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Prenatal and childhood polybrominated diphenyl ether (PBDE) exposure and attention and executive function at 9–12 years of age

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Abstract

Objective—California children's exposures to polybrominated diphenyl ether flame retardants (PBDEs) are among the highest measured worldwide. We previously reported associations for prenatal and childhood PBDE exposures with decrements in attention, processing speed, fine motor coordination, and cognition in children at ages 5 and 7 years. Here, we investigate associations of PBDEs with attention and executive function at ages 9 to 12 years in the expanded CHAMACOS cohort.

Methods—We measured PBDEs in prenatal and child age 9 year serum samples for families enrolled in the study since pregnancy ("CHAM1", N=321). In a subsequent cohort for which families were enrolled at child age 9 ("CHAM2", N=301), we measured PBDEs in maternal and

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child samples collected at child age 9, and used predictive modeling to estimate prenatal exposure levels. We examined associations of measured and estimated PBDE concentrations on children's attention and executive functioning at ages 9, 10½, and 12 years.

Results—Geometric means for prenatal and childhood ΣPBDE levels (sum of PBDE −47,−99,−100,−153) for the expanded CHAMACOS cohort were 26.3 and 63.2 ng/g lipid, respectively, and did not differ significantly between CHAM1 and CHAM2 families. We found consistent associations of prenatal exposure to PBDEs with poorer attention and executive function, measured with parent report and direct neuropsychological testing of the child. For example, using GEE models of repeated outcome measures at age 9 and 12, a 10-fold increase in prenatal ΣPBDE was associated with poorer response consistency on the Conners' Continuous Performance Test II (β=2.9; 95% CI: 0.9, 4.8) and poorer working memory on the Behavioral Rating Inventory of Executive Function (β=2.5; 95% CI: 0.5, 4.4). Child age 9 ΣPBDE levels were associated with poorer parent-reported attention and executive function for girls but not boys.

Conclusions—Our results suggest that the prefrontal cortex may be a potential target for PBDE exposure and add to a growing literature showing that these ubiquitous toxicants may adversely affect neurodevelopment.

Keywords

flame retardants; human exposure; Mexican; prenatal; ADHD; attention; executive function; neurodevelopment; motor skills; biomarkers; children; human blood serum; flammability standard; flammability

INTRODUCTION

The prefrontal cortex, which sits in the anterior region of the frontal lobe, regulates goal-directed thought and behavior and is involved in processes such as attention, inhibitory control, working memory and executive function (Kane and Engle, 2002). Impairment in these skills put children at risk for poor academic achievement, social difficulties, and other adverse psychosocial outcomes that may persist into adolescence and adulthood (Biederman et al., 2004; Ellis et al., 2004). In addition, strong connections with other brain regions, such as the basal ganglia and cerebellum, highlight the prefrontal cortex's critical role in a range of cognitive functions (Barbas et al., 2011; Puig et al., 2014). Extreme sensitivity of the prefrontal cortex to the neurochemical environment is most clearly demonstrated by functional impacts with even very small changes in catecholamine levels, such as dopamine and norepinephrine, in response to medications indicated for disorders such as attention deficit hyperactivity disorder (ADHD) (Faraone and Biederman, 1998). A number of epidemiologic studies report associations for a range of environmental chemicals, such as lead, polychlorinated biphenyls and methylmercury, with inattention, impulsive responding and impairments in executive function (Eubig et al., 2010; Yoshimasu et al., 2014), that may be mediated by reduced dopamine levels in the developing brain (Seegal et al., 2002; Tanida et al., 2009).

Animal studies suggest that polybrominated diphenyl ethers (PBDEs), flame retardant chemicals found in household products such as furniture and electronics, may disrupt the

nigrostriatal dopamine system and specifically target the prefrontal cortex (Bradner et al., 2013a; Bradner et al., 2013b), and a growing body of epidemiologic literature reports associations between prenatal exposure to PBDEs and behaviors related to attention and hyperactivity (Chen et al., 2014; Gascon et al., 2011; Hoffman et al., 2012; Roze et al., 2009). Human exposure to PBDEs occurs largely through ingestion and dermal absorption of contaminated housedust (Stapleton et al., 2008), though children are also exposed via placental transfer of maternal exposures as well as through breast milk (Bradman et al., 2012). Relative to their peers worldwide, U.S. children experience exceptionally high exposure to PBDEs, and biological levels are particularly high in California (Bradman et al., 2012; Zota et al., 2008), driven in part by 1970s California fire safety legislation, which introduced strict standards of flame repellence for products sold in-state, and which influenced production of many products destined for the general U.S. market.

We previously reported associations for prenatal and childhood exposure to PBDEs with decrements in attention, processing speed, fine motor coordination, and cognition at 5 and 7 years of age in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a large, well-characterized, California-based longitudinal pre-birth cohort of mothers recruited during pregnancy and their offspring (Eskenazi et al., 2013). In the current paper, we extend our investigation to functions specific to the prefrontal cortex, including attention, inhibitory control, working memory and executive function, measured at ages 9, 10½ , and 12 years in the recently-expanded CHAMACOS cohort, which now includes mothers and children enrolled at child age 9. Our expanded cohort doubles our sample size and offers the opportunity to replicate earlier findings in an independent, albeit demographically similar, sample.

