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Early Life Bisphenol A Exposure and Neurobehavior at 8 Years of Age: Identifying Windows of Heightened Vulnerability

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Abstract

Background—Early life BPA exposure could affect neurobehavior, but few studies have investigated whether there are developmental periods when the fetus or child is more vulnerable to these potential effects.

Objectives—We explored windows of vulnerability to BPA exposure in a multiethnic cohort of 228 mothers and their children from Cincinnati, Ohio.

Methods—We measured urinary BPA concentrations at up to two prenatal and six postnatal time points from the 2nd trimester of pregnancy until the child was age 8 years. At age 8 years, we administered the Behavioral Assessment System for Children-2 (BASC-2), Behavior Rating Inventory of Executive Function, and Wechsler Intelligence Scale for Children-IV. We estimated covariate-adjusted differences in composite scores from each instrument using a multiple informant model designed to identify heightened windows of vulnerability.

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Results—Among all children, there was not strong evidence that the associations between BPA and neurobehavior varied by the timing of exposure (Visit × BPA p-values=0.16). However, child sex modified the associations of repeated BPA measures with BASC-2 scores (Visit × Sex × BPA p-values=0.02–0.23). For example, each 10-fold increase in prenatal BPA was associated with more externalizing behaviors in girls (β=6.2, 95% CI: 0.8, 11.6), but not boys (β=−0.8, 95% CI: −5.0, 3.4). In contrast, a 10-fold increase in 8-year BPA was associated with more externalizing behaviors in boys (β=3.9, 95% CI: 0.6, 7.2), but not girls (β=0.3, 95% CI: −3.5, 4.1).

Conclusions—We found that sex-dependent associations between BPA and child neurobehavior may depend on the timing of BPA exposure.

Keywords

Bisphenol A; children; neurodevelopment; epidemiology

Introduction

Bisphenol A (BPA) is a weak estrogenic monomer widely used in the manufacture of plastics and resins found in a variety of consumer products, including some plastic food and beverage storage containers, food can linings, thermal paper receipts, medical equipment, dental sealants, and children's toys (Chapin et al. 2008). Exposure to BPA is almost universal in the United States; over 90% of the U.S. population has detectable levels of urinary BPA (Calafat et al. 2008). Diet is the primary route of exposure, although exposure may also occur via inhalation and dermal absorption, particularly in occupational settings (Ehrlich et al. 2014; Hehn 2016; Li et al. 2010; Hines et al. 2017; Thayer et al. 2015b; Von Goetz et al. 2010; Zalko et al. 2011). BPA is capable of binding to the membrane and nuclear estrogen receptors and can affect gonadal hormone signaling, which play critical roles in the developing brain, influencing pathways that lead to sex-specific development and behavior (Henrichs et al. 2013; Schug et al. 2015).

The fetus, infant, and child may be particularly vulnerable to the endocrine disrupting effects of BPA because exposures that occur during specific periods of development can have a lifelong impact on health (Barker 2007; Rice and Barone 2000). A number of epidemiologic studies have reported associations between urinary BPA concentrations at individual time points during gestation or childhood and maladaptive behaviors, such as hyperactivity and aggression, in children (Evans et al. 2014; Harley et al. 2013; Hong et al. 2013; Perera et al. 2012; Perez-Lobato et al. 2016; Roen et al. 2015). However, only a few of these studies have investigated whether there are windows of heightened vulnerability to BPA exposure, and none have employed statistical methods to formally identify these windows. Previously, we found that prenatal urinary BPA concentrations were associated with externalizing behaviors in 2-year-old children and with behavioral and emotional regulation in 3-year-olds, particularly among girls (Braun et al. 2009; Braun et al. 2011). The primary objective of the present study was to extend these prior findings and identify potential windows of vulnerability to the neurotoxic effects of BPA using repeated measures of prenatal and postnatal BPA exposures and neurobehavioral assessments at age 8 years.

Methods

Study Participants

We used data collected from mothers and their children who were participating in the Health Outcomes and Measures of the Environment (HOME) Study, a prospective pregnancy and birth cohort in the Cincinnati, Ohio, metropolitan area designed to study the health effects of environmental exposures. We previously described eligibility criteria and participant recruitment and follow-up (Braun et al. 2016). In summary, eligibility requirements included that women were ≥ 18 years of age, at 13–19 weeks of gestation, living in the Cincinnati, Ohio area in a home built before 1978, not on medications for thyroid disorders or seizures, planning to continue prenatal care and deliver at the collaborating clinics and hospitals, planning to live in the Cincinnati area for the next year, fluent in English, and had no diagnosis of diabetes, bipolar disorder, schizophrenia, HIV infection, or cancer that resulted in radiation treatment or chemotherapy. The institutional review boards (IRBs) at Cincinnati Children's Hospital Medical Center (CCHMC) and participating delivery hospitals approved this study. The Centers for Disease Control and Prevention (CDC) IRB relied on the determination made by the CCHMC IRB. All mothers provided written informed consent for themselves and their children.

Urinary BPA Concentrations

We collected up to 2 urine samples from mothers at 16- and 26-weeks of pregnancy between March 2003 and January 2006 and averaged BPA concentrations from these two measurements to obtain an estimate of prenatal BPA exposure for the present study. We collected up to 6 urine samples from children between 2004 and 2014 at annual clinic visits from 1–5 years of age and again at 7.5–10 years of age (the "8-year" visit). We collected urine onto Kendall abdominal pads placed inside the diaper for non-toilet trained children, a training potty lined with inserts for children who were being toilet trained, or directly into polypropylene specimen cups for children who were toilet trained and adults. BPA was not detected in the inserts prior to sample collection. Urine samples were stored at −20°C until shipment to the CDC Division of Laboratory Sciences, where they were stored at or below −20°C until analysis. We followed all provisions described in Ye et al. (2013) to minimize external contamination during sample storage and analysis.

