, 157.87)	0.71	−0.18	(−0.59, 0.23)	0.39
Mo	65.84	(−82.23, 213.92)	0.38	0.17	(−0.15, 0.48)	0.29
Ni	72.87	(−90.92, 236.65)	0.38	0.10	(−0.25, 0.45)	0.58
Pb	13.46	(−107.64, 134.57)	0.82	−0.07	(−0.31, 0.18)	0.60

	Birth-weight (g) [a]			*Fenton z score* [b]		
Exposure [c]	**β**	**(95% CI)**	**p-value**	**β**	**(95% CI)**	**p-value**
Se	−29.09	(−254.83, 196.65)	0.80	0.01	(−0.46, 0.49)	0.96
Sn	−25.45	(−140.31, 89.42)	0.67	−0.07	(−0.31, 0.17)	0.55
Tl	4.42	(−139.64, 148.48)	0.95	0.00	(−0.31, 0.30)	0.99
Zn	36.69	(−94.83, 168.21)	0.58	0.08	(−0.20, 0.36)	0.55
Σ scores						
Phthalates	9.46	(−3.71, 22.63)	0.16	0.01	(−0.01, 0.04)	0.33
Phenols	0.48	(−18.07, 19.04)	0.96	−0.01	(−0.04, 0.03)	0.82
Metals [f]	4.13	(−4.81, 19.11)	0.24	0.01	(−0.02, 0.03)	0.67
Total [f]	0.82	(−2.45, 7.56)	0.31	0.00	(−0.01, 0.01)	0.62

[a] Multiple linear regression models were run for each toxicant/element adjusting for specific gravity, gestational age, and gender

[b] Multiple linear regression models were run for each toxicant/element adjusting for Specific gravity

[c] Natural log transformation

[d] ΣDEHP includes metabolites: MeCPP, MeHHP, MEHP & MEOHP

[e] ΣDBP includes metabolites: MnBP & MiBP

[f] n=55

Table 5.

Associations between Exposure Biomarkers (μg/L) and Standardized Fetal Anthropometry in mm (n=56)

