Early-Life Bisphenol A Exposure and Child Body Mass Index: A Prospective Cohort Study

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BACKGROUND: Early-life exposure to bisphenol A (BPA) may increase childhood obesity risk, but few prospective epidemiological studies have investigated this relationship.

OBJECTIVE: We sought to determine whether early-life exposure to BPA was associated with increased body mass index (BMI) at 2–5 years of age in 297 mother–child pairs from Cincinnati, Ohio (HOME Study).

METHODS: Urinary BPA concentrations were measured in samples collected from pregnant women during the second and third trimesters and their children at 1 and 2 years of age. BMI z-scores were calculated from weight/height measures conducted annually from 2 through 5 years of age. We used linear mixed models to estimate BMI differences or trajectories with increasing creatinine-normalized BPA concentrations.

RESULTS: After confounder adjustment, each 10-fold increase in prenatal (β = −0.1; 95% CI: −0.5, 0.3) or early-childhood (β = −0.2; 95% CI: −0.6, 0.1) BPA concentrations was associated with a modest and nonsignificant reduction in child BMI. These inverse associations were suggestively stronger in girls than in boys [prenatal effect measure modification (EMM) p-value = 0.30, early-childhood EMM p-value = 0.05], but sex-specific associations were imprecise. Children in the highest early-childhood BPA tercile had lower BMI at 2 years (difference = −0.3; 95% CI: −0.6, 0.0) and larger increases in their BMI slope from 2 through 5 years (BMI increase per year = 0.12; 95% CI: 0.07, 0.18) than children in the lowest tercile (BMI increase per year = 0.07; 95% CI: 0.01, 0.13). All associations were attenuated without creatinine normalization.

CONCLUSIONS: Prenatal and early-childhood BPA exposures were not associated with increased BMI at 2–5 years of age, but higher early-childhood BPA exposures were associated with accelerated growth during this period.


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Supplemental Material is available online (http://dx.doi.org/10.1289/ehp.1408258).

We acknowledge C. Pfeiffer and Z. Fazili from the Centers for Disease Control and Prevention, who performed the whole blood folate assays, as well as other laboratory staff who performed chemical analyses.

This work was supported by National Institute of Environmental Health Sciences grants R00 ES020346, PO1 ES112261, R01 ES014575, and R01 ES020349. S.A.V. was supported by Canadian Institutes of Health Research (CIHR) grant 12301 and Michael Smith Foundation for Health Research (MSFHR) grant 5176.

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

J.M.B. was financially compensated for conducting a reanalysis of a study of child lead exposure for the plaintiffs in a public nuisance case related to childhood lead poisoning. B.P.L. has served as an expert witness and a consultant to the California Attorney General’s Office for the plaintiffs in a public nuisance case related to childhood lead poisoning, but he has not personally received any compensation for these services. B.P.L. has also served as a paid consultant on a U.S. Environmental Protection Agency research study related to childhood lead poisoning. None of these activities are directly related to the present study. The other authors declare they have no actual or potential competing financial interests.

Received: 10 February 2014; Accepted: 25 July 2014; Advance Publication: 29 July 2014; Final Publication: 1 November 2014.

Introduction

Child obesity is one of the greatest public health challenges worldwide (World Health Organization 2010). Excess food consumption and inadequate physical activity are major risk factors for obesity, but emerging evidence suggests that exposure to obesogens—chemicals that alter adipogenesis or metabolism—might play a role in increasing obesity risk beyond these traditional risk factors (Janssick and Blumberg 2012; Romano et al. 2014; Tang-Peronard et al. 2011). The developing fetus and infant may be especially sensitive to obesogens because of their immature detoxification pathways and sensitivity to environment inputs. Most epidemiological studies of environmental chemical obesogens have been limited to organochlorine compounds; few have examined contemporary chemicals, such as bisphenol A (BPA) (Tang-Peronard et al. 2011).

BPA is a high-production-volume chemical used to produce polycarbonate plastics and resins, and there is ubiquitous exposure among persons in industrialized countries (Braun et al. 2012; Lee et al. 2014; Quirós-Alcalá et al. 2013; Valvi et al. 2013). BPA is a suspected endocrine disruptor and may affect the metabolism or action of hormones or receptors involved in the etiology of obesity, including glucocorticoids, gonadal hormones, and peroxisome proliferator activated receptors (Janssick and Blumberg 2012; Ross and Desai 2013). One animal study suggests that the obesogenic effect of BPA may be modified by the availability of methyl donors (e.g., folate) for DNA methylation, thus permanently altering the programming of adipogenesis, appetite, or energy metabolism, and increasing later-life obesity risk (Dolinsky et al. 2007).

