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Postnatal BPA is associated with increasing executive function difficulties in preschool children

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Abstract

Background—Early bisphenol exposure may have consequences for executive function development, but less is known about potential sex effects. We hypothesized that early bisphenol A (BPA) and bisphenol S (BPS) exposures would be associated with sex-dependent changes in preschool executive function.

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Category of Study: Population study (cohort study).

Supplemental Material (online)

See supplemental materials for Table S1 and Figures S1–3.

Methods—A subsample of the Alberta Pregnancy Outcomes and Nutrition (APrON) cohort (n = 312) provided maternal second trimester (prenatal) and 3-months postpartum (postnatal) urine samples, from which BPA and BPS concentrations were quantified. When children were age 2 and 4, mothers completed the Behavior Rating Inventory of Executive Function- Preschool Version (BRIEF-P). Changes in standardized *T* scores on the BRIEF-P indexes of inhibitory self-control, flexibility, and emergent metacognition were investigated.

Results—Adjusted multivariate regression analyses showed that child sex modified the associations between maternal postnatal BPA and changes in executive function. Higher maternal postnatal BPA concentrations predicted increasing difficulties from age 2 to 4 in the domains of inhibitory self-control and emergent metacognition in female, but not male children. The other bisphenol concentrations were not associated with changes in executive function.

Conclusion—Due to the ubiquity of BPA exposure among breastfeeding women, these findings justify further investigation on effects of postnatal bisphenol exposure on child cognitive development.

INTRODUCTION

Bisphenol A (BPA) is an endocrine-disrupting chemical (EDC) found in a variety of consumer goods, including food and beverage containers, the lining of canned goods, thermal paper receipts, and children's toys (1). Exposure to BPA is ubiquitous, as over 90% of North American children and adults have detectable levels of urinary BPA (2). Early exposure to EDCs, including BPA, has been associated with cognitive dysfunction, including difficulties in executive function (i.e., inhibition, emotional control, working memory, and planning/organizing) during childhood (3, 4). The effect of ECDs on steroid levels and intracellular receptors could alter cognitive development in sexually dimorphic ways, leading to sex-specific deficits in executive functions (5). During fetal development and infancy, children may be especially vulnerable to endocrine disruption, and increased exposure to EDCs during these time periods may have negative consequences for executive function development, with differing effects on male and female children (6).

Sociodemographic factors (e.g., ethnicity, socioeconomic status) and gestational characteristics (e.g., maternal smoking) are known to impact executive function development in children (7, 8). However, the literature examining the effects of maternal bisphenol concentrations during pregnancy on child executive function development is limited and somewhat mixed. A cohort study including 244 families reported that higher maternal prenatal BPA was associated with greater difficulties in emotional control and inhibition in 3-year old children, with larger effect sizes reported for female children than male children (3). In contrast, another cohort study including 812 families reported that greater maternal prenatal BPA was associated with poorer working memory and planning/organizing skills in male preschool children, with null or significantly inverse associations among female preschool children (4). This previous work is limited by the lack of examination of maternal postnatal BPA. Further, structural analogs of BPA, such as bisphenol S (BPS), are known to demonstrate similar hormonal potency in estradiol-mediated pathways (9), but we are not aware of any prior work that has examined the effect of BPS on executive function development in children. In order to address these knowledge gaps, this study examined the

influence of maternal prenatal and postnatal concentrations of BPA and BPS on changes in the executive functioning of preschool children from ages 2 to 4 years. First, we hypothesized that higher maternal bisphenol concentrations would be associated with changes in executive function in preschool children. Second, based on the sex-differences reported in previous research (3,4), we hypothesized that maternal bisphenol concentrations would have differing effects on changes in executive functioning in female and male children.

METHODS

Design and Participants

Participants were recruited from an ongoing prospective pregnancy cohort, the Alberta Pregnancy Outcomes and Nutrition (APrON) study (N = 2169) (10). A sub-sample of APrON participants (n = 312) were recruited during pregnancy from 2009 to 2012 and completed the protocol in Calgary, Canada. APrON families were included if: i) a prenatal urine sample in the second trimester of pregnancy and a postnatal urine sample at 3-months postpartum was provided by the mother, ii) the mother was breastfeeding during the postpartum period, and iii) the mother completed the Behavior Rating Inventory of Executive Function- Preschool Version (BRIEF-P) (11) when their child was 2 and 4 years of age. Maternal urine was quantitatively analyzed for BPA and BPS. During sample collection, mothers completed background questionnaires on sociodemographic factors, gestational and birth-related characteristics, and infant feeding habits. When children (49.2% female) were approximately 2 years (M = 2.53, SD = 0.13) and 4 years of age (M = 4.26, SD = 0.50), mothers completed the BRIEF-P, a parent-report inventory on difficulties with executive function in children. At 2 and 4 years of age, when the BRIEF-P was completed, all children were healthy and typically developing (i.e., had not been diagnosed with a neurological or neurodevelopmental disorder, FSIQ ≥ 80). Maternal urinary samples and questionnaire data were collected from January 2009 to December 2016. The research protocol was approved by the Conjoint Health Research Ethics Board at the University of Calgary. Written, informed consent was provided by all participants prior to the collection of samples and completion of questionnaires.

