**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 exposures 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 urine BPA and individual and summed phthalate metabolites (∑Di(2-ethylhexyl phthalate, ∑high molecular weight, ∑low molecular weight) with measures of weight status and adiposity in children aged 8 to 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 thickness (β=-2.08, 95%CI: -3.80, -0.37), after adjusting for confounders. In the child exposure period, child 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 BMI z-score (β=3.47, 95%CI:-0.05, 6.40) while increased MEHP was inversely associated with sum of skinfold thickness in boys (β=-2.08, 95%CI: -3.80, -0.37); 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 phthalate metabolites at any exposure period with outcome measures. **Conclusion:** Our results suggest that associations between urinary BPA and phthalate metabolites with measures of weight status and adiposity differ by timing of exposure, sex, and pubertal status .Additional studies considering the influence of the pubertal transition are needed to confirm these findings in a larger population.

**Key Words**: BMI, Adiposity, Bisphenol A, Phthalates, Adolescence

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INTRODUCTION

Childhood obesity continues to be a globally persistent disease with a wide range of complications and is known to track into adulthood.1–3 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 endocrine-disrupting compounds (EDCs) such as bisphenol A (BPA) and phthalates are implicated in weight dysregulation.4,5

BPA and phthalates are multi-functional materials used in everyday products resulting in widespread exposure to these compounds and their metabolites.6,7 BPA is frequently found in plastic food containers, the lining of food cans, toys, and thermal receipt paper.8,9 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.10–13 These metabolites have been detected during pregnancy and are detected in amniotic sac and cord blood.7,8,14

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.15–29 Few longitudinal studies relate in utero exposures to obesity-related outcomes in later childhood and adolescence.30 A prospective study of prenatal exposure to BPA in the Rhea cohort from Greece found increased exposure to be positively associated with BMI 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.31 Phthalate studies are also inconclusive: *in utero* exposures were found to have no association with fat mass in children aged 4-9 years,28 decreased BMI *z-*scores only in girls aged 4-7 years,32 or only in boys aged 4 or 7 years old.33

BPA and phthalates are well-known to be an endocrine-disrupting chemicals5,34 Exposures to these compounds could increase risk of developing chronic diseases, such as altered weight status, through potential mechanisms such as alterations in thyroid hormone, in estrogen and androgen levels, in glucose tolerance and insulin resistance, or through the peroxisome proliferator pathways.5,8,35 Exposures to these compounds during pregnancy are of especial concern for later childhood obesity, as this period is considered a sensitive period for the development of obesity due to the rapid development and cell differentiation of organ systems occurring in the fetus..36,37 Accumulating evidence suggest these compounds play a role in influencing physiology from the perinatal period, with animal studies showing effects on weight gain, adiposity, and alterations in satiety hormones.38–42

In a population of children and youths aged 8-14 years old in Mexico City, this study investigated the impact of prenatal and concurrent exposures to BPA and phthalate 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.

MATERIALS AND METHODS

*Study population*

The study population involved participants (N=249) from the 19-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, such as living outside Mexico City, gestational diabetes, preeclampsia, or pregnancy-related hypertensive disorders, as well as other criteria as described elsewhere.43–45 Study methods have been described previously.43–48 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.

*Urinary BPA and phthalate 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 2010 when they were between the ages of 8-13 years. Samples were analyzed for total (free + glucuronidated) BPA and nine phthalate 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.12,49,50 The nine phthalate 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 and summing across. ΣDEHP included MEHP (molecular weight 278, MEHHP (molecular weight 294), MEOHP (molecular weight 292), and MECPP (molecular weight 308). ΣHMW included ΣDEHP, MCPP (molecular weight 251) and MBzP (molecular weight 256 ). ΣLMW included MEP (molecular weight 194), MiBP (molecular weight 222), and MBP (molecular weight 222). In order to enable comparisons to other studies, molar sums were expressed in nanograms/millilitre by multiplying ΣDEHP and ΣHMW with the molecular weight of MEHP, and multiplying ΣLMW with the molecular weight of MEP.51