Although some animal studies suggest that BPA is a candidate obesogen, others do not (reviewed by Harley et al. 2013). Cross-sectional human studies suggest that urinary BPA concentrations are associated with increased body mass index (BMI) or obesity in adults and children, but these findings could result from confounding or reverse causation because diet is an important source of BPA exposure and obesity is linked to certain dietary patterns (Carwile and Michels 2011; Sharpe and Drake 2013; Trasande et al. 2012; Wang et al. 2012). Two prospective cohort studies examining early-life BPA exposure report contradictory findings: One found higher BMI among children with higher prenatal BPA exposure (Valvi et al. 2013), and another reported lower BMI with higher prenatal exposure (Harley et al. 2013). These studies suggest that girls, as well as children born to women who smoke during pregnancy, may be more susceptible to prenatal BPA exposure.

We investigated whether prenatal or early-childhood BPA exposure was associated with BMI or waist circumference in children 2–5 years of age from a population-based, prospective cohort study conducted in Cincinnati, Ohio. We also determined whether the association between prenatal BPA exposure and child BMI was modified by maternal folate levels, child sex, or prenatal tobacco smoke exposure.

Environmental Health Perspectives • VOLUME 122 | NUMBER 11 | November 2014

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Methods

Study participants. We used data from the Health Outcomes and Measures of the Environment (HOME) Study, a prospective cohort study designed to examine the health impact of early-life exposure to prevalent environmental chemicals (Dietrich et al. 2005). We recruited pregnant women from nine prenatal clinics associated with three hospitals in the Cincinnati area from March 2003 through January 2006. Eligibility criteria and enrollment have been previously described (Braun et al. 2009). All women provided written informed consent for themselves and their children after the study protocols had been explained. The institutional review boards of Cincinnati Children’s Hospital Medical Center, the cooperating delivery hospitals, and the Centers for Disease Control and Prevention (CDC) approved this study.

Maternal and child BPA exposure assessment. Because there is concern that BPA exposures may adversely affect child health depending on the timing of exposure, we examined exposures during two distinct periods of development—prenatal and early childhood. Women provided up to two spot urine samples in polypropylene cups at their prenatal care clinic visits around 16 and 26 weeks of pregnancy. Children provided up to two spot urine samples at annual clinic or home visits when they were around 1 and 2 years of age (see Supplemental Material, Table S1, for means and ranges). If a child did not provide a sample at the 1- or 2-year clinic visits, we used urine samples collected during home visits. Before urine collection, each child’s genital area was wiped with a Wet-Nap (http://wetnap.com) by their caregiver. For children who were not toilet trained, we placed a surgical insert into a clean diaper at the beginning of the study visit and checked the diaper for urine at the end of the study visit. If the diaper was wet and free of stool, the insert was placed into a polyethylene urine collection cup, and urine was expressed from the insert with a syringe. For children who were being toilet trained, a training toilet was lined with inserts. For toilet-trained children, urine samples were collected directly into a urine collection cup with the aid of the child’s caregiver. All samples were refrigerated until they were processed, after which they were stored at or below –20°C until shipped on dry ice to CDC for analysis. BPA concentrations were measured at the CDC National Center for Environmental Health laboratories using previously described analytic chemistry methods (Ye et al. 2008). In 2009, we found nondetectable (<0.4 ng/mL) levels of BPA in surgical inserts and wipes used to collect child urine.

To account for urine dilution, urinary creatinine was measured by a kinetic Jaffé reaction, and BPA concentrations were divided by creatinine and multiplied by 100 to yield units of micrograms BPA per gram creatinine. We averaged log_{10}-transformed maternal and child creatinine-normalized BPA concentrations to create prenatal and early-childhood BPA exposure measures, respectively. The prenatal exposure measure used maternal urinary BPA concentrations at 16 and 26 weeks gestation (7 had one measure and 290 had two measures). The early-childhood exposure measure used child urinary BPA concentrations at 1 and 2 years of age (90 had one measure and 195 had two measures). We characterized creatinine-normalized urinary BPA concentrations as terciles or continuous log_{10}-transformed values in our statistical models.