Measures

Demographics and Covariates—Questionnaires collected information on sociodemographic variables (i.e., ethnicity, education, marital status, household income), gestational characteristics (i.e., age, body weight/height, alcohol and tobacco use, physical/mental illnesses), and infant feeding habits (i.e., breastfeeding status, breastfeeding frequency, formula use frequency). Information on birth outcomes were obtained from medical records (i.e., birth weight, gestational age, sex).

Urine Sample Collection—Maternal spot urine samples were collected during the second trimester (mean gestational weeks = 17.0 ± 2.1) and at 3-months postpartum (mean months = 2.7 ± 0.6). Sterile cups were used to collect urine samples, which were then immediately aliquoted into 9mL cryovials and stored at −80 °C. Quality control experiments examined potential contamination during collection, storage, and/or analysis by using liquid

chromatography grade water as a surrogate for urine (n = 20 control samples). No free BPA or BPS were detectable in any of the control samples.

Quantification of Bisphenols—The trace analytical methods for quantifying total (conjugated and free) bisphenol concentrations in the APrON study cohort have been previously reported (12). In brief, deconjugation of metabolites was completed through a reaction using a mixture of β-glucuronidase and sulfatase. Total bisphenol concentrations were quantified using online solid-phrase extraction coupled to high performance liquid chromatography and an Orbitrap Elite hybrid mass spectrometer (Thermo Fisher Scientific, Waltham, MA) (13). As low levels of BPA were detectable in blank samples, the limit of detection (LOD) of BPA was the average of the blank signal plus three times the standard deviation (0.32 ng/mL); whereas, for BPS the LOD was defined by a signal-to-noise ratio of three (0.10 ng/mL). Based on the recommended practices from previous research (3, 14), non-detectable concentrations of BPA (6.7% of prenatal and 10.9% of postnatal samples) and BPS (39.0% of prenatal and 35.8% of postnatal samples) were assigned values of LOD/√2. Aliquots of the same urine samples (1mL) were analyzed for creatinine. Total bisphenol concentrations were creatinine-adjusted prior to analyses.

Changes in Executive Functioning—Executive functioning was assessed using the Behavior Rating Inventory of Executive Function- Preschool Version (BRIEF-P) (PAR, Inc., Lutz, FL) (11). The BRIEF-P is a standardized 63-item parent-report inventory that is a valid and reliable tool for assessing problems with executive function behaviors in children aged 2.0 to 5.11 (15). Parents respond whether their child displays specific behavior problems (*never* = 1, *sometime*s = 2, *often* = 3), and higher scores indicate greater executive function difficulties. The BRIEF-P subscales combine into three broader indexes: inhibitory self-control (composed of the inhibit and emotional control subscales), flexibility (composed of the shift and emotional control subscales), and emergent metacognition (composed of the working memory and plan/organize subscales). Based on evidence from a previous confirmatory factor analysis (CFA) of the BRIEF-P indexes in preschool children (16), we constructed second-order (i.e., latent variables with indicators that were also latent variables) latent change score (LCS) models of the three indexes using the *T* scores from ages 2 and 4. For example, the LCS model of inhibitory self-control was constructed by considering the inhibit and emotional control subscale *T* scores from age 2 as one latent indicator (i.e., state 1) and the inhibit and emotional control subscale *T* scores from age 4 as the second latent indicator (i.e., state 2). Thus, these LCS models retained the original factor structure of the BRIEF-P indexes as established by the assessment manual, which have been widely used in neuropsychological research (11, 16). The LCS represents the rate of change (i.e., increasing, stable, decreasing) in a latent construct (17), and LCS models were used to determine whether children exhibited significant individual differences in changes on the BRIEF-P indexes over time.

Statistical Analysis

The bisphenol concentration distributions were skewed, so concentrations were log-transformed for multivariate analysis. Little's Missing Completely at Random (MCAR) test, x^2 (126) = 142.92, $p > 0.05$, indicated that missing data did not significantly deviate from an

MCAR pattern. Following the recommended procedure, 10 data files were imputed using expectation maximization methods in Mplus 7 (Muthén & Muthén, Los Angelos, CA), and then pooled estimates were used for the analyses (18, 19).

Based on the primary hypothesized associations between maternal bisphenol concentrations and changes in executive functioning in preschool children, which were determined *a priori*, the main analyses were performed in two stages. In the first stage, based on the established factor structure of the BRIEF-P indexes in preschool children (16), CFA was used to assess the fit of measurement models of latent changes in the three BRIEF-P indexes (inhibitory self-control, flexibility, emergent metacognition). In the second stage, LCS structural equation models (LCS-SEM) (20) were constructed in order to examine the hypothesized links between bisphenol concentrations and latent changes in executive function. As previous research indicates that maternal bisphenol concentrations during pregnancy are associated with sex-specific effects on executive functioning, for example that larger effect sizes are reported for female children (3,4), our secondary hypothesis was that the associations between maternal bisphenol concentrations and latent changes in executive function would be modified by child sex. In these LCS-SEM models, moderation analyses examined if the interaction between child sex (i.e., a binary variable) and continuous bisphenol concentrations predicted latent changes in executive function in preschool children. These models included potential covariates (e.g., sociodemographic variables, gestational characteristics, birth-related outcomes) previously found to be associated with bisphenol exposure and neurobehavioral development (4, 14, 21).