The concentrations of total (free plus conjugated) BPA were measured at the CDC using analytical chemistry methods described previously (Ye et al. 2005). The limit of detection (LOD) was 0.4 ng/mL for samples collected at the prenatal and 1–5 year visits and 0.1 ng/mL for the 8-year visit; concentrations below the LOD were assigned a value of LOD/√2 (Hornung and Reed 1990). More than 90% of women and children had detectable urinary BPA concentrations at our time points of interest (Braun et al. 2011, Stacy et al. 2016). Each analytic batch included low and high concentration quality control (QC) samples, and the coefficients of variation of repeated QC samples were less than 10%. We measured free BPA to evaluate potential external contamination in the first batch of samples, but free BPA concentrations were either undetectable or very close to the LOD. For subsequent analytic batches, we repeated total extractions only to check higher than expected results (Sathyanarayana et al. 2011), which never suggested contamination. We measured urinary

creatinine concentrations using a previously described assay (Larsen 1972). Urinary BPA concentrations were divided by creatinine concentrations to account for urine dilution and $\log_{10}$-transformed for statistical analysis.

8-Year Neurobehavioral Outcomes

We assessed children's behavior, executive function, and cognitive abilities at 7.5 to 10 years of age. Detailed descriptions of the scales and traits measured on each neurobehavioral assessment are available in the supplement (Table S1). Previous studies have shown that the traits measured using these assessments, briefly described below, are associated with prenatal exposure to environmental chemicals, including BPA (Braun et al. 2011; Dietrich et al. 2005; Harley et al. 2013). Some of these tests assess omnibus features of child cognitive function, such as IQ, while others measure specific features of behavioral disorders like Attention Deficit Hyperactivity Disorder (ADHD).

We evaluated children's behavior using the Behavioral Assessment for Children-2 (BASC-2), a 160-item, valid, reliable, parent-report assessment of a child's adaptive and problem behaviors in community and home settings (Reynolds and Kamphaus 2004). We analyzed three composite scales from the BASC-2: Externalizing Problems, which reflects disruptive behavior problems; Internalizing Problems, such as depression and anxiety; and the Behavioral Symptoms Index, a measure of a child's overall level of problem behaviors. To assess executive function, we used the Behavior Rating Inventory of Executive Function (BRIEF), an 86-item, parent-report inventory that includes 8 clinical scales and 3 composite scales (Strauss et al. 2006). We analyzed the 3 composite scores from the BRIEF: the Behavioral Regulation Index, Metacognition Index, and Global Executive Composite, a summary score for the former two composites. Finally, we administered the Wechsler Intelligence Scale for Children-IV (WISC-IV) to evaluate children's overall intellectual ability (Full-Scale IQ), speed of mental and graphomotor processing (Processing Speed Index), perceptual reasoning and organization skills (Perceptual Reasoning Index), and verbal abilities (Verbal Comprehension Index). All three assessments are age-standardized by the developers and the BASC-2 is additionally sex-standardized. Lower scores on the WISC-IV indicate lower cognitive abilities and higher scores on the BASC-2 and BRIEF indicate more behavior problems.

Covariates

We considered adjusting for variables associated with BPA exposure and child neurobehavior in previous studies or believed to confound other environmental toxicant-neurodevelopment relationships (Bellinger 2004a; Stacy et al. 2016). Child's sex was retrieved from hospital medical charts, while the remaining sociodemographic covariates (child's race, mother's education, household income, marital status, and prenatal vitamins) were obtained by trained interviewers. To assess gestational exposure to tobacco smoke, we calculated the mean concentration of cotinine (a metabolite of nicotine) from maternal serum samples collected during pregnancy or at birth. We administered the Home Observation for Measurement of the Environment during the 1-year home visit to assess the quality and quantity of the caregiving environment (Caldwell and Bradley 2003). We also considered measures of maternal depression, ADHD, and IQ. Maternal depressive

symptoms were measured at 20 weeks of gestation using the Beck Depression Inventory-II (Beck et al. 1997). We administered the Conners' Adult ADHD Rating Scale to mothers at the 8-year visit to assess her ADHD behaviors. Additionally, we administered the Wechsler Abbreviated Scale of Intelligence to each mother once at any of the eight visits to obtain her full-scale IQ. We considered baseline (prenatal) measurements of other sociodemographic covariates.

Statistical Analysis

We used a multiple informant model to investigate associations between repeated prenatal and postnatal urinary BPA concentrations and the 8-year neurobehavioral outcomes (Sanchez et al. 2011). This approach is applied when information gathered from multiple individuals or sources is used to measure the same construct and can be used when there are repeated and sparsely sampled environmental exposure measures at different time points (or windows) that serve as informants. Using linear regression, this method jointly estimated the difference in neurobehavioral score for a 10-fold increase in urinary BPA concentration at each time point (average prenatal and ages 1, 2, 3, 4, 5, and 8 years). The multiple informant model also provides a 6 degree-of-freedom heterogeneity p-value that assesses whether the timing of exposure modifies the BPA-outcome association. Lower heterogeneity p-values suggest that at least one of the exposure-outcome associations differs from the others (i.e., the association depends on the timing of exposure).

Using this approach, we examined associations of urinary BPA concentrations at each of our seven time points with BASC-2, BRIEF, and WISC-IV composite scores. We used the p-value of the BPA × visit interaction term (the heterogeneity p-value) to determine whether BPA-outcome associations differed across visits and considered those with p-values <0.2 to indicate that the association depended on timing (Rothman and Greenland 1998). All outcomes were analyzed as continuous variables, while each window was treated categorically. We adjusted all models for child's sex, child's race, mother's education, household income, caregiving environment, marital status, maternal serum cotinine, and prenatal vitamin use. For the BASC-2 and BRIEF models, we also adjusted for maternal depression and ADHD scores, while WISC-IV models also included maternal IQ. Since we previously observed that child sex modified the association between BPA concentrations and neurobehavior in this cohort (Braun et al. 2009; Braun et al. 2011), we repeated the multiple informant analysis including all 2- and 3-way interaction terms between urinary BPA concentrations, child sex, and visit.