Child anthropometry. Weight, height, and waist circumference were measured in triplicate and averaged at each annual study visit. We obtained child’s weight at 2-5 years to the nearest 0.01 kg, with the child dressed in undergarments or a dry diaper, using a Scale-Tronix scale (White Plains, NY). If the child was uncooperative, we obtained a sitting weight using a Scale-Tronix Pediatric Scale Model 4802. Height at 2-5 years was measured to the nearest 0.1 cm using an Aytron Stadiometer Model S100 with the child standing straight without shoes or head coverings and heels positioned against the wall. If the child had a hairstyle that prevented the child’s head from lying flush against the head board, the height of the hairstyle was subtracted from the height measure. Waist circumference was measured at 4 and 5 years of age by placing a plastic measuring tape around a horizontal plane defined by the left and right iliac crests. Child BMI was converted to age- and sex-specific z-scores using U.S. references available from the National Center for Health Statistics (Kuczmarski et al. 2000). Research staff who conducted anthropometric measures were blinded to children’s urinary BPA concentrations.

Confounding variables. We considered adjusting for potential confounders that might be associated with both BPA exposure and growth/size. Trained research assistants collected sociodemographic, perinatal, and dietary/activity variables using standardized computer-assisted interviews and medical chart reviews. Sociodemographic covariates included maternal race, age, education, marital status, household income, insurance status, and food security during pregnancy. Perinatal variables included maternal depressive symptoms at 16 weeks gestation (Beck Depression Inventory-II) (Beck et al. 1996), BMI at 16 weeks gestation, parity, and serum cotinine (a sensitive and specific biomarker of tobacco smoke exposure) (Braun et al. 2010).

Our dietary questions were originally designed to assess environmental chemical exposures (e.g., organophosphate pesticides), not macro- or micronutrient intake. We adjusted for frequency of maternal or child canned vegetable and fresh fruit/vegetable consumption because we previously found that canned vegetable consumption was associated with higher maternal urinary BPA concentrations and may be associated with diet quality (Braun et al. 2011). Dietary variables were collected during pregnancy for mothers and annually at 2-5 years of age for children. We adjusted for prenatal vitamin use and breastfeeding duration because vitamins may be a source of methyl donors, and breastfeeding may decrease childhood obesity risk, respectively (Anderson et al. 2012; Lefebvre and John 2014). Child activity variables were collected annually at 2-5 years of age and included parent-reported hours of daily television watching and outdoor time.

We created unadjusted and several sets of adjusted models to verify the robustness of our results to potential confounding and selection bias. We created a primary model adjusting for sociodemographic and perinatal variables, and then additionally adjusted for maternal nutrition, child nutrition, child activity, child age, or maternal/child urinary di(2-ethylhexyl) phthalate (DEHP) metabolite concentrations. Urinary DEHP concentrations were measured using previously described methods (Silva et al. 2007). We also adjusted for both prenatal and early-childhood urinary BPA concentrations simultaneously in the same model.

Statistical analyses. We began by describing the univariate characteristics of urinary BPA concentrations and calculating Pearson correlation coefficients between log_{10}-transformed concentrations. Next, we calculated the mean BMI z-score at each age, as well as the number and percent of children with BMI z-scores ≥ the 85th percentile (overweight). We then tabulated the mean BMI z-scores and median urinary BPA concentrations according to covariates.

We examined whether higher prenatal or early-childhood BPA concentrations were associated with differences in BMI z-scores at 2-5 years or waist circumference at 4 and 5 years using a linear mixed model with an unstructured correlation matrix, random intercept, and empirical standard errors. This model accounts for the repeated and correlated measurements within an individual and increases our statistical precision by borrowing information across repeated measures (Fitzmaurice et al. 2004). The unstructured covariance matrix produced the best model fit according to the Akaike Information Criterion compared to compound symmetric or auto-regressive covariance matrices. The coefficients from this model can be interpreted as the mean difference in BMI z-score averaged...
across 2–5 years of age with increasing BPA concentrations.

Then we used this same model to examine children’s BMI z-score slopes between 2 and 5 years of age according to BPA concentration tertiles. We modeled BMI z-scores as a function of BPA tercile, child age in months, an interaction term between age and BPA tercile, and covariates. This model allows each BPA tercile to have its own linear BMI z-score slope over time (i.e., 2–5 years of age). We then estimated the BMI slope per year for each BPA tercile and determined whether these slopes were statistically different from one another using the age × BPA interaction terms.