Based on Monte Carlo data simulation techniques, the current sample size of 312 allowed for the LSC-SEM models to produce unbiased estimates at a significance level of 0.05 and a power level of 0.89 (22). Models were run using an integration algorithm and maximum-likelihood estimation (MLR estimator) in order to effectively integrate a variety of variable types (e.g., continuous, binary), account for any non-normally distributed data, and produce robust standard errors (18). As the primary hypothesized associations were exampled in multiple models, the Benjamini-Hochberg procedure was used to correct for multiple comparisons and to control the false discovery rate (FDR) at $p < 0.05$ (23). This procedure decreases the likelihood of reporting false positives by controlling for the fact that sometimes significant *p*-values occur by chance (i.e., that 5% of significant tests will result in false positives). Following the Benjamini-Hochberg procedure, individual *p*-values are ranked in ascending order and each individual *p*-value's critical value (i.e., *q*-value or adjusted *p*-value; q = (rank/total number of tests)*FDR) is calculated. Individual *p*-values that are less than their critical value are significant (23). Herein, only results that withstood the FDR correction for multiple comparisons are reported.

RESULTS

Descriptives and Correlations

A previous study by our group reported no significant differences in characteristics (e.g., parity, maternal age, sociodemographic variables, etc.) between the participants in the overall APrON cohort and those who provided urine samples, which were quantitatively analyzed for BPA and BPS (12). At prenatal sample collection, women were age 20–42

years (M = 32.21, SD = 3.74 years), predominantly Caucasian (89.1%), in spousal relationships (97.5%), and had completed some post-secondary education (95.2%). The median household income was over $100,000 CND. At the 3-month postnatal sample collection, 92.9% of women were breastfeeding (7.1% had been breastfeeding but recently stopped) and 85.9% of women used formula less than once per day (3.2% used formula once a day, 1.6% used formula twice a day, and 9.6% used formula 3+ times a day). Children were born at an average of 39.3 weeks of gestation (SD = 1.6 weeks) and had an average birth weight of 3389.1 grams (SD = 500.8 grams). At 4 years of age, children's average full-scale intelligence quotient (FSIQ) on the Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition: Canadian was 106.2 (SD =12.4, range = 80 – 142). For further sample characteristics see Table S1 in the Supplemental Material (online).

Descriptives for quantified bisphenol concentrations are reported in Table 1. Less than 1% (n = 3) of prenatal and 3.5% (n = 11) of postnatal samples were missing. Total BPA was detectable in 93.3% of prenatal urine with a geometric mean (GM) of 1.22 ng/mL, and detectable in 89.1% of postnatal urine with a GM of 0.93 ng/mL. Total BPS was detectable in 61.0% of prenatal urine with a GM of 0.16 ng/mL, and in 64.2% of postnatal urine with a GM of 0.18 ng/mL. The concentrations and detection rate of BPA was comparable to biomonitoring data from Health Canada, which reported a detection frequency of 92% and a GM of 1.1 ng/mL (24). There is currently no available Health Canada biomonitoring data on BPS. However, the current results are similar to a multi-national study, which reported that BPS was detectable in 81% of adult urinary samples with GMs ranging from 0.16 to 1.18 ng/mL (25).

No significant bivariate correlations were found between the creatinine-adjusted bisphenol concentrations and children's T scores on the BRIEF-P at age 2 or age 4 (not shown). The creatinine-adjusted prenatal and postnatal bisphenol concentrations were positively correlated with each other (*Spearman's rho* ranged from 0.13–0.24, $p < 0.05$).

Latent Change Score Models (LCSM)

Latent change score models (LCSM) can be included in structural equation models (SEM) by the reparameterization of latent state models, such that change in a single latent construct is modeled by two indicators on two measurement occasions (26). Thus, in the first stage of the analyses, this approach was used to model latent change in executive function as measured by two indicators (i.e., two BRIEF-P subscale scores) on two measurement occasions (i.e., age 2/state1 and 4/state 2). Using T scores from the BRIEF-P subscales, separate LCSM were constructed for inhibitory self-control (i.e., inhibit and emotional control subscale scores from age 2 and 4), flexibility (i.e., shift and emotional control subscale scores from age 2 and 4), and emergent metacognition (i.e., working memory and plan/organize subscale scores from age 2 and 4). Based on the recommended indices (27, 28), the LCSM of inhibitory self-control (x^2 = 1.28, df = 2, p > 0.05, RMSEA = 0.01, CFI = 1.00, TLI = 1.00), flexibility (x^2 = 3.24, df = 2, p > 0.05, RMSEA = 0.04, CFI = 0.99, TLI = 0.99), and emergent metacognition (x^2 = 3.07, df = 2, p > 0.05, RMSEA = 0.04, CFI = 0.99, TLI = 0.99) all showed good model fit (see Figures S1–3 in the Supplemental Materials (online)).