Secondary Analyses

We conducted several sensitivity analyses for the multiple informant model. To compare different methods of accounting for urine dilution, we adjusted all models for $\log_{10}$-transformed urinary creatinine as a covariate, with unstandardized $\log_{10}$-transformed urinary BPA as the exposure variable. We also repeated the analysis by 1) jointly adjusting for prenatal and 8-year BPA in the same model and 2) further adjusting for year of birth, since BPA exposure may have been decreasing over the period of the study due to changes in manufacturing practices and personal behaviors. Given the speed of fetal and placental

growth and development during the prenatal period, we also repeated the analysis considering urinary BPA concentrations separately at 16- and 26-weeks of gestation.

It is possible children with certain behavioral problems may have higher urinary BPA concentrations because they are more likely to engage in behaviors (e.g., eating specific foods) that increase their BPA exposure. To address this possibility of reverse causality in our cross-sectional analysis of data at age 8 years, we conducted a sensitivity analysis adjusting for a summary variable of potential BPA exposures in the past 24 hours, which included consuming canned food, canned beverages, and beverages in carton or pouch, and receipt handling, variables previously found to be associated with higher child urinary BPA concentrations in the HOME Study (Stacy et al. 2016). Finally, we also adjusted the 8-year analysis for the number of cans of canned vegetables consumed in the last 24 hours (0, >0 to <0.5, ≥0.5) and the prenatal analysis for frequency of maternal canned vegetable consumption (≤1–3 times per month, 1–3 times per week, ≥4–6 times per week).

Results

Descriptive Statistics

Out of 1,263 eligible women, 468 enrolled in our study (37%) between March 2003 and January 2006. Of these, 67 dropped out before delivery, and we excluded 9 twins, 3 stillbirths, and 2 infants with congenital or genetic anomalies. Distributions of maternal and child urinary BPA concentrations are available in the Supplemental Material (Table S2), and we previously found BPA concentrations in HOME Study children decreased as they got older, with children's median BPA concentrations at 8 years of age being similar to median BPA concentrations among the mothers during pregnancy (Braun et al. 2011; Stacy et al. 2016).

Among the remaining 387 singleton children and their mothers, 228 (59%) parents completed the BASC-2 and BRIEF and 220 (57%) children completed the WISC-IV at 7.5 to 10 years of age. Of the 228 children in our sample, 40% (n=91) had all 7 BPA measures, 23% (n=53) had 6 measures, 14% (n=31) had 5 measures, 14% (n=31) had 4 measures, 6% (n=14) had 3 measures, and 3% (n=8) had 2 measures. The median 8-year urinary BPA concentration (25^{th}, 75^{th} percentile) was 1.6 (1.0, 3.6) ng/mL. Their mothers had a median prenatal BPA concentration of 2.1 (1.0, 3.5) ng/mL (Table 1). Urinary BPA concentrations during pregnancy and childhood had a 1.8 to 3.2 order of magnitude range. The demographic composition of the participants who completed follow-up at age 8 years was similar to the overall cohort (Braun et al. 2016).

On average, children in the HOME Study had typical composite scores on the BASC-2, BRIEF, and WISC-IV tests (see Table 1). Mean composite scores from the BASC-2 and BRIEF at 8 years of age differed across sociodemographic factors and increased with worsening categories of maternal depression and ADHD scores (Table 1). Full-scale IQ scores were lowest among children that were black, from the lowest income families (< $20,000 per year), born to mothers with less educational attainment, or had mothers with lower IQ scores (Table 1).

Urinary BPA Concentrations and Neurobehavioral Outcomes

After adjustment for potential confounders, prenatal urinary BPA concentrations were generally associated with more maladaptive behaviors and impaired executive functioning, although the 95% CI of these point estimates included the null value (Figure 1 and Table S3). In contrast, prenatal BPA was not associated with WISC-IV scores. Childhood urinary BPA concentrations at 3, 4, and 8 years were positively associated with the behavioral symptoms index as well as several composite scores on the BRIEF, indicating more problematic behaviors and executive functioning (Figure 1). Children's urinary BPA concentrations at most ages were not associated with worse WISC-IV scores, except at 8-years of age where BPA concentrations were inversely associated with overall cognition, verbal abilities, and speed of mental processing. BPA × visit interaction term p-values were <0.2 for the global executive composite and behavioral regulation index scores from the BRIEF (Table S4), suggesting that the associations between these scales and urinary BPA concentrations differed across windows of exposure.

Child's sex modified the patterns of associations between repeated BPA measures and several of the outcomes, particularly the behavioral symptoms index and externalizing scales of the BASC-2 (BPA × sex × visit interaction terms≤0.05) and the BRIEF behavioral regulation index (BPA × sex × visit interaction term=0.17; Table S4). Prenatal urinary BPA concentrations were associated with more externalizing scores on the BASC-2 and poorer behavioral regulation scores on the BRIEF among girls (Figure 2 and Table S5). Eight-year BPA was associated with higher scores on all the BASC-2 and BRIEF scales and lower scores on all the WISC-IV scales among boys. Urinary BPA concentrations at ages 3 and 4 years were also modestly associated with higher composite and behavioral regulation BRIEF scores among boys.

Secondary Analyses

Adjusting the multiple informant models for $\log_{10}$-creatinine to account for urine dilution did not substantially change the overall patterns of associations we observed for each outcome (Supplemental Table S6). Results using the multiple informant approach were similar after joint adjustment for prenatal and 8-year BPA in the same model and after additional adjustment for year of birth. For concision, we show results of these sensitivity analyses in Table S6 only for externalizing problems and prenatal (for girls) and 8-year BPA (for boys), since these associations were statistically significant in the primary analysis. When we investigated finer prenatal windows of vulnerability, we observed stronger associations of 16-week, as opposed to 26-week BPA, and several outcomes, including externalizing problems in girls (Table S7). The cross-sectional associations between 8-year urinary BPA concentrations and 8-year outcomes we observed among boys were similar when we further adjusted for BPA exposures in the past 24 hours (Supplemental Figure S1). Adjusting the prenatal and 8-year analyses for maternal and child canned vegetable consumption, respectively, did not appreciably change the results of these analyses (Table S6).

