## Title

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# Prenatal bisphenol A exposure in relation to behavioral outcomes in girls aged 4–5 and modification by socio-demographic factors in The Infant Development and Environment Study (TIDES)

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## Abstract

Bisphenol A (BPA) is a polymer used in the production of polycarbonate plastics and epoxy resins. An estrogen mimic, prenatal BPA exposure has been associated with several behavioral outcomes in children; however, the impact of maternal demographic and economic factors on associations between BPA and child behavioral outcomes have not been examined. The objective of this study was to examine associations between prenatal maternal urinary BPA and behavior in 4–5 year old girls, and to assess whether socio-demographic factors modify this relationship. Mothers enrolled in The Infant Development and Environment Study (TIDES) provided a single spot urine at enrollment (median gestational age 11 weeks) and completed the Behavior Assessment System for Children-2 (BASC-2) and Social Responsiveness Scale-2 (SRS-2) when

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

**Erona Ibroci, Shanna H Swan, Sarah F Evans:** Conceptualization, Methodology. **Erona Ibroci:** Writing – original draft, Formal analysis. **Shanna Swan, Sarah F Evans:** Supervision. **Sally W Thurston, Emily S Barrett, Nichole R Bush, Ruby HN Nguyen, Sheela Sathyanarayana, Abraham Reichenberg, Brent R Collett, Shanna H Swan, Sarah F Evans:** Writing – review & editing.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuro.2022.05.018.

their daughters were 4–5 years of age. Mother-daughter pairs with complete phthalate, BASC-2, SRS-2, and covariate data were included in this analysis (N = 244). BPA was detectable in 93 % of urine samples. We used multivariable linear regression analyses to estimate associations between maternal urinary $log_{10}$-transformed BPA concentration and BASC-2 subscale and composite scores and SRS-2 Total Score. To examine the role of socioeconomic and demographic factors associated with study site, we stratified by TIDES center, comparing those enrolled at University of Rochester Medical Center (URMC), a predominately lower socioeconomic population, and those enrolled elsewhere: University of Washington, University of Minnesota, and University of California San Francisco, whose populations share similar higher socioeconomic demographic characteristics. Across all centers, no associations were seen between BPA and BASC-2 or SRS-2 scores. When stratifying by center, BPA was significantly associated with greater social impairment as measured by the SRS-2 Total Score (β-coefficient [95 % confidence intervals]: 5.1 [1.0, 9.2]) in URMC participants (N = 61). In non-URMC participants (N = 183), BPA was significantly associated with lower BASC-2 Internalizing composite (−3.3 [−6.7, 0.0]) and Depression subscale scores (−3.4 [−6.7, 0.0]) while no associations were seen between BPA and SRS-2 scores. Our findings suggest that sociodemographic factors may modify the impacts of maternal prenatal BPA on developmental endpoints.

**Keywords**

Bisphenol A; Prenatal exposure; Neurobehavior; Endocrine disrupting chemicals

## 1. Introduction

Bisphenol A (BPA), a polymer used in the production of polycarbonate plastics and epoxy resins, is commonly found in food and beverage packaging, medical devices, linings of metal food cans and plastic bottle caps, thermal paper (e.g. receipts), and dental sealants/composites (NIEHS, 2020). The primary route of exposure is diet, which can occur when BPA leaches from can linings and food storage containers (LaKind and Naiman, 2011). Human exposure to BPA is ubiquitous; in a representative national sample, BPA was detected in the urine of 92.6 % of Americans (Calafat et al., 2008). Studies have detected BPA in the fetal environment, including the placenta (Balakrishnan et al., 2010; Schönfelder et al., 2002), cord blood (Ikezuki et al., 2002), and amniotic fluid (Edlow et al., 2012; Yamada et al., 2002), indicating that the developing fetus is likely to be exposed during gestation.

BPA is an endocrine disrupting chemical, a class of chemicals that may disrupt brain development *in utero* (Palanza et al., 1999). BPA weakly binds to nuclear and membrane estrogen receptors, and has been shown to both act as an estrogen agonist at high doses, and antagonist at low doses (Kurosawa et al., 2002; Li et al., 2012). In addition, BPA has been shown to interfere with androgen and thyroid hormone signaling (Schug et al., 2015). Gestational exposure to BPA alters offspring behavior in rodents, with several studies reporting increased anxiety in female offspring (Cox et al., 2010; Gioiosa et al., 2013; Kubo et al., 2001; Poimenova et al., 2010; Ryan and Vandenbergh, 2006) and one study finding the

opposite (Tian et al., 2010). Gestational BPA was also found to masculinize, or 'defeminize', social behaviors in female rodents (Dessì-Fulgheri et al., 2002; Porrini et al., 2005).