Moderation Analyses—For the second stage of the main analyses, multivariate regression analyses examined the influence of covariates and bisphenol concentrations on LCSM of executive function. In order to test our secondary hypothesis, child sex was examined as a potential modifier of these associations. Following a directed multiple regression approach (29), covariates and independent variables were entered in a stepwise fashion. First, the influence of the covariates (i.e., sociodemographic factors, gestational characteristics, birth-related outcomes, breastfeeding habits) was assessed for each model. Non-significant covariates were dropped from subsequent analyses. Second, bisphenol concentrations were added to the models. Finally, to test for moderation, a product interaction term between bisphenol exposure and child sex was added. Overall, as there were three LCSM (i.e., inhibitory self-control, flexibility, emergent metacognition), and moderation analyses examined the interaction between child sex and each of the bisphenol exposures (i.e., prenatal/postnatal BPA, prenatal/postnatal BPS), a total of 12 separate models were run.

In the initial steps of the inhibitory self-control models, none of the potential covariates nor any of the bisphenol concentrations were significant predictors. The moderation model including all of the bisphenol concentrations and the interaction between postnatal BPA and child sex revealed that postnatal BPA ($\beta = 0.21$, $t = 2.04$, $p = 0.03$) and the interaction term ($\beta = -0.19$, $t = -1.89$, $p = 0.04$) emerged as significant predictors of change in inhibitory control. However, no other bisphenol exposures (i.e., prenatal BPA, prenatal/postnatal BPS), nor any associated interactions were related to change in inhibitory self-control. In the most parsimonious model, postnatal BPA ($\beta = 0.21$, $t = 2.10$, $p = 0.02$) and the child sex interaction term $\beta = -0.19$, $t = -1.92$, $p = 0.04$) remained significant predictors of change in inhibitory self-control (Figure 1).

In the initial steps of the flexibility models, child sex ($\beta = 0.27$, $t = 3.47$, $p < 0.01$) and parity status ($\beta = -0.20$, $t = -2.54$, $p = 0.01$) emerged as significant predictors. However, the models including the bisphenol concentrations and the interaction terms did not reveal any significant associations.

In the initial steps of the emergent metacognition models, none of the potential covariates nor any of the bisphenol concentrations were significant predictors. The moderation model including all of the bisphenol concentrations and the interaction between postnatal BPA and child sex revealed that postnatal BPA ($\beta = 0.19$, $t = 2.00$, $p = 0.03$), and the interaction term ($\beta = -0.23$, $t = -2.38$, $p = 0.01$) emerged as significant predictors of change in emergent metacognition. In the most parsimonious model, postnatal BPA ($\beta = 0.18$, $t = 1.89$, $p = 0.04$), and the child sex interaction term ($\beta = -0.22$, $t = -2.30$, $p = 0.01$) remained significant predictors of change in emergent metacognition (Figure 2).

Interaction Effects—Interaction graphs were produced using LOOP plots and interaction effects were interpreted using simple slopes analyses (30). Simple slopes analyses examined the associations between postnatal BPA and change in executive function by child sex. For female children, higher maternal postnatal BPA was significantly related to greater changes in inhibitory self-control (b = 3.96, t = 2.01, $p = 0.04$) and emergent metacognition (b = 3.94, t = 1.91, $p = 0.04$). However, for male children, maternal postnatal BPA was unrelated

to changes in inhibitory self-control (b = −0.91, t = −0.51, $p > 0.05$) and emergent metacognition (b = −2.64, t = −1.98, $p > 0.05$). Using the unstandardized regression coefficients to interpret these relations, revealed that for female children, each 1-unit increase in maternal postnatal BPA concentration was related to a latent change score increase of 3.96 in difficulties in inhibitory self-control (i.e., children's difficulties in inhibitory self-control, as measured by *T* scores from the inhibition and emotional control subscales, increased by 3.96 from age 2 to 4) and a latent change score increase of 3.94 in difficulties in emergent metacognition (i.e., children's difficulties in emergent metacognition, as measured by *T* scores form the working memory and plan/organize subscales, increased by 3.94 from age 2 to 4).

The nature of the interaction effect was similar for changes in inhibitory self-control (Figure 3A) and emergent metacognition (Figure 3B). Specifically, greater maternal postnatal BPA concentrations predicted increasing difficulties from age 2 to 4 (i.e., increasing LCS) in inhibitory self-control ($\beta = 0.13$, $p = 0.04$) and emergent metacognition ($\beta = 0.16$, $p = 0.02$) in female children. Using the standardized regression coefficient as a measure of effect size (31), this can be interpreted as a small-to-moderate effect (i.e., $\beta > 0.02$) of maternal postnatal BPA on latent changes in inhibitory self-control in female children and a moderate effect (i.e., $\beta > 0.15$) of maternal postnatal BPA on latent changes in emergent metacognition in female children.