We calculated the odds of being overweight (BMI z-score ≥ 85th percentile) according to BPA concentration using generalized linear mixed models with an unstructured correlation matrix and random intercept. Finally, we examined whether the associations between BPA concentrations and BMI differed in boys and girls.

Secondary analyses. On the basis of prior studies examining prenatal BPA or other environmental chemical exposures and infant/child growth, we used product effect measure modification (EMM) terms to examine whether the association between prenatal urinary BPA concentrations and BMI was modified by prenatal tobacco smoke exposure, prenatal whole blood folate levels, and maternal race (Dolinoy et al. 2007; Rauch et al. 2012; Valvi et al. 2013). We classified women as smokers if they had serum cotinine levels ≥ 3 ng/mL at 16 or 26 weeks gestation or if they used any tobacco products. We classified women as nonsmokers (Benowitz et al. 2009). We re-ran our primary analyses without creatinine-normalizing urinary BPA concentrations. Finally, we examined the cross-sectional associations between children’s urinary BPA concentrations and BMI at 2–5 years of age. Urinary BPA concentrations were measured in urine samples collected at 3, 4, and 5 years of age using the methods described above.

Results

Of 389 women who gave birth to singleton infants, 297 (76%) with complete prenatal exposure data and covariates returned to our study clinic at least once for a total of 889 study visits during child’s age 2–5 years (285 for early-childhood exposure analyses, 73%, 864 visits).

Median urinary BPA concentrations were lower in women than in their children (Figure 1, Table 1; see also Supplemental Material, Table S2). Creatinine-normalized BPA concentrations at 16 and 26 weeks (Pearson $r = 0.09$) or 1 and 2 years (Pearson $r = 0.10$) were not correlated; however non-normalized concentrations were weakly correlated (Pearson $r ≤ 0.3$; see Supplemental Material, Table S3). Averaged creatinine-normalized maternal urinary BPA concentrations were not correlated with averaged children’s concentrations (Pearson $r = 0.03$, $p = 0.67$), but non-normalized concentrations were weakly correlated (Pearson $r = 0.17$, $p < 0.01$).

Children’s BMI z-scores ranged from a mean of 0 to 0.2 standard deviation scores (SDS) between 2 and 5 years of age; 16–19% of children had BMI z-scores ≥ the 85th percentile (Supplemental Material, Figure S1).

Higher prenatal urinary BPA concentrations were observed in mothers who were black, were younger at delivery, had less household income and education, consumed more canned vegetables and fewer fresh fruits and vegetables, or breastfed for a shorter duration (Table 1). Similar patterns were observed for early-childhood urinary BPA concentrations.

After confounder adjustment, higher prenatal or early-childhood urinary BPA concentrations were not associated with BMI z-scores in children at 2–5 years of age (Table 2). Results were similar regardless of adjustment for dietary/activity factors, child age, or both BPA exposures (see Supplemental Material, Table S4). Not normalizing BPA concentrations for creatinine attenuated both the prenatal and early-childhood estimates to null (see Supplemental Material, Table S5). Both prenatal and early-childhood urinary BPA concentrations were associated with smaller waist circumference at 4 and 5 years of age, but the 95% confidence intervals (CI) of the point estimates included the null value (see Supplemental Material, Table S6).

Inverse associations between maternal urinary BPA concentrations and child BMI were slightly stronger among girls ($β = –0.41$; 95% CI: –0.9 to 0.2; $n = 165$) compared with boys ($β = 0.00$; 95% CI: –0.5 to 0.6; $n = 132$), although the EMM $p$-value did not reach conventional levels of significance ($p = 0.32$) (Figure 2). The evidence for EMM was stronger for early-childhood urinary BPA concentrations ($p = 0.05$), where higher concentrations were associated with lower child BMI among girls ($β = –0.60$; 95% CI: –1.1 to –0.1; $n = 155$) than among boys ($β = 0.1$; 95% CI: –0.4 to 0.5; $n = 130$). The magnitude of the differences between the sexes was attenuated when BPA concentrations were not creatinine-normalized (see Supplemental Material, Table S7).