Several cohort studies have examined prenatal BPA exposure in relation to girls' behavior using the BASC-2, SRS-2, or similar behavioral scales, with mixed findings (Supplemental Table 1). More externalizing behaviors (i.e., outward expression of emotions, including hyperactivity and aggression) were seen in 2-year olds in relation to 2nd trimester maternal urinary BPA concentrations, an association which persisted in a follow-up study at 8 years of age (Braun et al., 2009, 2017b). Among 3-year old girls, 2nd trimester BPA was associated with more anxious, depressed, and hyperactive behaviors (Braun et al., 2011b). In contrast, some studies reported fewer internalizing (e.g. less anxious and depressed) behaviors in relation to 3rd trimester BPA in girls ages 3 or 9 years old (Perera et al., 2012; Roen et al., 2015). Others observed no association between 1st to 3rd trimester BPA exposure and girls' behavioral scores at various ages (Braun et al., 2014, 2017a; Evans et al., 2014; Harley et al., 2013). 2nd trimester BPA was significantly associated with impairments in social communication among 4-year old girls in Korea (Lim et al., 2017). Two other studies found no associations between 1st or 3rd trimester BPA and any type of social impairment among girls (Braun et al., 2017a; Miodovnik et al., 2011).

Increasing evidence suggests that socio-demographic factors modify associations between chemical exposures and child cognition and behavior (Cohen Hubal et al., 2020; Gump et al., 2009; Payne-Sturges et al., 2021; Rauh et al., 2004). These differences between socio-demographic groups could be correlated with differences in chemical exposure levels; for example, data from the National Health and Nutrition Examination Survey (NHANES) demonstrates higher urinary BPA concentration in lower income individuals, non-Hispanic Blacks, and females (Calafat et al., 2008; Nelson et al., 2012). Low-socioeconomic status (SES) groups with higher chemical exposure greatly affect those who are generally at-risk and often do not have the resources to lower their exposure, thus have more severe impacts from the exposure, compared to advantaged counterparts. To date, no studies have examined the role of maternal socio-demographic factors on the association between prenatal BPA exposure and child behavior. The primary objective of our analysis was to examine associations between early 1st trimester prenatal BPA exposure and behavioral outcomes in girls at 4–5 years of age and modification of these relationships by socio-demographic factors associated with location in the Infant Development and Environment Study pregnancy cohort (TIDES).

## 2. Methods

### 2.1. Study participants

Details of The Infant Development and Environment Study recruitment and follow-up have been published elsewhere (Barrett et al., 2014) and are summarized here briefly. Women who were in their first trimester of pregnancy were enrolled into TIDES between 2010 and 2012 at four academic medical centers: University of California, San Francisco (UCSF), University of Minnesota (UMN), University of Rochester Medical Center (New York) (URMC), and University of Washington (UW). Participation was limited to mothers who were at least 18 years of age, English speaking, less than 13 weeks pregnant, had no severe

threat to pregnancy, and intended to deliver at one of the study centers. Questionnaires including demographics, medical history, and lifestyle questions were completed in each trimester in-person, by an interviewer, or online as per patient's preference.

### 2.2. Urinary bisphenol A measurements

A urine sample was collected in each trimester. Urine sample collection and analysis methods have been described previously (Barrett et al., 2014). Briefly, urine samples were collected and stored in BPA-free materials at study entry and stored at −80 C until shipment to the CDC. Due to funding constraints, phenols, including BPA, were only measured in first trimester urinary samples of women who gave birth to girls. Specific gravity (SpG) was measured within 30 min of sample collection. Total urinary BPA (free plus conjugated species) was measured using online solid phase extraction–high-performance liquid chromatography–isotope dilution mass spectrometry (Ye et al., 2005). Procedure blanks were run with each batch of samples and isotopically labeled internal standards were used along with conjugated internal standards to increase precision and accuracy of the measurements. BPA concentrations were $\log_{10}$ transformed for statistical analyses. Values below the limit of detection (LOD) of 0.7 μg/L were assigned the value LOD divided by the square root of 2, as has been recommended when the data are not highly skewed (Hornung and Reed, 1990).

### 2.3. Neurobehavioral assessments

When participating children were 4–5 years of age, their mothers completed neurobehavioral questionnaires including the Behavioral Assessment System for Children, 2nd Edition (BASC-2) and the Social Responsiveness Scale, 2nd Edition (SRS-2). The BASC-2 is a 138-item assessment that uses a Likert-scale ("never," "sometimes," "often," or "always") and provides summary index scores for Externalizing Problems, Internalizing Problems, Behavioral Symptoms, and Adaptive Skills. The Externalizing composite score consists of Hyperactivity and Aggression subscale scores; Internalizing composite score includes Anxiety, Depression, and Somatization subscale scores; Adaptive Skills includes Activities of Daily Living, Adaptability, Functional Communication, and Social Skills subscale scores; and Behavioral Symptoms Index (BSI) includes attention problems, atypicality, and withdrawal subscale scores. Scores on the BASC-2 problem scales can be divided into three clinical categories: normal (T-score <60), at risk (T-score = 60–69), and clinically significant (T-score ≥70). Thus, higher scores indicate poorer (worse) outcomes (Cecil R. Reynolds, 2004).