METHODS

Study Sample

The CHAMACOS Study is a longitudinal birth cohort study of children born in California's Salinas Valley between February 2000 and August 2002. Families were recruited in two waves. The initial cohort (CHAM1) was recruited when the mother was pregnant in 1999 and 2000. Eligible pregnant women (≥18 years old, <20 weeks gestation, Spanish- or English-speaking, qualifying for low-income health insurance, and planning to deliver at the public hospital) were enrolled via the community clinics at which they received prenatal care. Through CHAM1 recruitment efforts, 601 women enrolled in the study, and they went on to deliver 536 live-born infants, including 5 twin sets, who remained in the study at birth. At age 9, 337 CHAM1 children remained in the study (i.e., we obtained neurodevelopmental outcome data on them through direct assessment and/or maternal report). In 2009–2011, we expanded the cohort through recruitment of 8- and 9-year old Salinas Valley residents who had been born in local hospitals to mothers who were ≥18 years old at delivery, who had qualified for low-income health insurance during pregnancy and had sought prenatal care in the first trimester, and who were Spanish- or English-speaking. CHAM2 families were recruited through local elementary schools, churches, libraries, food banks, and community events, as well as via newspaper and radio ads. At their initial age 9 study visit, 305 eligible CHAM2 children participated.

CHAM1 women were interviewed twice during pregnancy, after delivery, and when children were 6 months, and 1, 2, 3½, 5, 7, 9, 10½, and 12 years old. CHAM2 women completed a comprehensive baseline interview when their children were 9 years old, and completed an interview that was identical to that completed by CHAM1 women when children were 10½ and 12 years old. CHAM1 and CHAM2 women were administered the Peabody Picture Vocabulary Test (PPVT) to assess maternal verbal intelligence (age 9 visit), the Center for Epidemiologic Studies Depression Scale (CES-D) to assess maternal depression (age 9 visit), and the Home Observation for the Measurement of the Environment-Short Form (HOME-SF) to assess the home learning environment (age 10½ visit) as part of the study interview; CHAM1 women had also completed these assessments at previous points. At child age 12, mothers completed the Conners' Continuous Performance Task (CPT II) to assess attention; this task is described below.

Written informed consent was obtained from all mothers. Children provided verbal assent at 9 and 10½ years, and written assent at 12 years. Study activities were approved by the UC Berkeley Committee for the Protection of Human Subjects.

Neurodevelopmental Assessment

CHAM1 and CHAM2 children completed identical neurobehavioral assessments at ages 9, 10½, and 12. Assessments were completed in a private room by bilingual, bicultural psychometricians who were trained and supervised by a clinical neuropsychologist. Children were assessed in their dominant language, as ascertained via direct assessment. Our standardized assessment batteries included psychometrician-administered and computer-based tasks. Additional information on children's behavior was obtained via parental report on standardized child behavior scales, as well as through child self-report on a standardized behavior scale at age 10½. The specific instruments we used to assess children's attention and executive function are described here by domain. The breadth of data collected in the CHAMACOS cohort allowed us to include a number of tests that measure attention and executive function.

Attention

Conners' Continuous Performance Test (CPT II): (Conners and MHS Staff, 2000): At ages 9 and 12, children completed this computerized vigilance task that assesses hit rate, accuracy, and impulse control (T-scores; M=50, SD=10). We examined continuous *T*-scores (standardized to a non-clinical population) for errors of commission (false positives), errors of omission (non-response), and hit rate standard error overall, and by block and interstimulus interval. Higher variability in hit rate indicates performance inconsistency, a symptom of ADHD (Epstein et al., 2003). We also examined the continuous ADHD Confidence Index score, which indicates the probability that children are correctly classified as having clinical ADHD.

Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV): (Wechsler, 2003): At age 10½ years children were administered the WISC-IV. We examined the Processing Speed subscale (M=100; SD=15) as an indicator of attention. (We also examined WISC-IV measures related to executive function; see below).

Conners' ADHD/DSM-IV Scales, Parent Versions (CADS-P): (Conners, 2001): At child ages 9 and 12, parents completed the CADS-P, yielding four subscales: the Conners' ADHD index score, designed to identify children "at risk" for ADHD; and the DSM-IV-based Inattentive, Hyperactive/Impulsive, and Total subscales. CADS-P data are age- and sex-standardized (T-scores; M=50, SD=10).

Behavior Assessment System for Children, 2nd edition Parent Report (BASC-2) and Self Report of Personality (SRP): (Reynolds and Kamphaus, 2004): When the child was 10½ years of age parents completed the BASC-2 and children completed specific scales of the parallel SRP. We examined the Hyperactivity and Attention Problems scales from these tests, both of which are age- and sex-standardized (T-scores; M=50, SD=10).