Discussion

Our results suggest that the sex-dependent associations of pre- and postnatal urinary BPA concentrations with child neurobehavior in this cohort may depend on the timing of exposure. Prenatal urinary BPA concentrations were associated with more maladaptive behaviors, specifically externalizing problems among girls. In boys, postnatal urinary BPA concentrations at 8 years of age were associated with more behavioral, executive function, and cognitive impairments.

The results of an increasing number of epidemiological studies suggest that BPA exposure during gestation and/or early childhood influences neurobehavioral outcomes in young children (Braun et al. 2009; Braun et al. 2011; Casas et al. 2015; Evans et al. 2014; Harley et al. 2013; Hong et al. 2013; Perera et al. 2012; Perez-Lobato et al. 2016; Roen et al. 2015). Our finding of an association between prenatal BPA exposures and worse externalizing problems at 8 years of age among girls agrees with previous findings in the HOME Study (Braun et al. 2009; Braun et al. 2011). Another study of prenatal BPA and early infant neurobehavior in the HOME cohort found a trend toward increased infant hypotonia with increasing prenatal BPA concentrations (Yolton et al. 2011). Other studies have reported associations between prenatal BPA exposure and increases in behavioral problems primarily in boys (Casas et al. 2015; Evans et al. 2014; Harley et al. 2013; Perera et al. 2012). In a cohort of 198 low income, African-American and Dominican women and their children, prenatal BPA exposure was associated with higher emotional reactive and aggressive behaviors in boys, but lower scores in girls (Perera et al. 2012). Similarly, other investigators reported that maternal urinary BPA concentrations were associated with increases in externalizing and internalizing behaviors in mainly Caucasian boys (Evans et al. 2014). Miodovnik et al. did not find an association between maternal urinary BPA concentrations and neurobehavior in 7 to 9-year-old inner-city minority children, although their focus was social impairment related to autism spectrum disorders (Miodovnik et al. 2011).

Previous epidemiologic studies have found associations between postnatal exposure to BPA and neurobehavior primarily among girls (Mustieles et al. 2015). In our study, urinary BPA concentrations at approximately 3, 4, and 8 years of age were associated with several measures of behavior and executive function among boys. Eight-year BPA was also associated with lower WISC-IV scores in boys. Associations between childhood BPA and WISC-IV scores were mostly null among girls, except for BPA concentrations at age 1 year being associated with improved perceptual reasoning index scores. Harley et al. found that urinary BPA concentrations in 5-year-old children were associated with increased internalizing behaviors, inattention, and hyperactivity in both boys and girls at 7 years of age and with externalizing behaviors in girls (Harley et al. 2013). In an inner-city population, Roen et al. found that high postnatal urinary BPA concentrations were associated with increased internalizing and externalizing scores among 7 to 9-year-old girls (Roen et al. 2015). In another investigation, childhood urinary BPA concentrations in approximately 300 school-aged Spanish children were associated with more internalizing symptoms and with thought and social problems using the Child Behavior Checklist, although the study was cross-sectional and only included boys (Perez-Lobato et al. 2016). Urinary BPA concentrations have also been positively associated with ADHD diagnosis and behaviors in a

nationally representative sample of U.S. boys (Tewar et al. 2016). Some studies have not found a relationship between postnatal BPA exposure and some aspects of neurobehavior in children (Braun et al. 2011; Perera et al. 2012). Discrepancies in the literature could be partly due to differences in the characteristics of the study populations (e.g. race, socioeconomic status) or study designs, including differences in the timing of exposure or outcome assessment, types of neurobehavioral assessments, or BPA exposure misclassification.

Our findings are consistent with some experimental animal studies reporting increased hyperactivity, aggressive behaviors, and memory impairment in offspring following low-dose BPA exposure during gestation or lactation (Anderson et al. 2013; Gonçalves et al. 2010; Kundakovic et al. 2013; Poimenova et al. 2010; Wang et al. 2016). The doses evaluated in these animal studies ranged from 2 to over 500 μg/kg body weight/day, while estimated median intakes in the HOME Study and other human populations are in the 10s to 100s of ng/kg body weight/day range. For example, Kundakovic 2013 exposed pregnant mice to several doses of BPA, two of which (2 and 20 μg/kg bw/day) were less than the reference dose for BPA of 50 μg/kg bw/day (US EPA 2016), and found that low-dose prenatal BPA exposure induced enduring epigenetic disruption in the brain that might explain BPA's effects on brain function and behavior in offspring. However, the doses these animals were exposed to are several orders of magnitude higher than the estimated median intakes in humans. A study of rats found that maternal BPA exposure led to impairment of object recognition memory in male offspring, which the authors attribute to inhibition of the hippocampal extracellular regulated kinase pathway, believed to play a critical role in synaptic plasticity, learning, and memory (Wang et al. 2016). A recent study of postnatal BPA exposure in male mice attributed the impairment of spatial memory and adverse effects on synaptic remodeling of hippocampal neurons to BPA's anti-androgen effects (Fang et al. 2017).