The SRS-2 is a 65-item assessment that uses a Likert-type scale ("not true," "sometimes true," "often true," "almost always true") to identify social impairments consistent with the autism spectrum. SRS-2 subscales include Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behaviors. A Total Social Responsiveness Score is calculated as the sum of all the subscale scores. Higher scores indicate poorer (worse) outcomes (Gruber, 2005). Scores can be divided into three clinical categories: normal (T-score <60), moderate social impairment (T-score = 60–74), and severe social impairment (T-score ≥75).

We chose a priori to focus on seven behavioral outcomes based on previous studies: three BASC-2 composite scores (Behavioral Symptoms Index (BSI), Externalizing, and Internalizing), three subscale scores (Anxiety, Depression, and Hyperactivity), and one SRS-2 score (Total score). BASC-2 and SRS-2 raw scores were converted into age and sex-standardized, norm-referenced T-scores (mean=50, SD=10) using methods described in their respective manuals (WPS Publishing Torrance, CA, USA).

### 2.4. Covariates

Covariates were chosen based on published literature and included: first trimester SpG (μg/L), gestational age at birth (weeks), maternal age (years), child age (years), income (≤$75k, >$75k), maternal race/ethnicity (non-Hispanic Black, other), education (<college, ≥college), marital status (married or living together as married, other). We also adjusted for two maternal mental health covariates measured at the age 4–5 follow-up, the Patient Health Questionnaire (PHQ-9), a measure of depression severity, (Kroenke et al., 2001) and Cohen's Perceived Stress Scale (PSS), a measure of maternal stress (Cohen et al., 1983).

### 2.5. Statistical analysis

We examined the association between first-trimester maternal prenatal BPA concentration and behavioral outcomes in girls at 4–5 years of age among all mothers with first trimester urinary BPA measurements, behavioral assessments, and complete covariates. Several sociodemographic and economic factors differed significantly between participants from URMC and the other three study centers. For these reasons, we repeated the primary analysis in two strata: mothers enrolled at URMC and mothers enrolled elsewhere (UW, UMN, UCSF). URMC is representative of a lower socioeconomic status (SES) group and the other centers combined are representative of a higher SES group. Potential for non-linear relationships between prenatal BPA and behavioral outcomes were assessed using 3-knot restricted cubic splines. These models demonstrated a linear relationship between BPA and nearly all models (BASC-2 BSI, Externalizing, Internalizing, Depression, Hyperactivity; and SRS Total Score). Thus, unadjusted and adjusted linear regression models were used to examine $\log_{10}$-transformed BPA concentrations in relation to continuous, T-score normed behavioral composite scores and subscales. We also examined effect modification by URMC by including the URMC by $\log_{10}$-transformed BPA interaction in the primary model. Effect estimates and their 95 % CI were reported for all covariates for each in model conducted. Lastly, we explored the interaction of specific maternal SES variables marital status, education, age, income, and race/ethnicity with $\log_{10}$-transformed BPA in models adjusted for the above listed covariates and study center; the interaction p-values were reported. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

## 3. Results

### 3.1. Participant characteristics

Of the 969 women who were enrolled in TIDES, 787 had a live birth and 753 provided a first trimester urine sample. Bisphenol A was measured in the urine of 368 mothers who gave birth to girls. Of these, 113 did not complete behavioral questionnaires when their daughter was 4–5 years old. Of the 255 with completed behavioral questionnaires, 11

participants were missing at least one covariate. A comparison of the participants retained in this analysis (n = 244) with those not retained (n = 124) are presented in Supplemental Table 2.

Mothers not included were younger (30.2 yrs vs 31.8 yrs, p = 0.01) and less likely to have an income greater than $75,000 per year (41 % vs 56 %, p = 0.009) (Supplemental Table 2). Across all study centers, most of the women included held a college degree or higher (78 %), had an income greater than $75,000 per year (56 %), and were married (76 %). Few participants (9 %) were Black non-Hispanic. Mean (SD) gestational age at birth was 39.3 (SD = 1.9) weeks and 21 (9 %) of children were born preterm (<37 weeks gestation). 23 children (9 %) were born with low birth weight (≤ 2.5 kg). The mean age of the child at follow-up was 4.5 years (range 4–5.8 years). A comparison of URMC (n = 61) to all other study centers combined (n = 183) shows that URMC mothers were significantly younger (mean=28.2 yrs vs 32.9 yrs p < 0.0001), delivered earlier (38.7 wks vs 39.6 wks, p = 0.01), and more likely to: be non-Hispanic Black (31 % vs. 2 %, p < 0.0001), low income (83 % vs 31 % ≤$75,000, p < 0.0001), unmarried (62 % vs 11 % non-married, p < 0.0001), score higher (i.e., more depressed) on the PHQ-9 (13.7 vs 11.6, p = 0.0001), and less likely to have a college degree (38 % vs 92 % college educated or greater, p < 0.0001). Mothers enrolled at URMC provided urine samples slightly earlier in pregnancy compared to mothers enrolled elsewhere (10.2 wks vs 10.9 wks, p = 0.01) (Table 1).