Each 10-fold increase in maternal urinary BPA concentrations was associated with a modestly decreased odds of being overweight between 2 and 5 years of age (odds ratio

Figure 1. Urinary BPA concentrations during pregnancy at 16 and 26 weeks and the first 2 years of life among Cincinnati, Ohio, women and their children. Whiskers represent the 25th and 75th percentiles, the line in the box represents the median, and the diamond represents the arithmetic mean. The number of mothers/children for the average concentrations is greater than the individual concentrations because not all the same participants returned at the both visits.
(OR) = 0.65; 95% CI: 0.19, 2.18; p = 0.48], but the OR CI included the null value. The association between early-childhood urinary BPA concentrations and being overweight was much closer to null (OR = 0.93; 95% CI: 0.34, 2.53; p = 0.89).

There was not strong evidence that maternal urinary BPA concentrations were positively associated with rapid growth between 2 and 5 years of age (Figure 3) (age × BPA interaction term p-value = 0.26). There was stronger evidence that BMI slopes increased more rapidly between 2 and 5 years among children in the highest tercile of early-childhood BPA concentrations (BMI increase per year = 0.12; 95% CI: 0.07, 0.18) compared with children in the first tercile (BMI difference = –0.1; 95% CI: –0.5, 0.3). BMI slopes no longer differed when early-childhood BPA concentrations were not creatinine-normalized (first tercile = 0.04; 95% CI: –0.02, 0.10; second tercile = 0.09; 95% CI: 0.04, 0.15; third tercile = 0.09; 95% CI: 0.03, 0.15; p-value for interaction = 0.42).

There was not strong evidence that the associations between prenatal or early-childhood BPA concentrations and BMI z-score slopes differed according to child sex (EMM p-values = 0.18 to 0.80). However, we had a relatively small number of children for this analysis (see Supplemental Material, Figures S2 and S3).

Secondary analyses. Associations between continuous prenatal urinary BPA concentrations and child BMI did not differ (EMM p-value = 0.98) among children born to mothers who smoked during pregnancy (β = –0.1; 95% CI: –1.9, 1.6, n = 29) compared with those with mothers who did not smoke (β = –0.1; 95% CI: –0.5, 0.3, n = 268). The associations between prenatal urinary BPA concentrations and child BMI did not differ according to terciles of maternal whole-blood folate levels (EMM p = 0.74). There was no evidence that associations between prenatal or early-childhood urinary BPA concentrations and BMI differed between blacks or whites (EMM p-values > 0.34). Our results did not change appreciably when we adjusted for children’s serum cotinine levels, adjusted for maternal or child urinary DEHP concentrations, or excluded infants born small for gestational age, women