DISCUSSION

This study found that maternal postnatal BPA was associated with changes in executive function in female preschool children. In particular, higher postnatal BPA concentrations were associated with increasing difficulties in inhibitory self-control and emergent metacognition from age 2 to 4 years in female children. No significant associations were noted for male children. Overall, these results can be interpreted as a small-to-moderate effect of maternal postnatal BPA on changes in inhibitory control in female children and a moderate effect of maternal postnatal BPA on changes in emergent metacognition in female children. In contrast, maternal postnatal BPA was not associated with changes in flexibility in female or male children, and the other bisphenol concentrations (i.e., prenatal BPA, prenatal/postnatal BPS) were not significant predictors of changes in any of the BRIEF-P executive function indexes in female or male children. The current findings are consistent with other research that has suggested that early exposure to BPA is associated with harmful effects on cognitive development in preschool children (3, 4).

To our knowledge, this is one of the first studies to consider the influence of maternal postnatal BPA on child executive function development. During pregnancy, maternal BPA poses a risk to fetal development as it is capable of transferring across the placenta (32). After parturition, BPA is also detectable in maternal serum, urine, and breast milk samples (33). However, the processes underlying maternal transmission and infant metabolism of BPA via breastmilk have not yet been elucidated (34, 35). The current results suggest that maternal postnatal BPA levels could be a unique predictor of changes in executive function development in preschool children. Given the relative homogeneity in the current sample in terms of infant feeding habits, and the lack of information regarding other routes of

bisphenol exposure, it was not possible to disentangle potential mechanisms underlying these associations. To address this, future research needs to examine the effect of maternal postnatal BPA on other domains of child neurodevelopment, as well as the transfer and interrelations of mother-infant bisphenol concentrations during the postpartum period.

BPA affects the neuroendocrine pathways that are involved in the sexual differentiation of the brain, and this may influence neurocognitive development in a sex-specific manner (36). The prefrontal cortex is particularly vulnerable to environmental exposures during infancy, and postnatal exposure to neurotoxicants may result in executive function deficits in the preschool period by hindering prefrontal synaptogenesis (37). Previous neurodevelopmental studies have uncovered sex-dependent effects of prenatal BPA on preschool executive function; however, these findings are mixed (3,4). The current study considered early exposure to both BPA and BPS and found that only maternal postnatal BPA emerged as a significant predictor of changes in executive function in female children. This suggests that postnatal exposure to BPA may have sex-dependent influences on the maturation of the prefrontal cortex and the subsequent development of executive function. BPA is an estrogen receptor agonist, and the theory of sexual differentiation postulates that exposure to estrogen agonists, such as BPA, during early development may have a larger effect on the brains, epigenomes (e.g., alterations in DNA methylation), and behaviors (e.g., learning, anxiety) of females (38). It is possible that postnatal exposure to BPA changes the structural development of the brain (e.g., sexual dimorphism in the hypothalamus), disrupts the regulation of estrogen at several levels, and alters DNA methylation in primarily hormone-sensitive cells; which may serve as biological mechanisms underlying the associations between early exposure to BPA and adverse outcomes in females (36, 38). Further, a recent study in nonhuman female primates showed that estrogen dysregulation associated with BPA exposure adversely affected the hippocampus and prefrontal cortex (39), areas important for executive functions such as inhibitory self-control and metacognition (40). In order to better understand the biological pathways that may explain the present associations between maternal BPA and difficulties in inhibitory self-control and emergent metacognition in female preschool children, further examination of how exposure to bisphenols and other EDCs impact sexually dimorphic brain structure, estrogen regulation, DNA methylation, and neurocognitive development is warranted.

Strengths and Limitations

This study utilized sophisticated LCS-SEM analyses to delineate the associations between multiple maternal bisphenol concentrations (i.e., BPA and BPS) during pregnancy and the postpartum period and changes in executive function in preschool children. Due to study constraints, bisphenol concentrations were assessed via a single prenatal and postnatal urine sample. This may be a less stringent approach, compared to other environmental health studies, which collected urine at two or more points and used an average concentration for analyses (3, 14). Relatedly, research commonly examines quantiles of bisphenol concentrations in relation to child development outcomes (4, 21). However, our use of continuous bisphenol concentrations is in line with the recommendations of epidemiologists that exposure variables (e.g., bisphenol concentrations) should be kept continuous for analyses, as categorization of exposure variables into quantiles results in problematic

multiple hypothesis testing with pairwise comparisons, assumes homogeneity of risk within groups, which leads to inaccurate estimation, and creates difficulty when comparing results across studies (41).