Individual and summed metabolites were then corrected for SG using: Pc=P[SGp-1)/(SGi-1)], where Pc is the *SG*-corrected BPA or phthalate metabolite concentration (ng/mL), P is the measured urinary BPA or phthalate metabolite concentration, SGp is the median of the urinary specific gravities for the sample (*SGp* for mothers = 1.013, for children = 1.018), and SGi is the urinary specific gravity for the individual.52

*Anthropometric outcomes*

Children’s anthropometry was obtained at a single follow-up visit between the ages of 8 and 14 years by study personnel using established research protocol.53 Waist circumference was measured with a non-stretchable tape (QM2000; QuickMedical) to the nearest 0.1 cm. Triceps and subscapular skinfold thicknesses (TSF, SSF) were measured using a Lange skinfold caliper (Lange; Beta Technology) to the nearest 0.1 mm. Duplicate measures were taken of weight and height and triplicate measures were taken of waist circumference and skinfold measurements. An additional measurement was taken if intra-personal variability exceeded the measurement tolerance of 0.5 cm and observed values were averaged. To provide comparable indices with other international studies of weight status, age- and sex-specific BMI *z*-scores were calculated using the 2007 World Health Organization (WHO) reference growth standard.54

*Covariates*

Sociodemographic characteristics of the mother were collected via questionnaires administered by study personnel to the mother at the third trimester visit. Socioeconomic status was represented by the number of years of schooling completed by the mother at enrollment. At one month postpartum, maternal weight (BAME Mod 420; Catálogo Médico) was measured to the nearest 0.1 kg; height (BAME Mod 420; Catálogo Médico) was measured to the nearest 0.1 cm.

*Statistical analysis*

Data analysis was completed using SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA). Distributions of SG-corrected BPA and individual and summed phthalate metabolites were log-normally distributed and were ln-transformed to normality prior to regression analyses. Geometric means (standard deviation) and distributions of SG-corrected BPA and individual and summed phthalate metabolite concentrations were calculated for third trimester and child exposure periods.

We used linear regression to assess the association between ln-transformed BPA and individual and summed phthalate metabolites with continuous outcome measures (BMI *z-*score, waist circumference, and sum of skinfolds55) prospectively with maternal urinary concentrations and cross-sectionally when the youths were aged 8-14. Linear regression models were first constructed with ln-transformed and SG-corrected BPA and phthalate metabolites in crude models. We elected to adopt a confounders only approach to the *a priori* selection of covariates.56 All models were adjusted for mother’s age and years of education at enrollment and BMI at one month postpartum. In addition, models for waist circumference and sum of skinfolds were adjusted for child’s age and sex. Mother’s BMI at 1 month postpartum was used due to missing values of self-reported pre-pregnancy BMI in the analytic sample and because it would be correlated with pre-pregnancy BMI and gestational weight gain. To assess the potential modifying effect of child’s sex at follow-up, we then included appropriate interaction terms and estimated models stratified by sex for those EDCs with significant interaction terms, consistent with previous reports.16,33,57–59 In sensitivity analyses, we additionally adjusted for mother’s smoking history (yes/no). We repeated analyses after excluding children who had initiated puberty using physician-assessed Tanner stage for pubic hair (stage >1, n=54) as an indicator, where age 1 indicates no pubertal development and 5 indicates full pubertal development.60 We also repeated analyses excluding children who were born preterm (gestational age <37 weeks; n=57). We considered statistical significance as alpha level of 0.10 for interaction terms and 0.05 for effect estimates. We explored the possibility of non-monotonic relationships using generalized additive models and noted departures from linearity with deviance p values, but the small sample size precluded further meaningful exploration of associations across quantiles of exposure.