Table 1. Urinary BPA concentrations and child BMI z-scores according to maternal and child covariates among Cincinnati, Ohio, women and their children.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Maternal median BPA μg/L (25th, 75th)</th>
<th>Child median BPA μg/L (25th, 75th)</th>
<th>BMI z-score (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>297 21 (1.1, 3.9)</td>
<td>3.6 (1.8, 6.9)</td>
<td>0.04 ± 1.04</td>
</tr>
<tr>
<td>Maternal race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>198 1.7 (0.9, 2.9)</td>
<td>2.7 (1.5, 5.4)</td>
<td>0.03 ± 1.00</td>
</tr>
<tr>
<td>Black</td>
<td>82 3.9 (2.4, 6.3)</td>
<td>5.5 (3.4, 9.6)</td>
<td>0.10 ± 1.15</td>
</tr>
<tr>
<td>Other</td>
<td>17 2.3 (1.7, 3.2)</td>
<td>4.7 (2.6, 9.2)</td>
<td>–0.05 ± 1.00</td>
</tr>
<tr>
<td>Maternal age (years) at delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>58 3.5 (1.9, 6.2)</td>
<td>4.9 (2.5, 8.4)</td>
<td>0.05 ± 1.16</td>
</tr>
<tr>
<td>25 to &lt; 35</td>
<td>192 1.9 (1.0, 3.7)</td>
<td>3.4 (1.6, 6.2)</td>
<td>0.04 ± 1.02</td>
</tr>
<tr>
<td>≥ 35</td>
<td>47 1.7 (0.7, 3.2)</td>
<td>3.1 (1.7, 7.6)</td>
<td>0.04 ± 1.01</td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graduate/professional/bachelor</td>
<td>166 1.7 (0.8, 2.7)</td>
<td>2.6 (1.5, 5.3)</td>
<td>0.08 ± 0.90</td>
</tr>
<tr>
<td>Some college</td>
<td>74 2.8 (1.7, 4.8)</td>
<td>4.2 (2.6, 7.4)</td>
<td>–0.15 ± 1.08</td>
</tr>
<tr>
<td>High school</td>
<td>31 3.2 (2.1, 6.2)</td>
<td>4.9 (2.5, 7.1)</td>
<td>0.39 ± 1.04</td>
</tr>
<tr>
<td>&lt; High school</td>
<td>26 6.1 (3.2, 7.5)</td>
<td>5.9 (3.5, 12.0)</td>
<td>–0.10 ± 1.56</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>207 1.8 (0.9, 2.9)</td>
<td>2.9 (1.6, 5.8)</td>
<td>0.05 ± 1.01</td>
</tr>
<tr>
<td>Unmarried, living together</td>
<td>33 3.2 (2.2, 6.4)</td>
<td>4.2 (2.3, 7.3)</td>
<td>0.26 ± 1.00</td>
</tr>
<tr>
<td>Unmarried, living alone</td>
<td>57 3.7 (1.9, 6.3)</td>
<td>6.2 (3.9, 9.4)</td>
<td>–0.10 ± 1.16</td>
</tr>
<tr>
<td>Household income (per year)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≥ $80,000</td>
<td>88 1.6 (0.8, 2.6)</td>
<td>2.9 (1.5, 5.3)</td>
<td>0.01 ± 0.87</td>
</tr>
<tr>
<td>$40,000–$80,000</td>
<td>110 1.8 (0.9, 3.0)</td>
<td>2.7 (1.6, 5.7)</td>
<td>0.12 ± 1.10</td>
</tr>
<tr>
<td>$20,000–$40,000</td>
<td>41 2.9 (1.8, 4.5)</td>
<td>4.3 (2.8, 8.0)</td>
<td>–0.06 ± 1.14</td>
</tr>
<tr>
<td>&lt; $20,000</td>
<td>58 5.1 (2.6, 7.5)</td>
<td>5.3 (3.2, 9.2)</td>
<td>0.01 ± 1.10</td>
</tr>
<tr>
<td>Maternal employment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>52 2.3 (1.4, 6.2)</td>
<td>3.9 (2.0, 8.2)</td>
<td>–0.07 ± 1.06</td>
</tr>
<tr>
<td>Yes</td>
<td>245 2.0 (1.0, 3.8)</td>
<td>3.4 (1.7, 6.7)</td>
<td>0.07 ± 1.04</td>
</tr>
<tr>
<td>Maternal insurance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>226 1.8 (0.9, 3.0)</td>
<td>3.0 (1.6, 5.9)</td>
<td>0.06 ± 1.00</td>
</tr>
<tr>
<td>Public/private</td>
<td>71 4.3 (2.3, 6.9)</td>
<td>5.0 (3.1, 9.1)</td>
<td>–0.02 ± 1.15</td>
</tr>
<tr>
<td>Maternal depressive symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>245 2.0 (1.0, 3.8)</td>
<td>3.5 (1.8, 6.7)</td>
<td>–0.01 ± 1.02</td>
</tr>
<tr>
<td>Mild</td>
<td>32 2.8 (1.8, 6.3)</td>
<td>4.0 (1.7, 9.1)</td>
<td>0.21 ± 1.02</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>20 2.7 (1.3, 4.3)</td>
<td>3.7 (2.1, 7.0)</td>
<td>0.41 ± 1.25</td>
</tr>
<tr>
<td>Maternal serum cotinine concentration (ng/mL)</td>
<td>120 1.5 (0.8, 2.7)</td>
<td>2.7 (1.4, 6.2)</td>
<td>–0.04 ± 0.98</td>
</tr>
<tr>
<td>Secondhand (0.015–3)</td>
<td>150 2.7 (1.5, 4.4)</td>
<td>3.9 (2.3, 7.3)</td>
<td>0.09 ± 0.10</td>
</tr>
<tr>
<td>Active (≥3)</td>
<td>27 4.2 (2.3, 6.7)</td>
<td>3.7 (1.7, 6.2)</td>
<td>0.16 ± 1.14</td>
</tr>
</tbody>
</table>

25th and 75th are percentiles.