Executive Function

Wisconsin Card Sort Task-64: Computer Version 2- Research Edition (WCST): (Heaton, 2000): At ages 9 and 12, children completed this computerized task of set-shifting, which measures skills around strategic planning, ability to shift cognitive strategies and impulse control. We examined raw scores for categories completed and failure to maintain sets and t-scores for errors and perseverative errors.

NEPSY Tower: (Korkman et al., 1998): At age 9 years, children completed this manipulatives-based task which assesses planning, monitoring, self-regulation, and problem solving and yields a single scaled score (M=10, SD=3).

Balloon Analogue Risk Task (BART): (Lejuez et al., 2002): At ages 9 and 12, children completed this computerized task which assesses propensity for risk-taking, planning, and behavioral control by pumping a simulated balloon without knowing when it will explode over multiple trials. We examined the total number of pumps and explosions, both raw scores.

Luria-Nebraska Neuropsychological Battery (Luria): (Golden et al., 1980): At age 10½, children were assessed on select items of the Luria Motor Functions scales, including three – hand sequencing (dominant hand), hand sequencing (non-dominant hand), and successive oral movements – which require active motor regulation and are sensitive to executive function difficulties (Lezak et al., 2004).

Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV): (Wechsler, 2003): At age 10½ children were administered the WISC-IV. We examined the Working Memory subscale (M=100; SD=15), as well as three raw scores derived from subtests in the Working Memory Domain. Specifically, we calculated the longest Letter-Number Sequence and Digit Span reverse spans achieved by each child, and the difference between the longest forward and reverse spans achieved in the Digit Span subtest. Lezak (Lezak et al., 2004) has suggested that the latter measures may be particularly sensitive to executive dysfunction.

Behavior Rating Inventory of Executive Function (BRIEF): (Gioia et al., 2000): At child ages 9 and 12, parents completed the BRIEF, which reports scores for 8 non-overlapping scales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Planning, Organization

of Materials and Monitor scales. These scales form 2 broader indices: Behavioral Regulation and Metacognition, and one overarching summary score, the Global Executive Composite. Scores are age- and sex-standardized (T-scores; M=50, SD=10).

PBDE Exposure Assessment

Pregnancy blood samples were collected via venipuncture from CHAM1 women at either ~26 weeks gestation (M=26.7, SD=2.6 weeks gestation) or upon delivery. For women with delivery levels only, 26-week levels were back-extrapolated via regression models using data on mothers that had measures of both. At the time of the child age 9 visit, blood samples were collected via venipuncture from CHAM1 and CHAM2 women and children. Samples were analyzed for 10 congeners (BDE-17, −28, −47, −66, −85, −99, −100, −153, −154 and −183) at the Centers for Disease Control and Prevention (CDC; Atlanta, GA) using gas chromatography isotope dilution high-resolution mass spectrometry (GC-IDHRMS) (Sjödin et al., 2004). PBDE concentrations are expressed on a serum lipid basis (ng/g lipids), with lipid concentrations ascertained using standard enzymatic methods (Roche Chemicals, Indianapolis, IN) (Phillips et al., 1989). Limits of detection (LODs) for BDE-47 ranged from 0.2 to 2.6 ng/g lipids for maternal samples, and 0.4 to 8.0 ng/g lipids for child samples. For all other congeners, LODs ranged between 0.2 and 0.7 ng/g lipids for maternal and 0.3 and 5.6 ng/g lipids for child samples, respectively. For data analysis purposes, congener-specific concentrations <LOD were assigned either the machine-read value if detected, or were randomly imputed based on a log-normal probability distribution whose parameters were determined by maximum likelihood estimation (Baccarelli et al., 2005; Helsel, 1990; Helsel, 2005; Lubin et al., 2004).

All child age 9 and most CHAM1 prenatal exposure values were based on measured PBDE concentrations, whereas all CHAM2 prenatal exposure values were estimated via back-extrapolation. We back-extrapolated prenatal PBDE concentrations for all CHAM2 participants and the subset of CHAM1 participants lacking measured prenatal or delivery concentrations using the SuperLearner algorithm, an ensemble machine learning technique that uses a weighted combination of algorithms to return a prediction function that minimizes cross-validated mean squared error (van der Laan et al., 2007). Congener-specific prenatal PBDE prediction models were developed using data from a subset of CHAM1 families (n=89); for these families, PBDE concentrations as measured in maternal serum from the child age 9 visit plus relevant demographic information (e.g., years in the US, country of birth) were used to model measured prenatal concentrations (Verner et al., 2015). The SuperLearner algorithm showed moderate predictive ability for PBDEs, with R^2s for CHAM1 measured vs. back extrapolated values of 0.75 for BDE-47, 0.71 for BDE-99, 0.82 for BDE-100, 0.83 for BDE-153 and 0.77 for the sum of −47,−99,−100,−153.