This study was also limited by the examination of maternal urine samples as a proxy for fetal and infant exposure to bisphenols. Although the common practice for assessing fetal exposure to bisphenols is through measuring the concentrations present in maternal urine samples (3,4), measurements of bisphenol levels in maternal breast milk or infant urine samples would have provided more direct assessments of infant exposure to bisphenols. However, research has yet to determine how maternal bisphenol levels effect fetal levels via placental transfer and infant levels via breastfeeding (34, 35). Further, due to the high concentration of the enzyme responsible for metabolizing BPA (i.e., beta-glucuronidase) in the placenta, research suggests the ratio of free to conjugated BPA is higher in the fetus than the mother (42). Levels of BPA may also be higher in infants than in mothers, as animal research suggests that that the rate of BPA metabolism in adults is higher than newborns (43), and that beta-glucuronidase is not produced until after birth (44). Given these challenges, there are currently no recommended practices for directly assessing fetal or infant bisphenol levels (34, 35). Thus, future research that delineates maternal-fetal transfer of bisphenols through placenta and maternal-infant transfer of bisphenols through breastmilk, and develops processes to assess the rate that BPA is metabolized in the fetus and infants is needed in order to better understand the present associations.

Although this project considered both BPA and BPS, other analogs of BPA (i.e., bisphenol F/BPF), are also reported to have endocrine-disrupting effects (9). Due to the low detection rate of BPF (< 10%) in the APrON cohort (12), its influence could not be examined. Further, it possible that other environmental factors, such as maternal nutrition, may impact the present associations (45). However, few deficiencies in maternal nutrition were noted among women in the APrON cohort (46), and >90% of the women were taking a multivitamin/nutritional supplement (47). Investigations of the associations and potential interactions between maternal nutrient intake and status, maternal prenatal supplementation, and bisphenol exposures are important areas of research for future studies (48). Finally, executive function development was assessed via parent-report, which is thought to evaluate more global domains of executive function, compared to performance tasks, which are limited to specific aspects of executive function (49). Future research should consider the influence of both pre- and postnatal exposure to multiple bisphenols (i.e., BPA, BPS, BPF) on changes in both specific and comprehensive measures of neurodevelopment in early childhood.

Conclusion

Higher maternal postnatal BPA concentrations were associated with increasing difficulties in inhibitory self-control and emergent metacognition in female children from age 2 to 4 years. These sex-specific deficits are notable, as although no previous research has documented sex-differences in emergent metacognition development, prior research has indicated that female preschool children typically demonstrate greater inhibitory control than their male peers (50). The current study extends previous research on maternal prenatal BPA and child

executive function, to show that maternal postnatal BPA can also impact child executive function development. Cumulatively, this suggests that cohort studies considering bisphenol exposures during a range of early developmental stages are needed to buttress the existing evidence and further delineate possible sexually dimorphic effects. Although Canada was the first country to declare BPA a health hazard and ban its use in baby bottles, additional regulations that apply to the general population have yet to be introduced (51). The present results suggest that additional precautions to protect mothers from BPA during the postnatal period may help to reduce the indirect exposure of infants to BPA, such as indirect exposure though maternal sources (e.g., breastmilk), and could help support healthy cognitive development in children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Impact

- Higher concentrations of maternal BPA at 3-months postpartum were associated with increasing difficulties in inhibitory self-control and emergent metacognition from age 2 to 4 in girls, but not boys.
- Prenatal BPA and prenatal/postnatal BPS were not significant predictors of change in executive function in boys and girls.
- The current study extends previous research to show that maternal postnatal BPA could also impact child executive function.
- Due to the ubiquity of BPA exposure among breastfeeding women, the current findings suggest that additional precautions may be needed to protect infants' neurodevelopment from indirect exposure to BPA.

