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Bisphenol A and phthalates *in utero* and in childhood: association with child BMI z-score and adiposity

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ABSTRACT

Objective: To assess the relationship between *in utero* and concurrent child urinary exposures to bisphenol A (BPA) and phthalates with BMI *z*-score, waist circumference, and sum of triceps and subscapular skinfold thickness in Mexican children.

Methods: Among participants (N = 249) from the Early Life Exposure in Mexico to ENvironmental Toxicants study, we evaluated associations between maternal third trimester and concurrent urinary BPA and individual and summed phthalates metabolites (ΣDi(2-ethylhexyl phthalate), Σhigh molecular weight, Σlow molecular weight) with measures of weight status and adiposity in children aged 8–14 years. Linear regressions with specific-gravity corrected and natural log-transformed urinary concentrations were estimated, adjusting for covariates. Effect modification by sex was explored.

Results: Prenatal urinary exposure to monobenzyl phthalate (MBzP) was inversely associated with child's BMI *z*-score (β = −0.21, 95%CI: −0.41, −0.02) and child urinary exposure to mono(2-ethylhexyl)phthalate (MEHP) was inversely associated with waist circumference (β = −1.85, 95%CI: −3.36, −0.35) and sum of skinfold thicknesses (β = −2.08, 95%CI: −3.80, −0.37) after adjusting for confounders. In the childhood exposure period, sex modified the relationships with BPA, MEHP, MBzP, monoethyl phthalate (MEP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP). In girls, increased BPA exposure was positively associated with sum of skinfold thickness (β = 3.47, 95%CI: 0.05, 6.40) while increased MEHP was inversely associated with sum of skinfold thicknesses in boys (β = −2.95, 95%CI: −5.08, −0.82); these results remained in sensitivity analyses after excluding children who had initiated pubertal development (Tanner stage > 1 for pubic hair). We did not observe relationships between summed phthalates metabolites at any exposure period with outcome measures.

Conclusion: Our results identified associations between urinary BPA and phthalates metabolites with measures of weight status and adiposity that differed by timing of exposure, sex, and pubertal status. Additional studies are needed to explore how associations may differ between those who are pre- and post-pubertal.

1. Introduction

Childhood obesity continues to be a globally persistent disease with a wide range of complications and is known to track into adulthood (Guo et al., 1994; Mangner et al., 2014; Ebbeling et al., 2002). Differences between energy intake and physical activity expenditure are considered the largest risk factors for the development of obesity, but increasing evidence suggests exposures to environmental endo-

Abbreviations: BMI, Body mass index; BPA, Bisphenol A; CI, Confidence Interval; DEHP, Di(2-ethylhexyl) phthalate; EDC, Endocrine-disrupting compound; HMW, high molecular weight; LMW, low molecular weight; MBP, Mono-*n*-butyl phthalate; MBzP, Monobenzyl phthalate; MCPP, Mono(3-carboxypropyl) phthalate; MECPP, Mono(2-ethyl-5-carboxypentyl) phthalate; MEHP, Mono(2-ethyl-5-oxohexyl) phthalate; MEHHP, Mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, Mono(20ethyl-5-oxohexyl) phthalate; MEP, Monoethyl phthalate; MiBP, Mono-isobutyl phthalate; MW, Molecular weight; NHANES, National Health and Nutrition Examination Survey; SD, Standard Deviation

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crine-disrupting compounds (EDCs) such as bisphenol A (BPA) and phthalates are implicated in weight dysregulation (Baillie-Hamilton, 2002; Grün and Blumberg, 2009).

BPA and phthalates are multi-functional materials used in everyday products, resulting in widespread exposure to these compounds and their metabolites (Silva et al., 2004; Callan et al., 2012). BPA is frequently found in plastic food containers, the lining of food cans, toys, and thermal receipt paper (Vandenberg et al., 2007; Mendum et al., 2011). Phthalates are also found in a variety of common consumer goods. Low molecular weight (LMW) phthalates are generally used in personal care products such as lotions, creams, and perfumes, while high molecular weight (HMW) phthalates are used as a component of harder plastics, such as vinyl flooring, food containers, and medical tubing (Braun et al., 2013; Meeker et al., 2009; Lewis et al., 2013; Hauser and Calafat, 2005). These metabolites have been detected during pregnancy, as well as in the amniotic sac and cord blood (Callan et al., 2012; Vandenberg et al., 2007; Chou et al., 2011).

Cross-sectional studies in humans show that urinary BPA and phthalates metabolites may be associated with increased body mass index (BMI), waist circumference, and adiposity, with suggestions of sex differences, but results remain inconclusive depending on population, sex, and age of exposure (Yaghjyan et al., 2015; Zhang et al., 2014; Wang et al., 2012; Eng et al., 2013; Shankar et al., 2012; Carwile and Michels, 2011; Hatch et al., 2010; Trasande et al., 2013a, 2013b, 2012; Wells et al., 2013; Bhandari et al., 2013; Li et al., 2013; Buckley et al., 2016a, 2016b). Few longitudinal studies relate *in utero* exposures to obesity-related outcomes in later childhood and adolescence (Liu and Peterson, 2015). A prospective study of prenatal exposure to BPA in the Rhea cohort from Greece found increased exposure to be positively associated with BMI *z*-scores in boys at 4 years of age, but negatively with girls, while cross-sectional analyses of these children at 4 years old observed higher BPA concentrations to be associated with increased BMI *z*-scores, waist circumference, and sum of skinfold thickness (Vafeiadi et al., 2016). Phthalates studies are also inconclusive: *in utero* exposures were found to have no association with fat mass in children aged 4–9 years (Buckley et al., 2016a), decreased BMI *z*-scores only in girls aged 4–7 years (Buckley et al., 2016b), or only in boys aged 4 or 7 years old (Valvi et al., 2015).