Statistical Analysis

The present analysis is limited to children with prenatal PBDE exposure measurements or estimates and/or child age 9 PBDE exposure measurements, plus relevant neurodevelopmental outcome data from age 9, 10½, and/or 12 year study visits. From among otherwise eligible children, we excluded 6 twins, 1 deaf child, 1 child with cerebral

palsy/hydrocephalus, and 4 children with autism diagnosed before age 12, for a final sample size of 622 (321 CHAM1, 301 CHAM2).

We analyzed the lipid-adjusted sum of 4 PBDE congeners (−47,−99,−100,−153) expressed on the log10 scale as our primary exposure measure. We based most of our analyses on this subset because: 1) these 4 congeners accounted for the majority of the sum of the 10 congeners (e.g., the geometric mean concentrations for prenatal measured PBDEs was 26.2 for the sum of 4 congeners and 28.5 for the sum of 10); and 2) these 4 congeners had the highest proportion above the limit of detection, with detection frequencies ranging from 97.9–99.5% for the sum of 4 vs. 1.4–51.9% for the remaining 6 congeners. We modeled prenatal exposure in the full analysis cohort based on measured 26 week concentrations when available (n=205), estimates derived from regression models based on maternal concentrations measured at delivery (n=57), or estimates derived from SuperLearner based on maternal concentrations measured at child age 9 (n=347). We also ran prenatal exposure models limited to participants with measured prenatal or delivery concentrations. We modeled childhood exposure based on measured child age 9 concentrations (n=546). We used linear regression models to estimate associations with each of the attention and executive function measures described above, and used generalized estimating equations (GEE) to model attention (CPT II and CADS-P) and executive function (WCST and BRIEF) outcomes, each of which featured repeated measures (i.e., at child ages 9 and 12 years) (Zeger and Liang, 1986). For each model, we determined the shape of the dose-response function by running generalized additive models (GAMs) using penalized splines (Peng and Dominici, 2008).

Covariates were selected *a priori*, based on causal diagrams using directed acyclic graphs (DAGs) (Weng et al., 2009). Covariate data were derived primarily from maternal interviews conducted at 9, 10½, and 12 year visits. All models included child's sex, exact age at testing, duration of breastfeeding, and whether or not the child attended preschool; maternal age, education (categorical:<6^{th} grade, 7–12^{th} grade, completed high school), parity (continuous), prenatal smoking status, and verbal intelligence (standardized PPVT score in mother's dominant language, continuous) and depressive symptoms (CES-D, continuous) at child age 9; family structure (father present versus absent in household) at time of assessment; HOME score at 10½ years (continuous, standardized within our sample using z-scores); and average monthly income divided by number of household members supported during the study period (child ages 9–12 years, continuous). In addition, all models were adjusted for either the psychometrician who administered the child-completed tasks or the study interviewer who administered the maternal survey instruments, all child assessment models were adjusted for the time of day the testing occurred (categorical: before 12pm, 12pm-4pm, or after 4pm), and CPT II, WCST, and BART models were adjusted for children's video game usage (average hours per week) at age 9 as reported by mothers.

We assessed for interaction by sex and by cohort (CHAM1 vs. CHAM2) separately by including an interaction term between PBDEs and either sex or cohort in the main models, and then re-running analyses stratified by the potential interaction variable. A Wald test for interaction p-value <0.20 was considered statistically significantly different.

We also conducted several sensitivity analyses: 1) We adjusted for additional potential confounders to identify their impact on effect estimates, including a) maternal attention (ADHD confidence index from the CPT II completed by mothers at child age 12, missing for approximately 25% of mothers), b) maternal years living in the U.S. before giving birth, c) prenatal exposure to organophosphate pesticides (OPs) as represented by average urinary dialkylphosphate metabolites (DAPs) of OPs measured in mothers' urine at two points in pregnancy (available for CHAM1 only) (Bouchard et al., 2011), and d) prenatal exposure to dichlorodiphenyltrichloroethane (DDT) as measured in maternal serum collected at approximately 26 weeks gestation or at delivery (available for CHAM1 only) (Eskenazi et al., 2006). 2) We examined associations with attention and executive function for each of the four PBDE congeners (−47,−99,−100,−153) separately. 3) We fitted models with robust regression to determine how vulnerable our results were to outliers or influential observations. 4) We investigated confounding of prenatal PBDEs and attention/executive function by postnatal PBDEs and vice versa and included a product term between prenatal and postnatal PBDEs to look at a potential interaction of PBDE exposure are these time points.

RESULTS

Demographic characteristics of the 622 families included in this analysis are presented in Table 1. CHAMACOS mothers were predominantly Mexican-born (87%) with low educational attainment (76% did not complete H.S.), younger than 30 at the time of delivery (71%), and living below the federal poverty level at child age 9 (73%). CHAMACOS children had typically breastfed for at least 1 month (82%) and attended preschool (72%), and most performed in the low-normal range of intelligence at age 10½. CHAM2 families were more likely never to have breastfed their CHAMACOS child (p=0.007) and to live below the poverty level at child age 9 (p=0.004, comparisons not shown), but in all other respects, CHAM1 and CHAM2 families were similar demographically. Likewise, PBDE exposure levels as measured in maternal and child serum samples from the age 9 visit did not differ significantly between CHAM1 and CHAM2 mothers or children (comparisons not shown). Prenatal measured and back-extrapolated and child age 9 measured concentrations of the sum of 4 PBDE congeners (−47,−99,−100,−153) and each of the 4 congeners separately are shown in Table 2. Prenatal overall (measured and back-extrapolated) and child age 9 sum of 4 PBDE levels were moderately correlated (Pearson correlation coefficient=0.29). Prenatal and childhood measured concentrations for the other 6 PBDE congeners and the sum of all 10 congeners are presented in Supplemental Table 1.