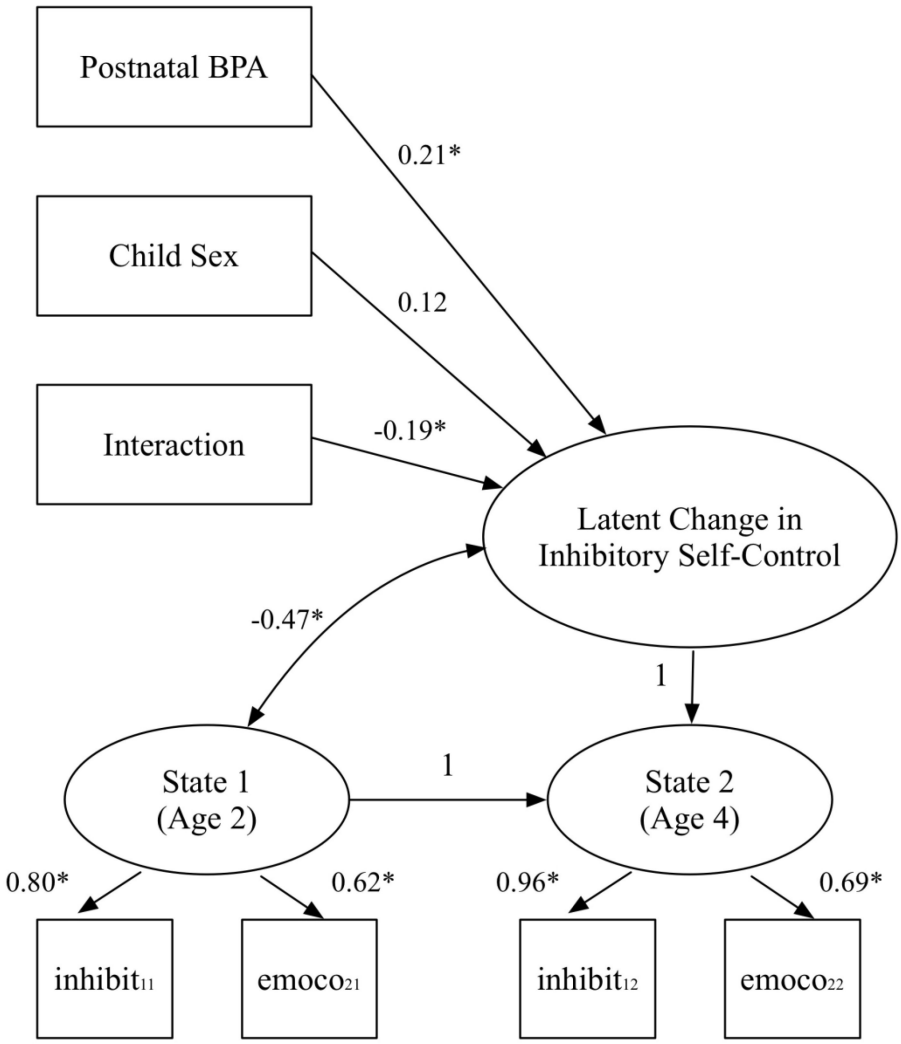

Figure 1.

Structural model and results for the final regression model in which postnatal BPA exposure and child sex were examined in relation to latent changes in preschool children's inhibitory self-control.

Note. The ovals represent latent variables and the rectangles represent observed variables. Standardized beta coefficients are reported; $*p \leq 0.05$

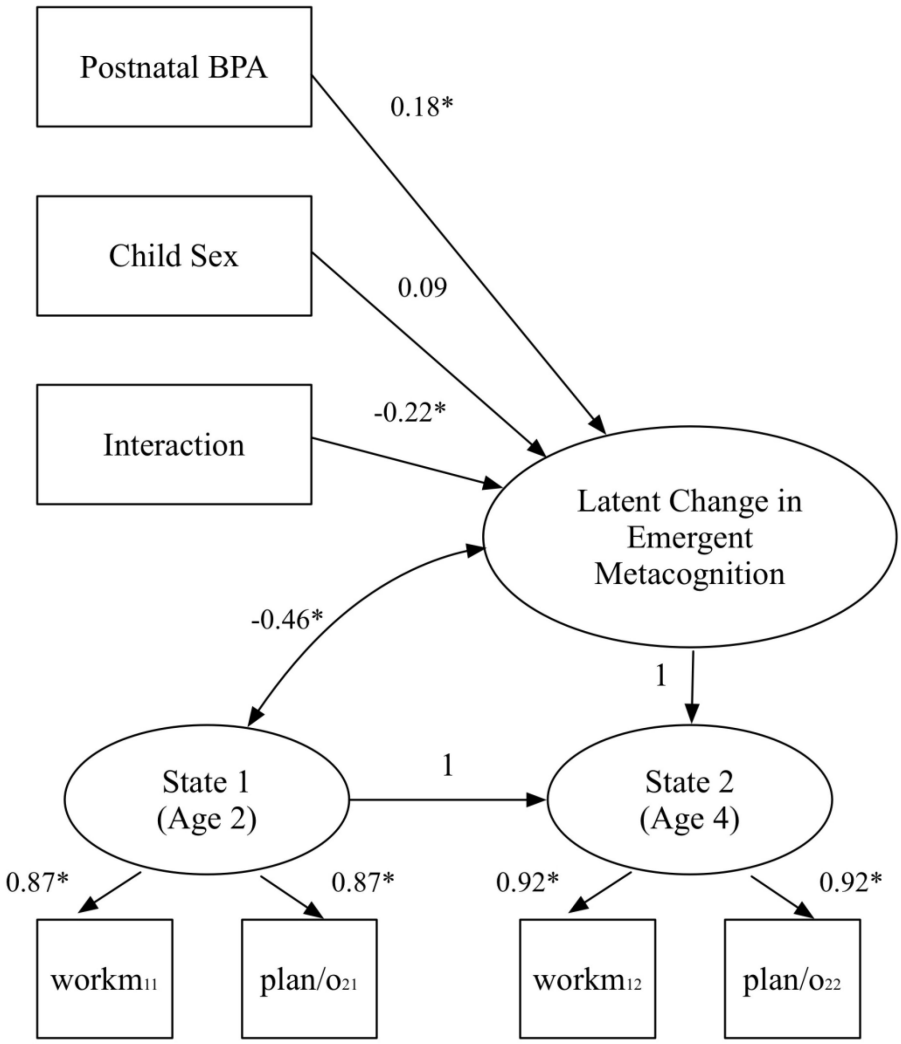

Figure 2.

Structural model and results for the final regression model in which postnatal BPA exposure and child sex were examined in relation to latent changes in preschool children's emergent metacognition.