BPA's ability to disrupt gonadal hormone pathways may explain the sex-dependent results we observed in the present study as these hormones play pivotal roles in sexually dimorphic neurodevelopment (Cohen-Bendahan et al. 2005; Zhang et al., 2011). Experimental animal studies have also reported sex-specific effects following BPA exposure (Arambula et al. 2016), although it is unclear as to whether exposure to BPA and other endocrine disruptors reduces, eliminates, or widens sex differences in behaviors (Palanza et al. 2008). Disruption of thyroid hormone homeostasis may be another mechanism through which BPA affects neurodevelopment (Chevrier et al. 2013; Romano et al. 2015). Deficiencies in thyroid hormones can alter cell migration in the developing brain and affect neuronal cell differentiation (Henrichs et al. 2013). We speculate, but could not confirm with these data, that BPA may have sex-specific associations with neurobehavior due to its ability to affect sex-specific neurodevelopmental mechanisms. However, we previously observed that prenatal BPA concentrations were associated with reduced cord serum thyroid stimulating hormone concentrations among girls in this cohort (Romano et al. 2015).

To date, few studies have comprehensively and systematically evaluated pre- and postnatal windows of heightened vulnerability to BPA exposure and neurobehavior in children. Our longitudinal data enabled us to study associations at seven potentially sensitive time points

from the 2nd trimester through age 8 years. We were able to apply a novel approach used in previous investigations of environmental exposures and health outcomes (Sánchez et al. 2011). This approach could be useful in future studies exploring windows of vulnerability to BPA exposure or other endocrine disruptors and health outcomes in children. Using the multiple informant model, we identified the prenatal period as an important window of vulnerability to the neurotoxic effects of BPA among girls and several relevant postnatal windows (ages 3, 4, and 8) among boys. Few prior studies have examined the relations between BPA exposure and child cognitive abilities, and we found an association between postnatal BPA exposure and reduced cognition among boys. Although further studies are needed to confirm these findings, identifying windows of vulnerability could inform population- or individual-level interventions to reduce BPA exposure during these time periods. Even the more subtle effects of exposure could have substantial population-level impacts by shifting the distribution of continuous neurobehavioral traits and thus increasing the risk for learning disabilities and other disorders (Bellinger 2004b, Bellinger 2012).

Additional strengths of our study include the use of valid and reliable tests to assess behavior, executive function, and cognition in children and the ability to account for many sociodemographic, caregiving, and maternal mental health factors related to BPA exposure or our outcomes of interest. As with any epidemiologic study, it is possible that the observed associations are due to confounding by other neurotoxic chemicals or to unknown or unmeasured confounders; however, these other factors would have to be correlated with BPA exposure and explain additional variation in our outcomes beyond the covariates we were able to adjust for in our models. The findings of our study are also limited to neurobehavioral assessments made at 8 years of age. It is possible that associations with urinary BPA could differ if the outcomes were measured at a later time point, such as adolescence. Further, we observed cross-sectional associations between 8-year urinary BPA concentrations and BASC-2, BRIEF, and WISC-IV scores. It is difficult to imagine how concurrent BPA exposure would result in neurobehavioral deficits. We tried to reduce the possibility of reverse causality by adjusting for some specific behaviors that might be associated BPA exposure (e.g., canned food consumption), and these cross-sectional associations remained after further adjustment for these behaviors.

Although we measured urinary BPA concentrations over several time points during pregnancy and childhood, BPA has a relatively short half-life in the body (<6 hours) (Thayer et al. 2015a), and urinary BPA concentrations can vary substantially within a day for an individual. We previously observed that HOME Study child urinary BPA concentrations, measured in six serial urine samples, have a low degree of reproducibility (ICC<0.2) (Stacy et al. 2016). One study performed a surrogate category analysis of over 2,000 urine specimens from 83 Utah couples and found that 6 or more samples were required to adequately predict categories of low, medium, and high BPA exposure (Cox et al. 2015). Thus, single spot urine measurements can result in misclassification of BPA exposure. To help reduce exposure variability, we averaged 16- and 26-week maternal urinary BPA concentrations to estimate prenatal exposure, but we only have one measurement at each postnatal visit to reflect approximately year-long exposures. Future studies might consider pooling multiple urine samples from each individual and analyzing the pooled sample to reduce the potential for exposure misclassification bias (Perrier et al. 2016). Our sample size

was modest, which reduced our ability to precisely estimate associations. Some years also had lower sample sizes than others, further reducing our statistical power to detect associations at these time points. Finally, we made a large number of comparisons between multiple measures of BPA exposure and neurobehavioral domains. While there are potential concerns when examining multiple exposure-outcome relations, the consistency of the associations of prenatal and 8-year BPA concentrations with multiple neurobehavioral domains suggests that these individual results may not be spurious. Further, the associations for prenatal and 8-year BPA remained when we mutually adjusted for these windows in the same models.

In conclusion, urinary BPA concentrations during gestation and early childhood were associated with impairments in behavior and executive function in children at age 8 years in this cohort; the associations differed in boys and girls. Most notably, the strength of the association between BPA and children's neurobehavior depended on the timing of BPA exposure in this cohort. Additional follow-up of this and other cohorts should determine if early life BPA exposure is associated with an increased risk of clinically significant behaviors or other sequelae related to the constellation of maladaptive behaviors associated with BPA exposure. Future studies to validate these findings in other cohorts would benefit from using the statistical approach we employed to identify windows of heightened vulnerability to BPA or other endocrine disruptors and from collecting serial urine samples to reduce BPA exposure misclassification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We propose a new method for exploring windows of vulnerability to BPA exposure.
- We examine BPA-neurobehavior associations across 7 windows of early life exposure.
- These associations depend on timing of BPA exposure and differ in girls and boys.