	Abdominal Circumference			Biparietal diameter			Femur length			Head Circumference		
Exposure [a,b]	**β**	**(95% CI)**	**p-value**	**β**	**(95% CI)**	**p-value**	**β**	**(95% CI)**	**p-value**	**β**	**(95% CI)**	**p-value**
Phthalate												
MnBP	−0.19	(−0.97, 0.58)	0.62	−0.12	(−0.37, 0.13)	0.35	−0.17	(−0.41, 0.07)	0.16	−0.42	(−1.85, 1.00)	0.55
MBzP	−0.04	(−0.59, 0.51)	0.88	0.13	(−0.05, 0.30)	0.16	−0.01	(−0.18, 0.18)	0.95	−0.09	(−1.12, 0.93)	0.85
MCOMHP	−0.04	(−0.59, 0.51)	0.88	0.13	(−0.05, 0.30)	0.16	−0.01	(−0.19, 0.17)	0.91	−0.10	(−1.12, 0.92)	0.85
mCINP	−0.24	(−1.02, 0.53)	0.53	0.04	(−0.22, 0.29)	0.78	0.02	(−0.23, 0.26)	0.90	0.06	(−1.38, 1.49)	0.93
MCPP	−0.18	(−0.69, 0.34)	0.49	0.07	(−0.10, 0.24)	0.41	−0.06	(−0.22, 0.11)	0.48	−0.05	(−1.01, 0.90)	0.91
meCPP	−0.26	(−0.99, 0.47)	0.48	0.10	(−0.14, 0.34)	0.42	−0.11	(−0.34, 0.12)	0.35	−0.24	(−1.60, 1.11)	0.72
MEHHP	−0.29	(−1.04, 0.47)	0.45	0.13	(−0.12, 0.37)	0.31	−0.13	(−0.37, 0.11)	0.27	−0.37	(−1.77, 1.03)	0.60
MEHP	−0.68	(−1.55, 0.21)	0.13	0.06	(−0.23, 0.36)	0.66	−0.20	(−0.49, 0.08)	0.15	−0.97	(−2.62, 0.67)	0.24
MEOHP	−0.22	(−0.97, 0.53)	0.56	0.12	(−0.12, 0.36)	0.33	−0.13	(−0.37, 0.10)	0.27	−0.26	(−1.66, 1.13)	0.70
MEP	**0.53**	**(0.05, 1.01)**	**0.03**	−0.01	(−0.17, 0.16)	0.94	−0.01	(−0.17, 0.15)	0.90	0.60	(−0.30, 1.51)	0.19
MiBP	−0.15	(−0.79, 0.49)	0.63	−0.11	(−0.32, 0.10)	0.30	−0.12	(−0.22, 0.19)	0.85	−0.30	(−1.49, 0.88)	0.61
ΣDEHP [c]	−0.34	(−1.15, 0.48)	0.41	0.13	(−0.13, 0.40)	0.32	−0.14	(−0.40, 0.11)	0.27	−0.39	(−1.90, 1.11)	0.60
ΣDBP [d]	−0.17	(−0.96, 0.61)	0.66	−0.14	(−0.40, 0.11)	0.27	−0.12	(−0.37, 0.13)	0.35	−0.41	(−1.87, 1.04)	0.57
Phenols												
2,4-DCP	0.41	(−0.29, 1.11)	0.25	0.05	(−0.18, 0.29)	0.64	−0.04	(−0.26, 0.19)	0.74	0.56	(−0.75, 1.86)	0.40
2,5-DCP	0.19	(−0.29, 0.66)	0.44	0.05	(−0.10, 0.21)	0.49	0.03	(−0.13, 0.18)	0.72	0.11	(−0.77, 1.00)	0.80
BP-3	0.25	(−0.09, 0.60)	0.15	0.01	(−0.10, 0.13)	0.85	0.004	(−0.11, 0.12)	0.94	0.41	(−0.23, 1.05)	0.21
BPA	0.09	(−0.58, 0.75)	0.79	0.16	(−0.05, 0.37)	0.14	−0.11	(−0.32, 0.11)	0.32	0.15	(−1.09, 1.38)	0.82
BPF	−0.07	(−0.74, 0.59)	0.82	−0.11	(−0.32, 0.11)	0.32	−0.03	(−0.25, 0.18)	0.75	−0.15	(−1.38, 1.09)	0.81
BPS	0.29	(−0.70, 1.27)	0.56	0.12	(−0.20, 0.44)	0.46	−0.07	(−0.38, 0.25)	0.67	0.36	(−1.47, 2.18)	0.70
BuPB	0.28	(−0.25, 0.81)	0.30	0.03	(−0.15, 0.20)	0.76	0.15	(−0.01, 0.32)	0.07	0.53	(−0.45, 1.51)	0.29
EtPB	0.04	(−0.26, 0.35)	0.78	0.02	(−0.08,0.12)	0.66	−0.001	(−0.10, 0.10)	0.99	0.02	(−0.54, 0.59)	0.94
MePB	0.29	(−0.07, 0.66)	0.12	−0.01	(−0.14, 0.11)	0.83	0.01	(−0.11, 0.13)	0.92	0.56	(−0.11, 1.24)	0.10
PrPB	0.10	(−0.21, 0.41)	0.51	−0.05	(−0.15, 0.05)	0.32	0.01	(−0.10, 0.11)	0.89	0.32	(−0.24, 0.89)	0.26
TCS	−0.07	(−0.44, 0.30)	0.69	−0.05	(−0.07, 0.07)	0.44	−0.04	(−0.16, 0.07)	0.46	−0.12	(−0.81, 0.56)	0.72