### 3.2. Urinary bisphenol A concentration

Summary statistics for first-trimester maternal urinary BPA concentrations are shown in Table 2. BPA was above the limit of detection (LOD) in 93 % of samples (n = 228). The geometric mean (GM (95 % CI)) of BPA for all centers combined was 0.75 μg/L (0.65, 0.88 μg/L). The GM BPA at URMC was significantly higher compared to the other centers combined (1.31 vs. 0.63 μg/L, p < 0.0001).

### 3.3. Neurobehavioral scores

Results from maternally completed BASC-2 and SRS-2 questionnaires at the 4–5 year old follow-up visit are summarized in Table 3. In comparisons where site-based scores were not adjusted for sociodemographic factors, mean BASC-2 Hyperactivity subscale and SRS-2 Total Score at URMC were 3- and 5-points higher than non-URMC, respectively (53 vs 50, p = 0.01; 48 vs 43, p < 0.0001). Although not statistically significant, the mean scores of URMC participants were higher for BASC-2 BSI and Externalizing, and mean scores from non-URMC were higher for BASC-2 Internalizing, Anxiety, and Depression.

### 3.4. Linear regression analyses

In unadjusted linear regression analyses on continuous $\log_{10}$ (BPA) and behavioral outcomes, BPA was not significantly associated with any BASC-2 composites and subscales, or SRS-2 total score (Supplemental Table 3). Stratified by center, BPA was non-significantly associated with higher BASC-2 subscale and composite and SRS-2 Total scores in URMC participants, and lower BASC-2 and SRS-2 total scores in non-URMC participants.

In covariate adjusted models, BPA was not associated with BASC-2 or SRS-2 scores among participants from all centers. In center-stratified models, BPA was associated with higher SRS-2 Total Scores among URMC participants (β-coefficient [95 % confidence intervals]: 4.3 [0.2, 0.5]) and with lower BASC-2 Internalizing composite (−3.3 [−6.7, 0.0]) and Depression subscale scores (−3.4 [−6.8, 0.0]) in non-URMC participants. There were no associations between BPA and BASC-2 scores in URMC participants or between BPA and SRS-2 Total Score in non-URMC participants; however, we observed a similar overall trend to the unadjusted analysis, with higher BPA associated with higher BASC-2 and SRS-2 scores in URMC participants and lower BASC-2 and SRS-2 scores in non-URMC participants. Results from our interaction models showed significantly different BPA slopes for BASC-2 BSI ($p = 0.02$) and Externalizing ($p = 0.009$) composite scores, Depression ($p = 0.02$) and Hyperactivity ($p = 0.02$) subscales, and SRS-2 Total Score ($p = 0.03$) for URMC versus non-URMC participants (Table 4).

Several covariates were significant predictors for SRS-2 scores in the URMC subjects: having less than a college degree (6.3 [1.6, 11.0]) and higher maternal depression scores (0.5 [0.2, 0.8]) were associated with higher SRS-2 scores, while being married was associated with lower scores (−4.1 [−8.1, −0.2]). No predictors were significant for BASC-2 Internalizing composite or Depression subscales in the non-URMC subjects (Supplemental Table 4). We observed significant interactions between Center and BPA for BASC-2 BSI ($p = 0.02$) and Externalizing ($p = 0.009$) composite scores, and BASC-2 Depression ($p = 0.02$) and Hyperactivity ($p = 0.02$) subscale scores, and SRS-2 Total Score ($p = 0.03$). When exploring the interactions between $\log_{10}$-transformed BPA and individual SES variables, we found a significant between education and BPA for SRS Total Score ($p = 0.04$) and income and BPA for BASC-2 Externalizing Score ($p = 0.02$), when adjusted for center and covariates (Supplemental Table 5).

## 4. Discussion

We examined the association between prenatal maternal urinary BPA concentration and behavior in 4–5 year old girls in TIDES, a multi-center pregnancy cohort. Across all centers, first-trimester urinary BPA concentration was not associated with any BASC-2 scores including Behavioral Symptoms Index (BSI), Externalizing composite (sum of hyperactivity, aggression, and conduct problem scores), Internalizing composite (sum of anxiety, depression, and somatization score), or BASC-2 Anxiety, Depression, and Hyperactivity Subscales, or SRS-2 total social impairment score. At URMC, where participants were predominately of lower-socioeconomic status (SES) with higher first-trimester BPA concentrations, prenatal BPA was associated with higher (worse) SRS-2 Total Scores while no associations were seen for any BASC-2 scores. In contrast, in participants enrolled at UW, UMN, and UCSF, predominately high-SES study centers with lower first-trimester BPA concentrations, prenatal BPA was associated with lower (better) BASC-2 Internalizing composite and Depression subscale scores, while no association was seen for SRS-2 Total Score. This is the first study to examine modification of the association between prenatal BPA exposure and child behavior by socio-demographic factors.