Our analysis of penalized splines did not show evidence for non-linearity of PBDE and attention/executive function associations. We therefore report results from linear regression models with exposure parameterized as a continuous variable.

Attention

Table 3 presents estimates from linear regression models for measures of attention, including the CPT II and the CADS-P at ages 9 and 12 years, and the WISC-IV and BASC-2 at 10½ years. PBDEs for the overall cohort, which includes measured levels and levels derived

using the SuperLearner algorithm, were associated with consistently poorer outcomes on the CPT II and the CADS-P at 9 years. Effect sizes were strongest for CPT II errors of omission (change in t-score per 10-fold increase in prenatal ΣPBDE p=3.9; 95% CI: −0.6, 8.3), hit rate SE by block (P=2.7; 95% CI: −0.3, 5.7) and ADHD Confidence Index (β=2.2; 95% CI: −2.9, 7.2), and the CADS-P ADHD Index (β=1.9; 95% CI: −0.2, 3.9). Prenatal PBDEs were also associated with poorer CPT II scores at 12 years, though CADS-P associations were null at age 12. We also observed a strong inverse association for prenatal PBDEs and WISC-IV processing speed (β=−4.2; 95% CI: −7.1, −1.3) at age 10½. When we restricted to measured prenatal PBDEs we saw similar associations for both tests. Associations for childhood PBDEs were suggestive at 9 but not 12 years for the CADS-P, in contrast to associations with the CPT II, which were more suggestive at 12 than 9 years. Associations were also detected for childhood PBDEs and WISC-IV processing speed at 10½ years (β= −2.3; 95% CI: −5.3, 0.8).

We detected similar, though more precise estimates of associations for PBDEs with the CPT II and the CADS-P accounting for repeated measures at age 9 and 12 using GEE models (Table 4). Again, associations with prenatal PBDEs were most pronounced for CPT II errors of omission, hit rate SE by block and ADHD confidence index, and CADS-P ADHD Index. Associations for childhood PBDE measures were suggestive for the CADS-P and completely attenuated for the CPT II.

Executive Function

As shown in Table 5, prenatal PBDEs (both measured and derived) were associated with poorer scores on measures of executive function at age 9 years, including WCST errors (change in t-score per 10-fold increase in prenatal ΣPBDE β =−2.6; 95% CI: −5.3, 0.0) and perseverative errors (β =−2.7; 95% CI: −6.3, 0.8), and the BRIEF working memory index (β =2.6; 95% CI: 0.4, 4.8). At age 12 years prenatal PBDE associations persisted for WCST scores but not BRIEF scores. Restricting to measured prenatal PBDEs resulted in stronger WCST and BRIEF associations. Childhood PBDEs were associated with a few isolated 9-year BRIEF and 12-year WCST scores. Associations of prenatal and childhood PBDEs with other measures of executive function, including the NEPSY Tower at 9 years, the BART at 9 and 12 years, and the Luria and WISC-IV at 10½ years, were null. We detected similar associations for tests with repeated measures at 9 and 12 years in GEE models; associations with WCST and BRIEF scores persisted while associations with the BART scores remained null (Table 6).

Sex and Cohort Differences

We observed significant differences by sex in associations between childhood PBDE exposure and parent-reported child functioning using GEE models (Table 5). Specifically, parents reported higher levels of attention (CADS-P) and executive function (BRIEF) problems in girls but not boys with increasing childhood PBDE levels. We did not observe sex differences for prenatal PBDE exposure and measures of attention and executive function, with the exception of one isolated finding for errors of commission on the CPT II (data not shown), in which boys demonstrated significantly more errors of commission than girls in association with prenatal PBDE exposure (p-value=0.05).

We observed largely consistent exposure-outcome associations for CHAM1 and CHAM2 families in GEE models, particularly with regards to prenatal exposure (Supplemental Table 2). With the exception of WCST perseverative errors, for which exposure-outcome estimates differed significantly by cohort, both child performance and maternal report-based outcomes trended towards poorer performance or more symptomatic behavior in association with increased prenatal PBDE exposure, whether measured or back-extrapolated. Exposure-outcome estimates for WISC-IV outcomes were particularly consistent across cohort. Exposure-outcome estimates based on childhood exposure were more likely to differ in direction by cohort, but did not contradict the generally null associations for childhood exposures observed in Table 3 and Table 4.