RESULTS

There were 249 children (47% female) with an average age of 10 years (Table 1). Girls had significantly higher sum of skinfolds (30 vs 25 mm; p<0.001) but did not differ in waist circumference or BMI *z*-score. Mothers were, on average, 27 (SD: 5.4) years old at time of delivery, had completed 11(SD: 2.8) years of schooling, and overweight (BMI ≥25).

The majority of prenatal urinary samples show detectable concentrations of SG-corrected metabolites, with the lowest detection in BPA measures (30%<LOQ) (Table 2). There were fewer samples below the LOQ among child urinary measures and, with the exception of MEP, higher geometric means were reported in child compared to prenatal measures. Spearman correlations of SG-corrected BPA and individual phthalate metabolites were weakly to highly correlated (range 0.13-0.98) within each time period while concentrations between prenatal and child measures were weakly correlated (range 0.14-0.19) (data not shown).

Ln-transformed SG-corrected prenatal MBzP was significantly associated with a decrease in child’s BMI *z*-score at ages 8-14 (β=-0.21, 95%CI: -0.41, -0.02) after controlling for confounders (Table 3). There were no other associations detected from the prenatal exposure period and we did not observe any modification of associations by sex.

In child urinary measures, we observed inverse associations between MEHP and waist circumference (β=-1.85, 95%CI:-3.36, -0.35) and sum of skinfold measurements (β=-2.08, 95%CI: -3.80, -0.37) after controlling for confounders (Table 4). Child sex modified the relationships between BPA and BMI *z*-score (*p* for interaction=0.06) and sum of skinfolds (*p* for interaction =0.03), MEHP and sum of skinfolds (*p* for interaction=0.08), and between MBzP, MEP, MECPP, MEHHP, and MEOHP across the three outcome measures. These metabolites were reanalyzed after stratifying by sex (Table 5). Increased concentrations of ln-transformed SG-corrected BPA in girls was associated with an increase in sum of skinfolds (β=3.47, 95%CI:-0.05, 6.40) while exposure to MEHP, MECPP, MEHHP, and MEOHP were inversely associated with child outcomes in boys.

In our sensitivity analyses, results did not differ with the exclusion of preterm births or additional adjustment for mother’s smoking history. When we excluded children who had initiated puberty, prenatal MBzP was no longer significantly associated with BMI *z-*score in our regression analyses (results not shown) and sex-stratified analyses with child exposure measures show significant results only between BPA exposure and sum of skinfolds in girls, and MEHP exposure and sum of skinfolds in boys (Supplementary Table 1).

DISCUSSION

In this prospective cohort in Mexico City, we found that higher concentrations of child urinary MEHP was inversely associated with child’s waist circumference and sum of skinfold thickness in children aged 8-14. We observed effect modification by sex with BPA, MEP, and individual metabolites from the high molecular weight phthalates in the child exposure period. Sex-stratified analyses found increased exposure to urinary concentrations of BPA to be positively associated with girls’ sum of skinfold thickness, while exposures to MEHP, MEHHP, MECPP, and MEOHP were inversely related to BMI *z*-score, waist circumference, and sum of skinfold thickness in boys. When we restricted our analyses to children who had not yet begun the pubertal transition, our results showed the positive relationships between BPA in girls and MEHP in boys, with sum of skinfold thickness. From the prenatal exposure period, we had observed an inverse relationship between MBzP and child’s BMI *z­-*score, but this finding did not persist when we restricted our analyses to children who had not initiated puberty. We did not observe any associations between the sum of DEHP metabolites or sum of HMW or LMW metabolites with any child outcome.