We observed several sociodemographic differences between URMC and non-URMC study sites. URMC mothers were more likely to be lower income, non-Hispanic Black, younger, unmarried, and less likely have a college degree. In addition, URMC mothers had over 2-times greater urinary BPA concentrations than the other centers combined (1.31 μg/L vs 0.63 μg/L), and 77 % URMC participants had BPA concentrations greater than the cohort geometric mean (0.75 ug/l) compared with 48 % of non-URMC participants. The differences in BPA concentrations could be attributed to sociodemographic, economic, cultural differences, as cited by several studies (Calafat et al., 2008; Lehmler et al., 2018; Nelson et al., 2012), reporting greater mean BPA levels among non-Hispanic Blacks, those who have some college experience or less, and low-income or low income-to-poverty ratio. It should be noted, lower income, those who are non-Hispanic Black, had some college experience or less had higher mean BPA; however, Calafat et al. and Nelson et al. report these differences among non-Hispanic Blacks and non-Hispanic Whites were not statistically significant, and found income to be a stronger factor. Additionally, BPA concentrations can also be attributed to occupational exposures; one study reported workers working with BPA-based resins or wax had approximately 70 times higher mean BPA levels than in US adults (Hines et al., 2017).

Our finding that higher prenatal BPA concentrations were associated with better (lower) BASC-2 Internalizing and Depression scores among non-URMC participants is similar to that reported from the Columbia Center for Children's Environmental Health (CCCEH), where higher 3rd trimester urinary BPA concentration was associated with lower (better) Child Behavior Checklist (CBCL) anxious/depressive scores in girls at ages 3–5 years (Perera et al., 2012). There are several differences between the cohorts that need considered when comparing the results. CCCEH participants are primarily low-income, urban Dominican and African American women, while non-URMC TIDES participants are primarily non-Hispanic White and generally higher income. Notably, timing and exposure concentration also differ between the two cohorts; CCCEH analyses utilized samples collected later in pregnancy (3rd trimester versus 1st trimester) and participants had higher BPA concentrations (GM = 1.84 μg/L) compared to TIDES (GM=0.75 μg/L). The phase out of BPA from many plastic products beginning in 2008 may partly explain the lower concentrations of BPA detected in our population (recruited 2010–2012) compared with CCCEH (recruited 1998–2003). CCCEH analyzed both girls and boys, finding significant interactions by child sex for emotional reactivity, aggressive behavior, and internalization. Perera et al. measured child behavioral symptoms with the Child Behavior Checklist (CBCL); a study found that both the CBCL and BASC-2 consistently measured some constructs, other constructs were not (Myers et al., 2010). Despite these differences, associations with depressive behavior are consistent across the cohorts.

Our findings for the BASC-2 differ from findings reported elsewhere including those of The Health Outcomes and Measures of the Environment (HOME) pregnancy cohort which observed associations between BPA and worse BASC-2 Externalizing scores among girls at ages 2 and 8 years, and worse BASC-2 Anxiety, Depression, and Hyperactivity subscale scores in girls at age 3 years (Braun et al., 2009, 2011b, 2017b). This contrasts with our findings of better BASC-2 Depression subscale scores in non-URMC girls at ages 4–5. Although non-URMC TIDES mothers and HOME mothers are demographically similar

(predominately non-Hispanic White, high income, and college educated), we measured BPA at a single time point in the 1st trimester whereas the HOME study measured BPA at multiple timepoints beginning in the 2nd trimester. The use of different exposure time points may, in part, explain the differences in observed associations across the two cohorts (Mustieles and Fernández, 2020). Similar to CCCEH, 16-week and 26-week BPA concentrations among HOME mother/daughter dyads was higher (mean 1.9 and 1.5 μg/L, respectively) than TIDES.

The Environment and Development of Children (EDC) cohort, a large pregnancy cohort in South Korea, reported associations between 2nd trimester BPA concentration ≥ 3.0 μg/g creatinine and total and social communication impairment scores in girls at age 4 using the Korean version of the Social Communication Questionnaire (K-SCQ) (Lim et al., 2017), a measure similar to the SRS-2. These results are consistent with our findings in URMC participants, where increasing prenatal BPA was significantly associated with higher (worse) SRS-2 total scores. In the Korean study sample, 18 % of mothers of boys and girls had prenatal BPA concentrations greater than 3.0 ug/g, 1.8-times greater than the cohort mean of 1.6 ug/g-creatine and similar to the URMC population within TIDES. While cohorts in South Korea and URMC may differ socio-demographically and culturally, the associations between SRS and high concentrations of prenatal BPA are consistent.