Sensitivity Analyses

Exposure-outcome estimates did not change when we included maternal attention (CPT II ADHD confidence index), maternal years living in the U.S. before giving birth, prenatal DAP concentrations, or prenatal DDT concentrations in the model (data not shown). In addition, we saw similar associations for each of the four PBDE congeners (−47,−99,−100,−153) modeled separately (Supplementary Table 3), though associations with PBDE-153 were weaker compared with the other 3 congeners.

Results from robust regression were similar to linear models (data not shown), with the exception of CPT II errors of omission and ADHD confidence index. For example, associations of prenatal PBDE (measured and derived) with 9-year CPT II errors of omission attenuated from β =3.9; 95% CI: −0.6, 8.3 in linear models (Table 3) to −1.8; 95% CI: −4.4, 0.8 in robust regression models.

We did not see consistent evidence for confounding or interaction between prenatal and childhood PBDE exposure.

DISCUSSION

Our results show consistent associations of prenatal exposure to PBDEs with poorer attention and executive function, measured with parent report and direct neuropsychological testing of the child. Though the mechanisms for developmental neurotoxicity of PBDEs are not yet known (Costa et al., 2014), we focused our analysis on functions primarily regulated by the prefrontal cortex based on literature suggesting that PBDEs may target this region of the brain (Bradner et al., 2013a; Bradner et al., 2013b), and because these functions have important consequences for educational and psychosocial outcomes in childhood and beyond (Biederman et al., 2004; Ellis et al., 2004).

Our finding of stronger exposure-outcome associations for prenatal vs. childhood exposure is consistent with previous literature that shows that the prenatal period is especially sensitive to environmental exposures (Grandjean and Landrigan, 2006). These stronger associations with prenatal exposure are particularly notable given that prenatal PBDE levels in CHAMACOS were much lower than childhood levels, due to many mothers' recent immigration to California at the time that their levels were measured during pregnancy (Castorina et al., 2011; Eskenazi et al., 2011). Nonetheless, we did observe associations for

childhood exposure levels with some attention and executive function outcomes, particularly among girls. As development of the prefrontal cortex continues into adolescence and early adulthood (Dumontheil et al., 2008), it is biologically plausible that postnatal exposures also adversely affect these behaviors.

Our results are also consistent with other studies that report associations for prenatal and postnatal PBDE exposure with inattention and hyperactivity in preschool and early school-aged children (Chen et al., 2014; Gascon et al., 2011; Hoffman et al., 2012; Roze et al., 2009), including our own (Eskenazi et al., 2013). Specifically, in our previous analysis of CHAM1 children, we reported adverse associations of measured prenatal PBDE exposure with errors of omission and ADHD Confidence Index scores at child age 5 using the Conners' Kiddie Continuous Performance Test (K-CPT) (Conners and Staff, 2001), and with CADS-P ADHD Index and Inattentive subscale scores at child age 7 years (at age 7 we administered the CADS to both parents and teachers; stronger associations were found for prenatal exposure with parent report). We also reported adverse associations of childhood PBDE exposure as measured at age 7 with the ADHD Index and Inattentive subscales of the CADS teacher report, the BASC-2 teacher report, and the WISC-IV Processing Speed subscale at age 7. Our findings in the current analysis build upon these earlier findings in three important ways. First, our observation of similar exposure-outcome associations at ages 9 and 12 suggest persistent effects of prenatal PBDE exposure. Second, our finding of similar associations in the CHAM1 and CHAM2 cohorts provides some validation of these results. Third, our study includes executive function, which has not been previously reported in the literature in relation to PBDEs, and supports the hypothesis that frontal lobe functions may be undermined by PBDE exposure.

Our study raises the possibility that PBDEs affect males and females differently. Specifically, we observed higher maternal report of attention and executive function difficulties with childhood PBDE exposure among girls only. Only two previous studies of PBDEs and behavior investigated sex differences and reported no statistically significant sex interactions (Chen et al., 2014; Eskenazi et al., 2013). The biologic mechanism for sex differences in exposure-related neurotoxicity remains unknown, however a growing literature suggests that endocrine disrupting chemicals may indeed impact males and females differently (Braun et al., 2009; Engel et al., 2010; Sagiv et al., 2012; Weiss, 2011).

An important strength of this study is that we include both parent-rated behavior and more objective neuropsychological tests administered directly to the children. We observed relatively consistent PBDE-related associations across these assessment methods, which strengthens our findings.

We note that prenatal PBDE associations with parent-reported attention and executive function were not consistent across 9 and 12 year reports; associations attenuated to the null at 12 years for both the CADS-P and the BRIEF. One potential explanation for this attenuation is that parent report of their children's behavior may not be as reliable at older ages, when children are more independent and spend more of their time away from their parents. This is supported by previous literature which suggests that adolescents' behavior may be less observable by parents compared to younger children's behavior (Achenbach et

al., 1987). Thus, while associations between PBDE exposure and attention and executive function may persist at older time periods, dampened outcome measures could make them more difficult to detect, driving estimates towards the null.