*Average BPA concentration in maternal 16- and 26-week gestation urine samples (n = 297). *Average BPA concentration in child 1- and 2-year urine samples (n = 285). *BMI z-score at the child’s first visit, if more than one was available.
with gestational diabetes or pregnancy-induced hypertension, or the woman with the exceptionally high BPA concentration (see Supplemental Material, Table S5). The cross-sectional associations between children’s concurrent urinary BPA concentrations and BMI z-scores at 2–5 years were both positive and negative in direction (see Supplemental Material, Table S8).

**Discussion**

Prenatal urinary BPA concentrations were not associated with increased BMI or waist circumference in these preschool-age children. In fact, consistent with the results from a prospective birth cohort study in California, we found that higher maternal urinary BPA concentrations were generally, but not significantly, associated with lower BMI among girls born to women with the highest prenatal urinary BPA concentrations.

Our findings and those of Harley et al. (2013) reported modest decreases in child BMI at 9 years of age among girls born to women with the highest prenatal urinary BPA concentrations. Harley et al. (2013) reported that these associations were stronger among girls born to women with gestational diabetes or pregnancy-induced hypertension, or the woman with the exceptionally high BPA concentration (see Supplemental Material, Table S5). Consistent with our findings, the New England Children’s Amalgam Trial, a randomized, prospective birth cohort study in California, measured urinary BPA concentrations twice during pregnancy, and the two U.S. studies measured children’s BPA concentrations at the time BMI was assessed. Maternal urinary BPA concentrations were generally, but not significantly, associated with lower BMI in our cohort, the New England Children’s Amalgam Trial, a randomized, prospective birth cohort study in California, and with early childhood urinary BPA concentrations in our cohort, the New England Children’s Amalgam Trial, a randomized, prospective birth cohort study in California.

**Table 2. Adjusted change in child BMI z-score between 2–5 years of age (β) by tercile of or with a 10-fold increase in maternal or early childhood urinary BPA concentrations among Cincinnati, Ohio, women and their children.***

<table>
<thead>
<tr>
<th>BPA exposure measure</th>
<th>n</th>
<th>Mean BMI (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prenatal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st tercile (0.4–1.6 μg/g creatinine)</td>
<td>99</td>
<td>0.00 (Referent)</td>
<td>Referent</td>
</tr>
<tr>
<td>2nd tercile (1.6–2.6 μg/g creatinine)</td>
<td>99</td>
<td>–0.01 (0.0–0.3)</td>
<td>0.48</td>
</tr>
<tr>
<td>3rd tercile (2.6–4.9 μg/g creatinine)</td>
<td>99</td>
<td>0.05 (0.1–0.2)</td>
<td>0.66</td>
</tr>
<tr>
<td>Continuous, log_{10}-transformed</td>
<td>293</td>
<td>–0.1 (0.0–0.3)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Early childhood</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st tercile (2.1–11 μg/g creatinine)</td>
<td>95</td>
<td>0.13 (Referent)</td>
<td>Referent</td>
</tr>
<tr>
<td>2nd tercile (11–20 μg/g creatinine)</td>
<td>95</td>
<td>0.12 (0.0–0.3)</td>
<td>0.96</td>
</tr>
<tr>
<td>3rd tercile (20–314 μg/g creatinine)</td>
<td>95</td>
<td>–0.10 (–0.2–0.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Continuous, log_{10}-transformed</td>
<td>285</td>
<td>–0.2 (–0.6–0.1)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Adjusted for maternal race (white, black, and other), marital status (married living together, unmarried living together, and unmarried living alone), parity (0, 1, and ≥2), age at delivery (continuous, years), household income (continuous, $10,000 increments), education (< high school, high school, some college, and ≥ bachelors’ degree), employment (any and none), insurance (private and public/none), BMI at 16 weeks of pregnancy (continuous, kg/m²), depressive symptoms at baseline (continuous), and prenatal serum cotinine (continuous, log_{10}-transformed).