Our cross-sectional findings of BPA are in agreement with findings from a cross-sectional NHANES study of children aged 6-19 years old who showed increased urinary BPA concentrations to be positively associated with BMI *z-*score,26 as well as the CHAMACOS cohort in the US, where Harley et al. (2013) observed increased BMI *z-*scores, waist circumference, and body fat percentage in children with higher BPA concentrations at 9 years of age.59 In the NHANES study, the majority of the children would likely have begun the pubertal transition, and the CHAMACOS population at 9 years had 43% of girls and 16% of boys who had entered puberty. Therefore, Harley et al. suggested that these positive cross-sectional associations between BPA and BMI *z-*score are only observed in older children. However, our results persisted whether we included or excluded children who had entered puberty. In a study population with younger children, cross-sectional child urinary concentrations of BPA were associated with BMI *z-*score, waist circumference, and sum of skinfold thickness at 4 years of age in one study from Greece,61 but not in a study of US children aged 2-5 years old.42 Unlike studies reporting relationship between prenatal BPA exposure and child anthropometric outcomes,41,58,59 we did not observe any associations, which is consistent with a study by Braun et al (2014)42 in the US and Vafeiadi et al (2016)61 with the Rhea cohort.

We did not observe any relationships between prenatal urinary phthalate concentrations and child outcomes after excluding children who had initiated puberty, consistent with findings from a New York City cohort, where no associations with fat mass in children aged 4-9 years were observed.28 However, other studies report mixed findings, depending on age, sex, and phthalate metabolite.32,33,57,62,63 Prenatal exposure to MEP was associated with decreased BMI *z*-scores only in girls 4-7 years old in one US cohort,32 while ∑HMW prenatal phthalates were associated with lower BMI *z-*scores only in boys age 4 and 7 in the INMA-Sabadell cohort.33 In contrast, prenatal exposure to non-DEHP metabolites was negatively associated with BMI *z*-score, waist circumference, and fat mass in boys aged 5 and 7 years old in the US.57

Our cross-sectional findings with phthalate metabolites showed increased child MEHP urinary concentration to be negatively associated with waist circumference and sum of skinfold thickness. This relationship was modified by sex and the association with sum of skinfold thickness was observed only in boys and is not consistent with other studies. Deierlein et al., observed an association between MEHP exposure at ages 6-8 years with a predicted decrease in BMI from the ages of 7-1362, but only in girls, a cross-sectional study of children aged 6-8 years using NHANES found an inverse relationship between MEHP and BMI in girls and no association with boys,64 and MEHP exposure was negatively associated with obesity in girls in a Chinese study.16

Overall, we found no relationships between prenatal exposures and child outcomes, and sex-specific associations between BPA and MEHP exposures and sum of skinfold thickness in the child exposure period. Sex differences have been observed in other epidemiological studies, as well as animal studies and are likely due to the endocrine-disrupting mechanisms of BPA and phthalate metabolites.65–67 BPA is known to alter binding to estrogen receptors, promote differentiation of, and lipid accumulation in, adipocytes, and inhibit adiponectin release, which may increase risk of hypertension, dyslipidemia, and diabetes by increasing muscle and liver catabolism of fatty acids and glucose.68–70 Phthalates are anti-androgenic, can possibly alter thyroid levels, which are important for maintaining metabolism and energy balance, and can, like BPA, activate the peroxisome proliferator-activated receptors (PPAR) family of receptors, a family of lipid-sensors that are involved in energy homeostasis and can redirect metabolism when activated, through adipogenesis, lipogenesis, and insulin sensitivity.71,72 Given the evidence that phthalates have anti-androgenic effects, we expected that our association between MEHP and sum of skinfold thickness in boys would have been a positive association rather than an inverse association; nonetheless, similar to the assertion by Maresca et al. (2016),57 these results still support evidence that phthalates can disrupt metabolism.

Limitations of our study include the use of a single spot-urine during pregnancy and in childhood. As previously reported, metabolite concentrations in the prenatal and child exposure periods are similar to those described in other studies.12 BPA and phthalates have short metabolite half-lives, with <5-6 hours for BPA and <24 hours for phthalates.73,74 These metabolites are subject to temporal variability and a single spot-urine sample may not be capable of capturing accurate individual levels, but previous studies have shown that a single measure may be a relatively good measure of exposure due to the consistency of behaviors and similar assumptions about the validity of a single urine measurement has been made in other studies.75–77 Various methods for correcting variations in urinary dilutions, such as adjusting or correcting for urinary creatinine levels or specific gravity in regression models, are currently used. We chose to control for urinary dilution by correcting for specific gravity, not creatinine because it has been shown to be a better marker in children; unlike specific gravity, creatinine can be influenced by age and seasonality, as well as muscle mass, race, and sex.78,79 Recently, it has been suggested that how urinary dilution is adjusted, such as standardization, covariate adjustment, or covariate-adjusted standardization, may influence the interpretation of results.80