We observed stronger associations across tests for measured prenatal exposure vs. the combined measured and back-extrapolated values. Back-extrapolation of prenatal PBDE exposure likely resulted in a degree of random error, which would have attenuated estimates. Our results demonstrate the tradeoff in precision when including the larger sample (narrower confidence intervals) vs. directly measured exposure (stronger effect estimates). Nonetheless, the fact that these groups show similar associations suggests that thoughtful back extrapolation of persistent environmental chemicals offers a viable means of retrospective exposure assessment.

Using robust regression, we found that some of our CPT II findings (errors of omission and the ADHD confidence index) were attenuated, suggesting that these results were sensitive to influential observations. However, CPT II hit rate SE by block, a measure of response consistency over the duration of the test (vigilance), and all other results were unchanged in our robust regression analyses and we therefore have more confidence in these findings.

We examined a large number of outcome measures in this study in relation to multiple exposure measures, which results in multiple comparisons; we recognize that this could produce spurious associations by chance alone. Given that conventional approaches for correcting for multiple comparisons have low efficiency and poor accuracy (Rothman et al., 2008), we were careful to only point out patterns in our results that were consistent with our a priori hypothesis that PBDEs target the prefrontal cortex, rather than highlighting any one isolated finding.

With the exception of PBDE-153, associations were similar across the other 3 PBDE congeners (Supplementary Table 3). These analyses should be interpreted with caution, however, given the high correlation between these congeners.

We did not examine associations with clinically diagnosed ADHD or executive function disorders. However, investigating associations with quantitative, dimensional traits related to these disorders in this prospective cohort study has a number of advantages for etiologic research, including excellent exposure assessment during the developmentally relevant window(s), reduced outcome misclassification and enhanced statistical power (Sagiv et al., 2015). In addition, demonstrating even small exposure-related impacts on attention/executive function, which may be considered clinically unimportant, can translate into a substantial increase in the number of cases of clinically diagnosed disorder in the population, particularly for an exposure as ubiquitous as PBDEs.

CONCLUSION

Our results suggest associations of prenatal PBDEs with attention and executive function, measured with parental report and via neuropsychological testing of the child at ages 9–12. Consistency across these related behaviors supports our hypothesis that the prefrontal cortex may be a potential target for PBDE exposure. Associations with childhood PBDE exposure,

though weaker than prenatal exposure, indicate that the postnatal period may also be sensitive to these exposures. These findings add to a growing literature pointing to PBDEs as developmental neurotoxicants. This information is critical for informing policy measures regarding these ubiquitous, modifiable exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BART	Balloon Analogue Risk Task
BASC	Behavior Assessment Scale for Children
BDE	Brominated diphenyl ether
BRIEF	Behavior Rating Inventory of Executive Function
CADS-P	Conners' ADHD/DSM-IV Scales, Parent version
CES-D	Center for Epidemiologic Studies Depression Scale
CHAMACOS	Center for the Health Assessment of Mothers and Children of Salinas
CI	Confidence interval
CPT II	Continuous Performance Test II
DAPs	Dialkylphosphate metabolites of organophosphate pesticides
DDT	Dichlorodiphenyltrichloroethane
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
GM	Geometric Mean
HOME	Home Observation for Measurement of the Environment
LOD	Limit of Detection
M	Mean
Ops	Organophosphate pesticides

PBDE	Polybrominated diphenyl ether
SD	Standard Deviation
TB	Technical Bulletin
WCST	Wisconsin Card Sort Task
WISC-IV	Weschler Intelligence Scale for Children, Fourth Edition

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Table 1

Sociodemographic characteristics of CHAMACOS children (n=622)[a].

Maternal/Family Factors	N	%
Maternal country of birth (n=2 missing)		
U.S.	74	(11.9)
Mexico	538	(86.8)
Other	8	(1.3)
Maternal years in US at child delivery (n=2 missing)		
<=1	127	(20.5)
2–5	169	(27.3)
6–10	149	(24.0)
11+	116	(18.7)
Entire Life	59	(9.5)
Maternal age at child delivery (n=2 missing)		
18–24	252	(40.7)
25–29	187	(30.2)
30–34	115	(18.5)
35–45	66	(10.6)
Parity at child delivery (n=3 missing)		
0	208	(33.6)
1+	411	(66.4)
Maternal education at child delivery (n=4 missing)		
<6th grade	263	(42.6)
7th-12th grade	204	(33.0)
Completed high school	151	(24.4)

Child Factors	N	%
Sex		
Male	310	(49.8)
Female	312	(50.2)
Breastfeeding duration (n=3 missing)		
Never breastfed	45	(7.3)
<=1 Month	69	(11.1)
1–6 Months	199	(32.1)
6–12 Months	147	(23.7)
>12 Months	159	(25.7)
History of preschool attendance (n= 48 missing)		
Did not attend	162	(28.2)
Attended preschool	412	(71.8)
Video game usage at age 9 (n=17 missing)		
Never plays video games	161	(26.6)
Plays video games	444	(73.4)
Intelligence 10½ years (WISC-IV FSIQ) (n=31 missing)		
≤79	89	(15.0)
80–99	384	(65.0)
≥100	118	(20.0)
Conners' CPT II 9 years[c] (n=16 missing)		
Normal (<70%)	457	(75.4)
Inattentive/Impulsive (≥70%)	149	(24.6)