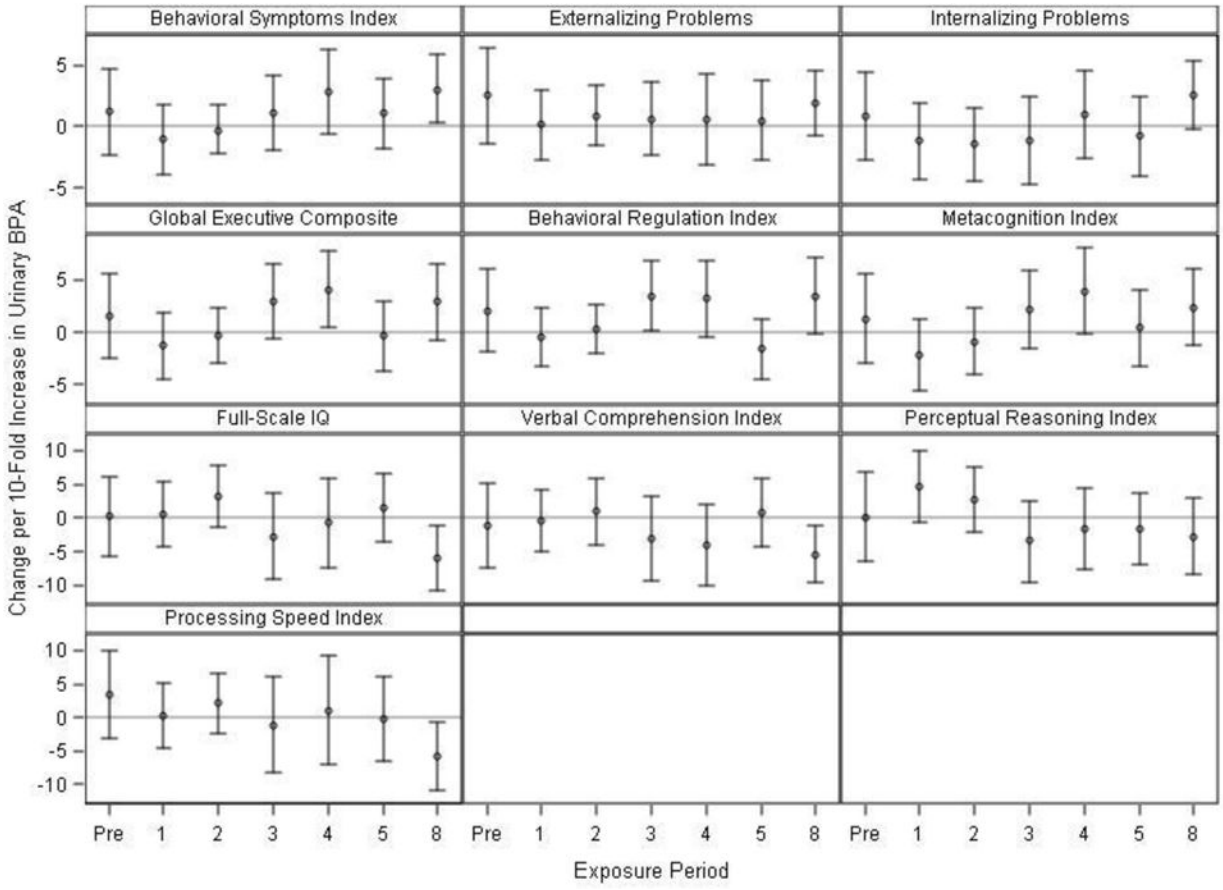

Figure 1.

Adjusted differences in BASC-2 (row 1),[1] BRIEF (row 2),[1] and WISC-IV (rows 3–4)[2] scores at 8 years of age with 10-fold increases in prenatal and childhood creatinine-standardized urinary BPA concentrations (Prenatal: N=202–210, Age 1: N=178–185, Age 2: N=159–165, Age 3: N=163–168, Age 4: N=131–132, Age 5: N=159–161, Age 8: N=200–204).

[1]Adjusted for: visit, BPA × visit, child's sex, child's race, mother's education, household income, caregiving environment, marital status, prenatal serum cotinine concentrations, prenatal vitamins, mother's BDI, and mother's CAARS.

[2]Adjusted for: visit, BPA × visit, child's sex, child's race, mother's education, household income, caregiving environment, marital status, prenatal serum cotinine concentrations, prenatal vitamins, and mother's full-scale IQ.

BPA × visit interaction term p-values were 0.18 for the global executive composite and 0.16 for the behavioral regulation index, indicating that these associations depended on the timing of BPA exposure. Heterogeneity p-values were >0.2 for all other outcomes. Exact sample sizes at each visit are available in Supplemental Table S3.

Higher BASC-2 and BRIEF scores indicate worse behavior or executive function, while higher WISC-IV scores indicate better cognitive abilities.

Abbreviations: Pre=Prenatal, BASC-2=Behavioral Assessment for Children-2, BRIEF=Behavior Rating Inventory of Executive Function, WISC-IV=Wechsler Intelligence

Scale for Children-IV, BDI=Beck Depression Inventory, CAARS= Conners' Adult ADHD Rating Scale