Note. The ovals represent latent variables and the rectangles represent observed variables. Standardized beta coefficients are reported; $*p \leq 0.05$

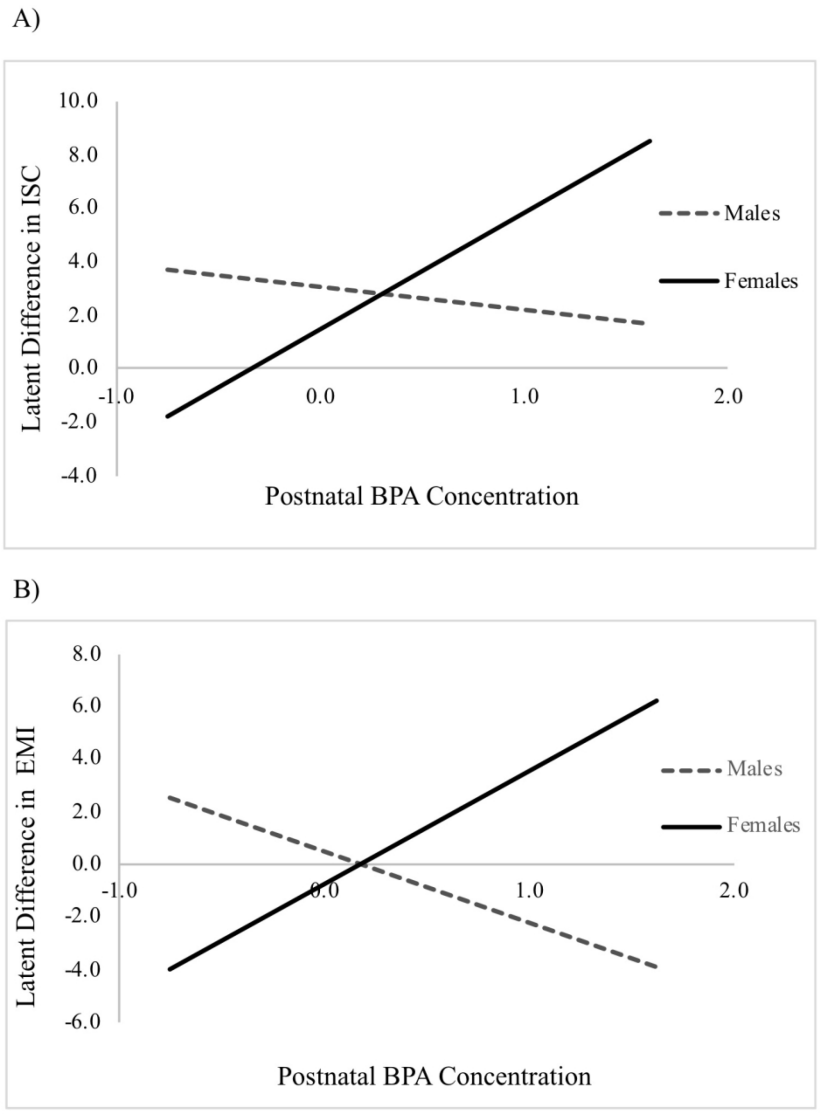

Figure 3.

Figure A shows child sex moderating the association between the log-transformed, creatinine-adjusted postnatal BPA concentration (x-axis) and the latent change score for inhibitory self-control (ISC) (y-axis). Figure B shows child sex moderating the association between the log-transformed, creatinine-adjusted postnatal BPA concentration (x-axis) and the latent change score for emergent metacognition (EM) (y-axis).

Table 1.

Total bisphenol, creatinine-adjusted bisphenol, and creatinine concentrations in urine.

	n	Proportion < LOD (%)	Minimum	Maximum	Arithmetic Mean ± SD	Geometric Mean
Total BPA[a]						
Prenatal Sample	310	6.7	0.16	43.20	2.51 ± 0.29	1.22
Postnatal Sample	302	10.9	0.17	54.64	1.76 ± 0.24	0.93
Total BPA[b] *(creatinine-adjusted)*						
Prenatal Sample	310	6.7	0.14	59.73	2.85 ± 0.31	1.64
Postnatal Sample	302	10.9	0.18	41.62	1.90 ± 0.22	1.11
Total BPS[a]						
Prenatal Sample	310	39.0	< LOD	10.79	0.37 ± 0.05	0.16
Postnatal Sample	302	35.8	< LOD	72.11	0.75 ± 0.26	0.18
Total BPS[b] *(creatinine-adjusted)*						
Prenatal Sample	310	39.0	< LOD	23.18	0.50 ± 0.09	0.22
Postnatal Sample	302	35.8	< LOD	67.17	0.80 ± 0.25	0.21
Creatinine[c]						
Prenatal Sample	310	0.0	56.50	3706.40	937.10 ± 630.20	739.71
Postnatal Sample	302	0.0	56.50	3231.80	1071.41 ± 691.18	839.26

Note. Prenatal sample refers to second trimester urine and postnatal sample refers to 3-months postpartum urine. LOD_{BPA} = 0.32 ng/mL; LOD_{BPS} = 0.10 ng/mL; $LOD_{creatinine}$ = 10mg/dL

[a] ng/mL

[b] µg/g creatinine

[c] µg/mL urine