Our results differ from those studies that found no association between prenatal BPA concentration and social behavior in girls between ages 3–9 years using the SRS-2 assessments. These include the HOME study, Maternal–Infant Research on Environmental Chemicals (MIREC), and Mount Sinai Children's Environmental Health Study (MSCEH) cohorts (Braun et al., 2014, 2017a; Miodovnik et al., 2011). Differences may be due in part to differing BPA concentration, timing of exposure, and participant demographics. Both HOME and MSCEH samples were collected later in pregnancy and BPA concentrations were higher compared to TIDES. In addition, these cohorts vary by location and year of recruitment, factors that could affect both exposure and outcome. Lastly, it is possible that unmeasured covariates contributed to these differences.

Numerous studies have demonstrated endocrine disrupting activity of BPA that is both timing- and dose- dependent. BPA's estrogenic properties suggest a potential mechanism by which it may affect brain development and behavior. Circulating estrogens play a critical role in fetal neurodevelopmental processes, including neurogenesis and neuronal migration (Simerly, 2002). In rodents, effects of both BPA and estrogen on brain structure and function are well documented. Evidence from rodent studies suggests that BPA may affect anxious behaviors (Cox et al., 2010; Gioiosa et al., 2013; Kubo et al., 2001; Ryan and Vandenbergh, 2006) and that this may occur through deregulation of estrogen receptor ER-α in the hypothalamus of female, and not male, rodents (Kundakovic et al., 2013). BPA has also been shown to be anti-androgenic (Sohoni and Sumpter, 1998) and to act as a thyroid receptor antagonist (Moriyama et al., 2002). Estrogen, testosterone, and thyroid hormones are important in the development of the central nervous system, suggesting multiple possible mechanisms by which BPA may impact the brain and behavior.

Studies that examine the mechanisms by which BPA alters behavior in humans are limited. Only one study to date assessed physical brain structures as a mediator of prenatal BPA exposure and behavioral outcomes measured by the CBCL (Grohs et al., 2019). BPA exposure at 17 weeks' gestation was associated with worse CBCL Internalizing scores in both girls and boys. They also found changes in white matter microstructure in brain regions and the inferior longitudinal fasciculus, associated with anxiety and depression, suggesting that developmental myelination processes may by disrupted by BPA exposure in early pregnancy and contribute to behavioral change.

We acknowledge that study center may not be an accurate proxy for SES in this analysis. Recommendations for a composite SES include family income, parental education attainment, occupational status, neighborhood SES, and contextual psychological variables (Cowan, 2012). In this analysis, we were able to adjust for family income and maternal psychological variables like depression and perceived stress, but were unable to account for occupational status and neighborhood SES within each center. We assessed the interaction between BPA and several individual marker of SES regression. In the primary analysis, we found the interaction between study center and BPA to be significant for BASC-2 Behavioral Symptoms Index, Externalizing, and Internalizing composite scores, BASC-2 Depression and Hyperactivity subscale scores, and SRS Total Score. Interactions between individual maternal SES variables with BPA and education were significant for SRS Total Score only and BPA and income significant for BASC-2 Externalizing only. Our observed differences by study site could reflect a combination of demographic, economic, and unmeasured factors that contribute to the increased risk at URMC.

Our study has several strengths, including the prospective nature of the cohort which assured that exposure preceded outcome and eliminated recall bias in the exposure assessment. Ours is one of the few studies to analyze BPA in urine collected during the first trimester in relation to child development. The number of girls at all centers combined (n = 244) and among non-URMC centers (n = 179) is greater than several other studies to date (Braun et al., 2009: 131 girls; Braun et al., 2011b: 128 girls; Perera et al., 2012: 111 girls; Roen et al., 2015: 135 girls; Braun et al., 2017b: 148 girls; Lim et al., 2017: 144 girls); although there were few URMC participants (n = 61). Lastly, we also adjusted for maternal stress and depression in our analysis, which most other studies did not.