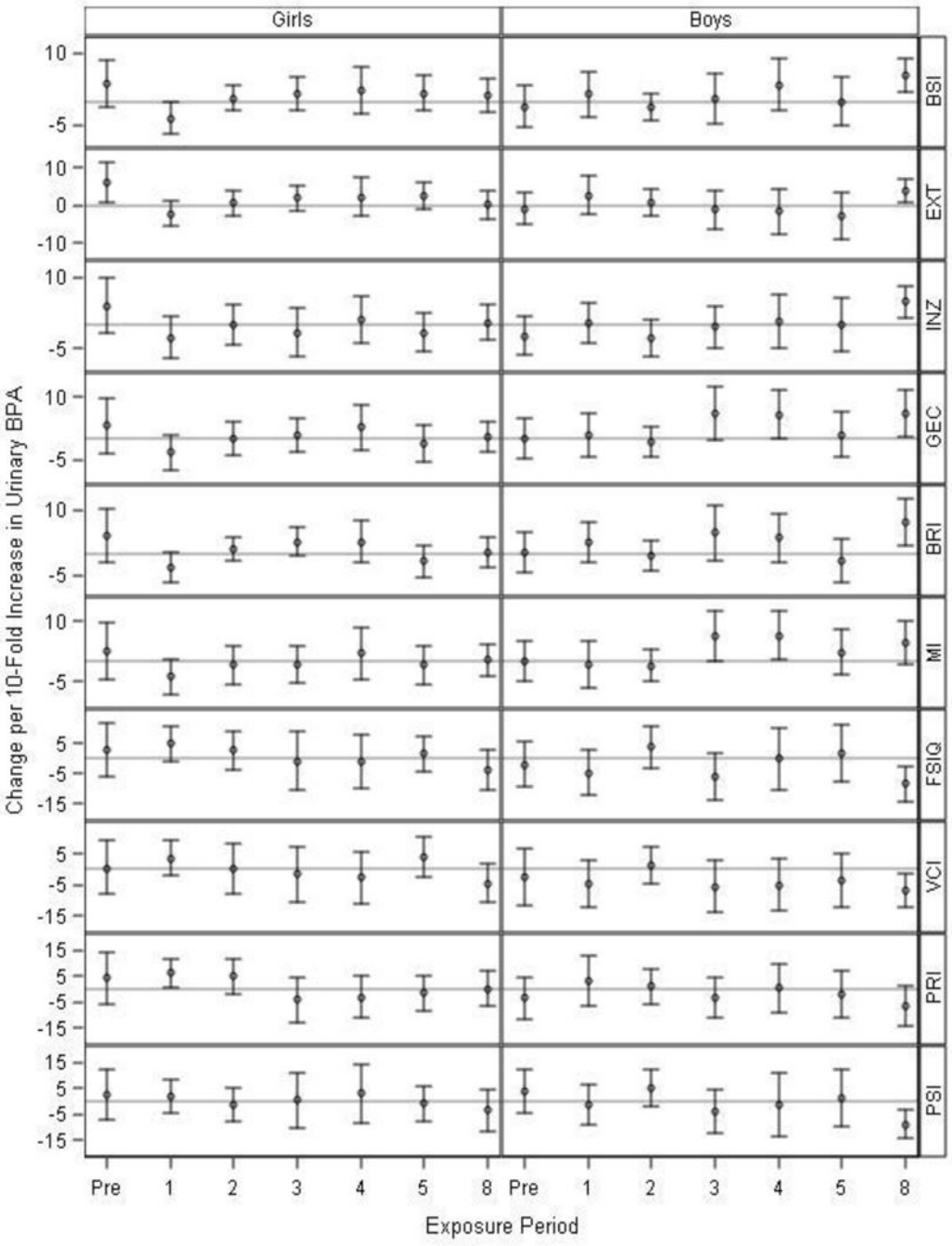

Figure 2.

Adjusted[1] difference in BASC-2,[1] BRIEF,[1] and WISC-IV[2] IV scores at 8 years of age with 10-fold increases in prenatal and childhood creatinine-standardized urinary BPA concentrations, in girls (N=72–117) and boys (N=59–93).

[1]Adjusted for: visit, BPA × visit, child's sex × visit, BPA × child's sex, BPA × visit × child's sex, child's race, mother's education, household income, caregiving environment, marital status, prenatal serum cotinine concentrations, prenatal vitamins, mother's BDI, and mother's CAARS.

[2]Adjusted for: visit, BPA × visit, child's sex × visit, BPA × child's sex, BPA × visit × child's sex, child's race, mother's education, household income, caregiving environment, marital status, prenatal serum cotinine concentrations, prenatal vitamins, and mother's full-scale IQ. BPA × visit × sex interaction term p-values were 0.05, 0.02, 0.23, and 0.17 for the BSI, EXT, INZ, and BRI, respectively, indicating differences in time windows of BPA exposure between girls and boys. Heterogeneity p-values were >0.2 for all other outcomes. Exact sample sizes at each visit are available in Supplemental Table S5.

Higher BASC-2 and BRIEF scores indicate worse behavior or executive function, while higher WISC-IV scores indicate better cognitive abilities.

Abbreviations: Pre=Prenatal, BASC-2=Behavioral Assessment for Children-2, BRIEF=Behavior Rating Inventory of Executive Function, WISC-IV=Wechsler Intelligence Scale for Children-IV, BSI=Behavioral Symptom Index, EXT=Externalizing Problems, INZ=Internalizing Problems, GEC=Global Executive Composite, BRI=Behavioral Regulation Index, MI=Metacognition Index, FSIQ=Full-Scale IQ, VCI=Verbal Comprehension Index, PRI=Perceptual Reasoning Index, PSI=Processing Speed Index, BDI=Beck Depression Inventory, CAARS= Conners' Adult ADHD Rating Scale

Table 1

Prenatal maternal and child 8-year urinary BPA concentrations and 8-year Behavioral Symptom Index (BSI), Global Executive Composite (GEC), and Full-Scale IQ (FSIQ) scores according to sociodemographic, caregiving, maternal, and behavioral factors.