**Figure 2. Adjusted change in child BMI z-score between 2 and 5 years of age with a 10-fold increase in maternal or early-childhood urinary BPA concentrations among Cincinnati, Ohio, women and their children.**

*With regard to the three prospective cohort studies (including the present study) with urinary BPA measurements, the differences in study design, urinary BPA concentrations, or the timing of BMI measurements do not seem to explain the discrepancies in their results. All three cohorts measured urinary BPA concentrations twice during pregnancy, and the two U.S. studies measured children’s BPA concentrations at the time BMI was assessed. Maternal urinary BPA concentrations were generally, but not significantly, associated with lower BMI in our cohort, the New England Children’s Amalgam Trial, a randomized, prospective birth cohort study in California, and with early childhood urinary BPA concentrations in our cohort, the New England Children’s Amalgam Trial, a randomized, prospective birth cohort study in California.
study. Confounding, BPA exposure misclassi-
cation, differences in distributions of effect
measure modifiers, incorrect model specifi-
cation, or residual sources of selection bias may
explain the discrepancies across epidemi-
ological studies (Howe et al. 2011).

Positive associations between urinary BPA
concentrations and BMI or percent body fat
in cross-sectional analyses may be attribut-
able to residual confounding from unmea-
sured dietary sources of BPA exposure that
are also important determinants of adiposity
(e.g., soda or canned foods). It has also been
suggested that BPA may simply be a marker
certain dietary patterns associated with
obesity (Sharpe and Drake 2013). However,
this hypothesis bears further scrutiny in
light of the known dietary sources of BPA
and the effect of these foods on obesity or
cardiometabolic disease risk. For instance,
canned foods are a major source of BPA in
adults (Carwile et al. 2011; von Goetz et al.
2010), and some canned foods contain high
levels of fiber and other micronutrients (e.g.,
canned beans), whereas others may be less
nutritious (e.g., canned pasta). Thus,
direction of confounding will depend on the
dietary source of BPA exposure and its asso-
ciation with obesity. Traditional measures of
dietary quality, like food frequency question-
naires, may misspecify dietary confounding
because these measures are designed to assess
macro- or micronutrient intake rather than
contaminants present in the food. Thus,
there is a need to develop and control for dietary
quality measures that incorporate potential
sources of BPA exposure.

One strength of our study was the ability
to control for socioeconomic, perinatal, and
environmental factors, including tobacco
smoke and phthalate exposures. However, we
did not include measures of maternal and
child diet and physical activity. Our results were
not substantially different when we controlled
for these measures of diet or physical activity;
however, the inability to adjust for more
accurate diet and activity measures may have
biased our results.

Associations between urinary BPA
concentrations and BMI may be attributable
to physiological changes during pregnancy
or early childhood that affect BPA excretion
and fetal/child growth. For instance, children
with BMI trajectories that have an early BMI
nadir are at an increased risk of obesity or
overweight compared with children who grow
normally (Williams and Goulding 2009).
Children on different growth trajectories
may have different BPA or creatinine excre-
tion patterns before they develop obesity,
making it difficult to disentangle associations
between urinary BPA concentrations and
body composition from prodromal obesity-
induced pharmacokinetic changes, even with

Figure 3. Adjusted BMI z-scores slopes between 2 and 5 years of age by prenatal and early-childhood
BPA tercile among Cincinnati, Ohio, women and their children. Adjusted for maternal race (white, black,
and other), marital status (married living together, unmarried living together, and unmarried living alone),
parity (0, 1, ≥ 2), age at delivery (continuous, years), household income (continuous, $10,000 increments),
education (< high school, high school, high school, college, and ≥ bachelor’s degree), employment (any and
none), insurance (private and public/none), BMI at 16 weeks (continuous, kg/m²), depressive symptoms at
baseline (continuous), and prenatal serum cotinine (continuous, log₁₀-transformed). Prenatal BPA terciles:
1st tercile: 0.4–1.6 μg/g creatinine; 2nd tercile: 1.6–2.6 μg/g creatinine; and 3rd tercile: 2.6–49 μg/g creati-
nine. Early-childhood BPA terciles: 1st tercile: 2.1–11 μg/g creatinine; 2nd tercile: 11–20 μg/g creatinine;
and 3rd tercile: 20–314 μg/g creatinine. Prenatal BPA × age interaction p-values: 2nd vs. 1st tercile: 0.42;
3rd vs. 1st tercile: 0.43. Early-childhood BPA × age interaction p-values: 2nd vs. 1st tercile: 0.51; 3rd vs. 1st
tercile: 0.22.
BPA exposure and childhood obesity


References


Braun JM, Daniels JL, Poole C, Olshan AF, Hornung R, Bernett JT, et al. 2010. A prospective cohort study of...