Limitations of this study include the fact that, because of funding limitations, we were only able to examine BPA in mothers of girls. Examining these associations in boys is an important next step, as some studies show evidence that the neurobehavioral consequences of prenatal exposure to BPA differ in boys and girls (Braun et al., 2011b, 2017a; Evans et al., 2014; Harley et al., 2013; Perera et al., 2012, 2016; Roen et al., 2015). We utilized maternally completed questionnaires to assess behavior, which may have introduced both error and bias, although concurrent maternal stress and depression and other key factors that influence reporting were adjusted, increasing confidence in the associations found. Ideally, future studies should include data from other sources (e.g., teacher report, observational measures); however, the assessments we utilized are both validated and widely used. A single spot urine sample may not be representative of BPA exposure throughout pregnancy; an analysis on BPA concentrations measured at multiple points during pregnancy found

serial BPA concentrations to be variable but correlated (Braun et al., 2011a). Selection bias may have affected our results. Overall, of the 368 participants with measured BPA concentrations, 124 girls without behavioral assessments or complete covariate information were excluded. There is notable loss-to-follow-up among (1) participants from URMC, with follow-up data from approximately 60 % (61/102) of those enrolled at URMC compared with 69 % (210/266) of those enrolled at the other centers; (2) younger participants; and (3) participants with lower income (Supplemental Table 2). This loss-to-follow-up may attenuate the true association towards the null. In the outcome BASC-2 assessment of the girls, the distribution of the gender and ethnic representation of the BASC-2 instrument has been cited to be extremely close to the U.S. population estimated between 2-to-18-year olds. This is a strength for models with the TIDES centers are combined; however, in the stratified models by center, which it has been established that URMC and non-URMC centers are socio-demographically different, the results might be influenced by these differences. Though we examined several maternal socio-demographic differences between centers, these are not likely to fully explain the differences in associations by study site. Further studies are needed to identify risk factors that interact with BPA to heighten vulnerability. Lastly, future studies should take into consideration other factors such as stressors, nutrition, access to health care, social support, and other social determinants, to further understand the potential long-lasting effects of BPA on girls' mental and behavioral health.

## 5. Conclusion

In conclusion, we observed associations between first trimester BPA concentration and BASC-2 and SRS-2 scores in girls ages 4–5 that varied by study center. In girls from URMC, a predominately lower SES study center with high prenatal BPA levels, BPA was associated with poorer SRS-2 Total Scores. Among girls at study centers with higher SES and lower prenatal BPA, BPA was associated with better BASC-2 Depression Scores. These findings add to the growing literature on endocrine disrupting chemicals neurodevelopment and suggest that a combination of demographic and economic factors may modify the relationship between BPA exposure and behavioral outcomes in childhood.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Table 1

Summary statistics of mother-daughter pairs at all centers, University of Rochester Medical Center (URMC), and non-URMC centers in The Infant Development and Environment Study.

| | **All Centers** **N = 244** | **URMC** **N = 61** | **Non-URMC** **N = 183** | ***p-value*** [a] |
|---|---|---|---|---|
| Gestational Age of Urine Collection (weeks); *mean (SD)* | 10.7 (2.0) | 10.2 (1.9) | 10.9 (2.0) | **0.01** |
| Gestational Age at Birth (weeks); *mean (SD)* | 39.3 (1.9) | 38.7 (2.5) | 39.6 (1.6) | **0.01** |
| Birthweight (kg); *mean (SD)* | 3.3 (0.6) | 3.1 (0.6) | 3.3 (0.6) | 0.08 |
| Child Age (years); *mean (SD)* | 4.5 (0.3) | 4.6 (0.2) | 4.5 (0.4) | 0.76 |
| Maternal Age (years); *mean (SD)* | 31.8 (5.4) | 28.2 (6.6) | 32.9 (4.3) | **<0.0001** |
| Perceived Stress Score (CPS); *mean (SD)* | 20.3 (4.0) | 19.6 (5.5) | 20.6 (3.4) | 0.10 |
| Depression Severity Score (PHQ-9); *mean (SD)* | 12.1 (3.8) | 13.7 (5.6) | 11.6 (2.8) | **0.0001** |
| Black, Non-Hispanic; *n(%)* | 22 (9) | 19 (31) | 3 (2) | **<0.0001** |
| High Income (>$75,000); *n(%)* | 136 (56) | 10 (16) | 126 (69) | **<0.0001** |
| ≥ College Graduate; *n(%)* | 191 (78) | 23 (38) | 168 (92) | **<0.0001** |
| Married or Living as Married; *n(%)* | 197 (81) | 27 (44) | 170 (93) | **<0.0001** |

[a] p-values for URMC vs. non-URMC study centers derived by two-sided independent t-tests for continuous variables and Pearson's chi square tests for categorical variables.

## Table 2

Summary statistics for unadjusted first trimester maternal urinary BPA concentrations for TIDES participants at all centers, University of Rochester Medical Center (URMC), and non-URMC study centers.

| | Geometric mean (95 % CI) | *Percentiles* | | | Min | Max | *p-value* [a] |
|---|---|---|---|---|---|---|---|
| | | 25th | 50th | 75th | | | |
| **BPA (ug/L)** | | | | | | | |
| All Centers (N = 244) | 0.75 (0.65, 0.88) | 0.3 | 0.8 | 1.8 | <LOD | 21.4 | |
| URMC (N = 61) | 1.31 (0.99, 1.74) | 0.9 | 1.4 | 2.4 | <LOD | 15.4 | |
| Non-URMC (N = 183) | 0.63 (0.53, 0.75) | 0.3 | 0.6 | 1.6 | <LOD | 21.4 | **<0.0001** |

[a] p-values for URMC vs. non-URMC study centers derived by two-sided independent t-test.