BPA and phthalates are well-known to be endocrine-disrupting chemicals (Grün and Blumberg, 2009; Meeker et al., 2007). Exposures to these compounds could increase risk of developing chronic diseases, such as altered weight status, through potential mechanisms: alterations in thyroid hormone, in estrogen and androgen levels, in glucose tolerance and insulin resistance, or through the peroxisome proliferator pathways (Grün and Blumberg, 2009; Vandenberg et al., 2007; De Coster and van Larebeke, 2012). As pregnancy is a sensitive period for the development of obesity in offspring due to rapid cell differentiation occurring in the fetus, exposures to these compounds during this period are of special concern (Dietz, 1994; Gluckman et al., 2007). Accumulating evidence suggests these compounds play a role in influencing physiology from the perinatal period onwards, with animal studies showing effects on weight gain, adiposity, and alterations in satiety hormones (Angle et al., 2013; Xu et al., 2011; Wei et al., 2011; Valvi et al., 2013; Braun et al., 2014).

In a population of children and youths aged 8–14 years in Mexico City, this study investigated the impact of prenatal and concurrent exposures to BPA and phthalates metabolites on BMI *z*-score, waist circumference, and skinfolds in children older than previously reported in the literature. We also explored sex-specific differences in these associations.

2. Materials and methods

2.1. Study population

The study population involved participants (N = 249) from the 22-year Early Life Exposure in Mexico to ENvironmental Toxicants (ELEMENT) research collaboration with Mexico's *Instituto Nacional de Salud Pública* (INSP) that consists of three birth cohorts developed to study the role that exposures to environmental toxicants play on health and development in early life. Between 1994 and 2003, 2075 mothers were recruited during the first trimester of pregnancy or at delivery from maternity hospitals in Mexico City. Similar exclusion criteria were applied to all cohorts, including living outside Mexico City, gestational diabetes, preeclampsia, or pregnancy-related hypertensive disorders, as well as other criteria as described elsewhere (Gonzalez-Cossio et al., 1997; Téllez-Rojo et al., 2004; Ettinger et al., 2009). Study methods have been described previously (Gonzalez-Cossio et al., 1997; Téllez-Rojo et al., 2004, 2002; Ettinger et al., 2009; Hernandez-Avila et al., 2003; Hu et al., 2006). In 2012, 250 mother-child pairs from cohorts 2 and 3 were re-recruited when the children were between the ages of 8 and 14 years, in order to prioritize the peripubertal period and the availability archived maternal biological specimens. Among the 250 children, 249 had complete data on all outcomes; of these, 132 were males and 117 were females.

Mothers were given detailed information regarding study procedures and signed a letter of informed consent at the time of initial recruitment and follow-up when children were 8–14 years old. The research protocols were approved by the Ethics and Research Committees of INSP in Mexico, and the Institutional Review Boards at Harvard University and University of Michigan Schools of Public Health.

2.2. Urinary BPA and phthalates metabolites

A spot (second morning void) urine sample was collected from each woman during her third-trimester visit to the project's research center and frozen at −80 °C; these samples were later matched to the urine samples collected from children at the follow-up visit in 2012 when they were between the ages of 8–14 years. Samples were analyzed for total (free + glucuronidated) BPA and nine phthalates metabolites by isotope dilution-liquid chromatography-tandem mass spectrometry using validated modification of the Centers for Disease Control and Prevention (CDC) methods by NSF International (Ann Arbor, MI, USA); further details are described elsewhere (Lewis et al., 2013; Calafat et al., 2008; Silva et al., 2007). The nine phthalates metabolites measured were monoethyl phthalate (MEP), mono-*n*-butyl phthalate (MBP), mono-isobutyl phthalate (MiBP), mono(3-carboxypropyl) phthalate (MCPP), monobenzyl phthalate (MBzP), 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). Specific gravity (SG) of the urine samples was measured using a handheld digital refractometer (ATAGO Company Ltd., Tokyo, Japan). Urinary concentrations below the limit of quantitation (LOQ) were assigned a value of LOQ/sqrt(2).

We calculated the molar sums of the DEHP metabolites (ΣDEHP) because they occur from the same parent phthalate, and also of HMW (ΣHMW) and LMW (ΣLMW) phthalates because they represent similar sources and biological activity. Molar sums were calculated by dividing metabolite concentrations by their molecular weight (MW) and summing across. ΣDEHP included MEHP (MW 278), MEHHP (MW 294), MEOHP (MW 292), and MECPP (MW 308). ΣHMW included ΣDEHP, MCPP (MW 251) and MBzP (MW 256). ΣLMW included MEP (MW 194), MiBP (MW 222), and MBP (MW 222). In order to enable comparisons to other studies, molar sums were expressed in nanograms/milliliter by multiplying ΣDEHP and ΣHMW with the molecular weight of MEHP, and multiplying ΣLMW with the molecular weight of MEP (Wolff et al., 2010).

Individual and summed metabolites were then corrected for SG using: $P_c = P[(SG_p-1)/(SG_i-1)]$, where P_c is the *SG*-corrected BPA or phthalates metabolite concentration (ng/mL), P is the measured urinary BPA or phthalates metabolite concentration, SG_p is the median of the

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