We did not include dietary data, physical activity, and consumer product use as potential confounders and therefore residual confounding may exist. BPA and phthalates exposures are thought to occur primarily through ingestion and dermal absorption, as these compounds are found in common consumer goods such as food containers, toys, and personal care products.8,11,12 It is possible that individuals with higher canned and/or packaged food intake would have higher urinary concentrations. Heavier individuals may also have higher urinary concentrations due to increased dietary intake and product use, which may influence our cross-sectional results.

Our study population was not large, which limited the interpretation of our findings. Some studies have observed that endocrine-disrupting compounds have a non-monotonic relationship with health outcomes,18,26 but our sample size limited investigation of nonlinear associations. Available toxicant measures and sample size also account for residual confounding by other perinatal or childhood exposures or to consider mixtures of endocrine disrupting chemicals in the genesis of adiposity outcomes. We utilized the WHO growth standard to calculate BMI *z*-score which could have implications for direct comparisons with studies conducted in the United States that rely on CDC reference growth curves. Nevertheless, this measure would permit comparisons with studies conducted in Europe, Latin American and other worldwide settings. We also had very limited information on pre-pregnancy BMI due to availability of self-reported weight and the timing of recruitment in our original birth cohorts; we therefore had to rely on maternal BMI at one month postpartum as a covariate. We also did not control for multiple comparisons as this analysis was exploratory, which increases the likelihood of false significant findings. However, strengths of our study include its prospective design and length of follow-up, which allowed us to assess child outcomes at ages later than those currently reported in the literature. We also had information on pubertal status, allowing us to explore whether associations are influenced in this time of transition. Associations between metabolite exposure and outcomes may change as children enter the ages of the pubertal transition may hormonal fluctuations, as well as changes in dietary, physical activity, and habits around consumer product use changes requires further studies.

CONCLUSIONS

We found higher concentrations of the phthalate metabolite MEHP was associated with a decrease in sum of skinfold thickness in boys aged 8-14 while BPA exposure was associated with an increase in BMI *z-*score in girls among children who had not entered puberty. In contrast, we did not find any relationships between prenatal exposures to BPA or phthalate metabolites after excluding children who had entered the pubertal transition. Our findings suggest associations depend on timing of exposure, as well as sex and pubertal status. Further follow-up in this and other studies are needed to further our understanding of how timing of exposures influence adiposity in different periods of development.

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Table 1. Maternal and child characteristics in the ELEMENT cohort in Mexico City, Mexico..

Table 2. Distribution of specific-gravity corrected prenatal BPA and individual and ∑DEHP, ∑HMW,and ∑LMW phthalate metabolites in the prenatal and child exposure periods.

Table 3. Associations between prenatal urinary BPA, individual, and summed ∑DEHP, ∑HMW, ∑LMW phthalate metabolites with BMI z-score, waist circumference, and sum of skinfolds in children aged 8-14 years old.

Table 4. Associations between child urinary BPA, individual, and summed ∑DEHP, ∑HMW, ∑LMW phthalate metabolites with BMI z-score, waist circumference, and sum of skinfolds in children aged 8-14 years old.

Table 5. Sex-stratified associations between child urinary metabolites and BMI z-score, waist circumference, and sum of skinfolds identified.

Supplementary Table 1. Associations between p-sex interaction identified ln-transformed SG-

corrected child urinary metabolites with BMI z-score, waist circumference, and sum of skinfolds

identified from, restricted to children who have not initiated puberty.