Exposure [a,b]	Abdominal Circumference β	Abdominal Circumference (95% CI)	Abdominal Circumference p-value	Biparietal diameter β	Biparietal diameter (95% CI)	Biparietal diameter p-value	Femur length β	Femur length (95% CI)	Femur length p-value	Head Circumference β	Head Circumference (95% CI)	Head Circumference p-value
Metals [e]												
As	−0.36	(−1.01, 0.30)	0.28	0.05	(−0.16, 0.27)	0.51	**−0.26**	**(−0.46, −0.07)**	**0.01**	−0.76	(−1.97, 0.44)	0.21
Ba	−0.37	(−1.08, 0.33)	0.29	−0.08	(−0.31, 0.15)	0.50	**−0.25**	**(−0.55, −0.15**	**0.001**	−0.58	(−1.88, 0.72)	0.38
Cd	0.44	(−0.53, 1.40)	0.37	0.02	(−0.30, 0.34)	0.89	−0.28	(−0.58, 0.02)	0.06	0.73	(−1.05, 2.52)	0.41
Cr	−0.06	(−1.45, 1.33)	0.93	−0.16	(−0.61, 0.29)	0.48	−0.42	(−0.84, 0.004)	0.05	0.09	(−2.46, 2.64)	0.94
Cu	0.38	(−0.71, 1.48)	0.48	0.17	(−0.18, 0.52)	0.34	−0.01	(−0.36, 0.33)	0.94	0.86	(−1.14, 2.86)	0.39
Hg	0.30	(−0.48, 1.08)	0.44	0.10	(−0.15, 0.35)	0.43	−0.08	(−0.32, 0.17)	0.54	1.13	(−0.27, 2.53)	0.11
Mn	0.20	(−1.07, 1.48)	0.75	0.39	(−0.02, 0.79)	0.06	0.12	(−0.28, 0.52)	0.55	0.79	(−1.54, 3.13)	0.50
Mo	0.39	(−0.58, 1.36)	0.42	0.02	(−0.30, 0.33)	0.92	−0.13	(−0.43, 0.17)	0.39	0.66	(−1.12, 2.44)	0.46
N	−0.26	(−1.34, 0.82)	0.63	0.03	(−0.32, 0.38)	0.87	−0.27	(−0.60, 0.06)	0.11	−0.29	(−2.28, 1.70)	0.77
Pb	−0.46	(−1.24, 0.32)	0.25	0.16	(−0.10, 0.41)	0.23	**−0.28**	**(−0.51, −0.04)**	**0.02**	−0.38	(−1.83, 1.08)	0.61
Se	0.73	(−0.73,2.20)	0.32	−0.12	(−0.59, 0.37)	0.65	−0.26	(−0.72, 0.20)	0.26	1.31	(−1.39, 4.01)	0.33
Sn	0.52	(−0.22, 1.26)	0.17	0.12	(−0.12, 0.37)	0.32	−0.16	(−0.40, 0.07)	0.16	1.16	(−0.19, 2.51)	0.09
Tl	0.19	(−0.75, 1.12)	0.69	0.07	(−0.23, 0.38)	0.64	−0.16	(−0.45, 0.13)	0.28	0.71	(−1.00, 2.43)	0.41
Zn	0.07	(−0.79, 0.93)	0.86	0.03	(−0.25, 0.31)	0.86	−0.23	(−0.49, 0.03)	0.08	0.41	(−1.16, 2.00)	0.60
Σ scores												
Phthalates	−0.02	(−0.10, 0.07)	0.70	−0.01	(−0.04, 0.02)	0.36	−0.01	(−0.04, 0.02)	0.41	−0.02	(−0.19, 0.14)	0.76
Phenols	0.05	(−0.07,0.17)	0.42	−0.02	(−0.06, 0.02)	0.37	−0.01	(−0.05, 0.03)	0.62	0.10	(−0.12, 0.32)	0.37
Metals [e]	0.01	(−0.07, 0.09)	0.82	−0.01	(−0.01, 0.01)	0.39	−0.02	(−0.04, 0.01)	0.17	0.03	(−0.11, 0.17)	0.69
Total [e]	0.004	(−1.36, 1.20)	0.90	−0.01	(−0.02, 0.01)	0.35	−0.01	(−0.02, 0.004)	0.22	0.01	(−0.05, 0.07)	0.67

[a] All analyses adjusted for Specific gravity and gender

[b] Natural log transformation of exposure

[c] ΣDEHP includes metabolites: meCPP, MEHHP, MEHP & MEOHP

[d] ΣDBP includes metabolites: MnBP & MiBP

[e] n=55