## Table 3

Distribution of BASC-2 Composite and Subscales and SRS-2 Total Score for TIDES participants at all centers, University of Rochester Medical Center (URMC), and non-URMC study centers.

| | Mean (SD) | 25th PCT | 50th PCT | 75th PCT | p-value |
|---|---|---|---|---|---|
| **BASC-2** | | | | | |
| **Behavioral Symptoms Index** | | | | | |
| All Centers | 50 (9) | 44 | 49 | 54 | |
| URMC | 51 (12) | 43 | 49 | 57 | |
| Non-URMC | 49 (8) | 44 | 48 | 54 | 0.09 |
| **Externalizing** | | | | | |
| All Centers | 50 (9) | 44 | 48 | 53 | |
| URMC | 52 (13) | 43 | 48 | 57 | |
| Non-URMC | 49 (7) | 44 | 48 | 53 | 0.13 |
| **Internalizing** | | | | | |
| All Centers | 50 (9) | 43 | 50 | 56 | |
| URMC | 49 (9) | 41 | 47 | 56 | |
| Non-URMC | 50 (9) | 44 | 50 | 56 | 0.36 |
| **Anxiety** | | | | | |
| All Centers | 52 (10) | 44 | 52 | 58 | |
| URMC | 50 (10) | 42 | 49 | 58 | |
| Non-URMC | 52 (10) | 44 | 52 | 60 | 0.15 |
| **Depression** | | | | | |
| All Centers | 51 (10) | 43 | 51 | 56 | |
| URMC | 50 (11) | 43 | 48 | 56 | |
| Non-URMC | 51 (9) | 43 | 51 | 56 | 0.82 |
| **Hyperactivity** | | | | | |
| All Centers | 51 (9) | 46 | 50 | 56 | |
| URMC | 53 (14) | 43 | 50 | 59 | |
| Non-URMC | 50 (7) | 46 | 50 | 54 | **0.01** |
| **SRS-2** | | | | | |
| **Total Score** | | | | | |
| All Centers | 44 (7) | 40 | 44 | 47 | |
| URMC | 48 (7) | 43 | 47 | 51 | |
| Non-URMC | 43 (6) | 39 | 42 | 45 | **<0.0001** |

[a] p-values for URMC vs. non-URMC study centers derived by two-sided independent t-test.

**Table 4**

Adjusted linear regression coefficients for continuous ($log_{10}$-transformed) first-trimester BPA and BASC-2/ SRS-2 scores in girls age 4 – 5 years at all centers, University of Rochester Medical Center (URMC), and non-URMC study centers.

| | **All Centers** $\beta$ ***(95 % CI)*** [a] ***N = 244*** | **URMC Only** $\beta$ ***(95 % CI)*** [b] ***N = 61*** | **Non-URMC** $\beta$ ***(95 % CI)*** [b] ***N = 183*** | ***Center × BPA Interaction*** [a] |
|---|---|---|---|---|
| **BASC-2** | | | | |
| Behavioral symptoms index | −0.7 (−3.5, 2.0) | 6.4 (−1.2, 13.9) | −2.2 (−5.1, 0.6) | **0.02** |
| Externalizing | −1.0 (−3.7, 1.8) | 6.4 (−2.0, 14.7) | −2.5 (−5.2, 0.1) | **0.009** |
| Internalizing | −1.8 (−4.7, 1.0) | 2.9 (−3.4, 9.3) | **−3.3 (−6.7, 0.0)** | 0.19 |
| Anxiety | −0.7 (−3.9, 2.4) | 2.2 (−4.8, 9.2) | −2.1 (−5.8, 1.6) | 0.62 |
| Depression | −1.6 (−4.5, 1.4) | 4.8 (−1.6, 11.3) | **−3.4 (−6.8, 0.0)** | **0.02** |
| Hyperactivity | −1.0 (−3.8, 1.8) | 4.5 (−4.5, 13.5) | −2.0 (−4.7, 0.6) | **0.02** |
| **SRS-2** | | | | |
| Total Score | −0.7 (−2.7, 1.2) | **4.3 (0.2, 8.5)** | −1.7 (−4.0, 0.5) | **0.03** |

[a] Adjusted for URMC site, mean specific gravity, gestational age at birth, marital status, education, maternal age, child age, income, maternal perceived stress score, maternal depression score, and race/ethnicity

[b] Adjusted for mean specific gravity, gestational age at birth, marital status, education, maternal age, child age, income, maternal perceived stress score, maternal depression score, and race/ethnicity