	Prenatal BPA (ng/mL)		8-Year BPA (ng/mL)		BSI Score		GEC Score		Full-Scale IQ	
Covariate	***N***	***Median (25th, 75th)***	***N***	***Median (25th, 75th)***	***N***	***Mean (SD)***	***N***	***Mean (SD)***	***N***	***Mean (SD)***
Overall	228	2.1 (1.0, 3.5)	222	1.6 (1.0, 3.6)	228	50 (9)	228	48 (11)	220	102 (16)
Child Sex										
Female	127	2.2 (0.9, 3.6)	122	1.6 (1.0, 3.9)	127	49 (9)	127	49 (10)	122	102 (16)
Male	101	2.0 (1.1, 3.1)	100	1.7 (1.0, 3.3)	101	51 (9)	101	48 (11)	98	101 (15)
Child Race										
White	128	1.5 (0.7, 2.5)	126	1.5 (0.8, 3.1)	128	49 (9)	128	47 (10)	124	108 (12)
Black	80	3.3 (2.4, 5.2)	78	2.3 (1.3, 4.8)	80	51 (10)	80	51 (11)	78	91 (15)
Other	15	1.4 (1.1, 1.9)	13	1.5 (1.0, 1.9)	15	49 (9)	15	50 (13)	13	110 (16)
Maternal Education										
College graduate Tech school/Some	106	1.4 (0.7, 2.2)	102	1.5 (1.0, 2.9)	106	49 (9)	106	46(10)	101	109 (12)
College	63	2.6 (1.4, 4.0)	63	2.1 (1.1, 4.1)	63	51 (10)	63	50 (11)	62	100 (14)
High school graduate	35	3.1 (2.1, 5.3)	33	1.6 (1.1, 3.4)	35	49 (8)	35	49 (10)	33	90 (18)
Less than grade 12	24	3.2 (2.2, 5.1)	24	2.4 (1.2, 3.4)	24	52 (10)	24	52 (9)	24	90 (13)
Household Income										
>$80K	58	1.5 (0.8, 2.8)	57	1.5 (0.9, 3.5)	58	49 (8)	58	46 (10)	56	112 (12)
$40–80K	75	1.5 (0.7, 2.7)	71	1.5 (1.0, 3.0)	75	49 (9)	75	47 (11)	71	104 (14)
$20–40K	34	2.6 (1.6, 3.8)	34	1.5 (0.7, 3.7)	34	49 (8)	34	50 (11)	34	101 (12)
<$20K	61	3.4 (2.2, 5.3)	60	2.3 (1.4, 4.0)	61	52 (10)	61	51 (10)	59	89 (15)
Marital Status										
Married	141	1.6 (0.8, 2.7)	136	1.5 (0.9, 3.0)	141	49 (9)	141	47 (10)	135	108 (13)
Unmarried, living with someone	28	3.1 (2.1, 5.4)	27	3.4 (1.8, 4.6)	28	49 (7)	28	49 (9)	27	94 (17)

	Prenatal BPA (ng/mL)		8-Year BPA (ng/mL)		BSI Score		GEC Score		Full-Scale IQ	
Covariate	***N***	***Median (25th, 75th)***	***N***	***Median (25th, 75th)***	***N***	***Mean (SD)***	***N***	***Mean (SD)***	***N***	***Mean (SD)***
Unmarried, living alone	59	3.1 (1.9, 5.0)	59	1.8 (1.1, 4.0)	59	51 (10)	59	52 (11)	58	91(15)
Caregiving Environment										
<35	37	3.6 (2.7, 5.8)	36	2.9 (1.3, 5.9)	37	50 (8)	37	50 (9)	36	91(15)
35–<40	42	2.5 (1.5, 4.0)	42	1.7 (1.0, 4.0)	42	52 (10)	42	52 (11)	42	96 (16)
40+	133	1.6 (0.8, 2.7)	128	1.5 (1.0, 3.0)	133	49 (9)	133	47 (11)	126	108 (13)
Maternal BDI–II										
Minimal: <14	176	1.8 (0.9, 3.3)	172	1.6 (1.0, 3.4)	176	49 (9)	176	47 (11)	170	104 (15)
Mild: 14–19	30	2.5 (1.8, 4.2)	30	2.3 (1.3, 4.0)	30	52 (10)	30	52 (11)	29	93 (16)
Moderate/Severe: >19	20	2.6 (1.3, 3.9)	18	1.6 (1.0, 3.4)	20	55 (9)	20	55 (8)	19	95 (15)
Maternal CAARS										
<40	56	2.3 (1.4, 4.2)	54	1.4 (0.9, 3.2)	56	43 (8)	56	41 (8)	54	100 (17)
40–45	62	2.2 (1.2, 3.5)	60	1.8 (1.3, 3.7)	62	50 (9)	62	49 (10)	61	101 (15)
46–52	58	1.6 (0.7, 3.3)	58	1.6 (1.0, 3.5)	58	51 (7)	58	49 (9)	54	102 (15)
>52	52	2.0 (1.3, 2.8)	50	1.8 (1.0, 3.9)	52	55 (9)	52	54 (11)	51	104 (17)
Maternal FSIQ										
<96	68	3.3 (2.3, 5.0)	67	2.0 (1.3, 4.0)	68	50 (10)	68	50 (10)	67	92 (14)
96–109	46	1.8 (0.9, 2.9)	45	1.6 (0.9, 4.0)	46	48 (8)	46	49 (11)	44	98(17)
109–117	49	1.8 (1.0, 3.2)	48	1.6 (1.0, 3.3)	49	49 (8)	49	48 (11)	47	108 (10)
>=117	65	1.3 (0.7, 2.3)	62	1.5 (0.8, 2.5)	65	50 (10)	65	47 (11)	62	110 (14)
Maternal Cotinine										
<LOD	78	1.3 (0.7, 2.2)	75	1.5 (0.8, 3.0)	78	49 (9)	78	45 (9)	74	107 (13)
LOD - 3 ng/mL	123	2.5 (1.3, 4.0)	121	1.7 (1.1, 3.7)	123	50 (9)	123	50 (11)	121	100 (16)
>3 ng/mL	27	2.7 (2.1, 5.3)	26	2.8 (1.1, 4.1)	27	51 (9)	27	52 (11)	25	94 (16)
Prenatal Vitamin										

	Prenatal BPA (ng/mL)		8-Year BPA (ng/mL)		BSI Score		GEC Score		Full-Scale IQ	
Covariate	***N***	***Median (25th, 75th)***	***N***	***Median (25th, 75th)***	***N***	***Mean (SD)***	***N***	***Mean (SD)***	***N***	***Mean (SD)***
Rarely/Never	34	2.7 (1.8, 4.2)	32	1.9 (1.2, 3.7)	34	52 (9)	34	51 (10)	32	91(17)
Weekly/Daily	194	1.9 (0.9, 3.3)	190	1.6 (1.0, 3.5)	194	49 (9)	194	48 (11)	188	103 (15)

Abbreviations: BSI=Behavioral Symptom Index, GEC=Global Executive Composite, FSIQ=Full-Scale IQ, BDI= Beck Depression Inventory, CAARS= Conners' Adult ADHD Rating Scale