Maternal/Family Factors	N	%	Child Factors	N	%
Maternal Intelligence (PPVT Score)[b] (n=25 missing)					
≤74	134	(22.5)	CADS-P 9 years[d] (n=8 missing)		
75–99	196	(32.8)	Typical	475	(77.3)
≥100	267	(44.7)	Slightly Atypical	98	(16.0)
			Moderately to Markedly Atypical	41	(6.7)
Maternal Attention[c] (n=124 missing)					
Normal (<70%)	441	(88.6)	Conners' CPT II 12 years[c] (n=32 missing)		
Inattentive/Impulsive (≥70%)	57	(11.4)	Normal (<70%)	519	(88.0)
			Inattentive/Impulsive (≥70%)	71	(12.0)
Maternal marital status at child age 9 (n=11 missing)					
Married to/living with child's father	453	(74.1)	CADS-P 12 years[d] (n=25 missing)		
Not married to/living with child's father	158	(25.9)	Typical	487	(81.6)
			Slightly Atypical	80	(13.4)
Family poverty at child age 9 (m=14 missing)			Moderately to Markedly Atypical	30	(5.0)
< Poverty level	446	(73.3)			
Within 200% of poverty level	161	(26.5)			
> 200% of poverty level	1	(0.2)			

[a] Combined CHAM1 (n=321) and CHAM2 (n=301).

[b] Maternal Peabody Picture Vocabulary Test completed at child age 9 visit.

[c] ADHD Confidence Index Score from Conners' CPT II administered to mothers at child's age 12 or to child at ages 9 and 12.

[d] ADHD Interpretative Category from maternal report on Conners' ADHD DSM-IV Scales - Parent Version (CADS-P) at child ages 9 and 12.

Table 2

Distributions of measured and back-extrapolated concentrations of the sum of four PBDE congeners (−47, −99,−100,−153) on a serum lipid basis in CHAMACOS during pregnancy (26 weeks) and in children at age 9.

		Serum concentrations (ng/g lipid)							Geometric mean (95% CI)
Congener	**N**	**min**	**10th**	**25th**	**50th**	**75th**	**90th**	**max**	
ΣPBDE (−47,−99,−100,−153)									
Prenatal Measured[a]	262	2.6	8.0	14.8	25.0	42.0	71.9	1293.7	26.2 (23.3–29.4)
Prenatal Back-extrapolated[b]	347	5.2	12.1	15.8	24.5	37.9	64.4	1715.3	26.5 (24.5–28.6)
Prenatal Overall	609	2.6	10.7	15.5	24.9	39.5	66.4	1715.3	26.3 (24.7–28.1)
Child Measured	546	6.5	22.9	37.9	62.5	112.5	174.6	430.2	63.2 (59.2–67.4)
PBDE-47									
Prenatal Measured[a]	262	0.5	4.8	8.5	15.8	26.5	47.1	761.0	15.5 (13.9–17.7)
Prenatal Back-extrapolated[b]	347	2.9	7.2	9.4	14.0	22.9	38.0	639.0	15.6 (14.4–16.8)
Prenatal Overall	609	0.5	5.9	9.1	15.0	24.4	41.9	761.0	15.6 (14.6–16.7)
Child Measured	546	2.1	11.3	20.2	35.7	64.3	103.6	267.8	35.2 (32.8–37.8)
PBDE-99									
Prenatal Measured[a]	262	0.2	1.5	2.4	4.2	7.1	12.1	297.6	4.5 (4.0–5.1)
Prenatal Back-extrapolated[b]	347	0.8	2.1	3.0	4.5	7.6	12.3	590.6	4.9 (4.6–5.3)
Prenatal Overall	609	0.2	1.8	2.7	4.4	7.3	12.3	590.6	4.7 (4.4–5.1)
Child Measured	546	0.5	2.3	4.1	7.8	14.9	27.8	77.8	7.8 (7.3–8.5)
PBDE-100									
Prenatal Measured[a]	262	0.2	0.8	1.6	2.6	4.6	7.7	138.3	2.8 (2.5–3.1)
Prenatal Back-extrapolated[b]	347	0.6	1.4	1.8	2.8	4.7	8.2	86.2	3.1 (2.8–3.3)
Prenatal Overall	609	0.2	1.2	1.7	2.7	4.7	8.1	138.3	3.0 (2.8–3.2)
Child Measured	546	0.4	2.8	4.5	7.6	13.0	21.2	82.2	7.6 (7.1–8.1)
PBDE-153									
Prenatal Measured[a]	262	0.1	0.9	1.4	2.2	3.8	6.8	96.9	2.4 (2.1–2.6)
Prenatal Back-extrapolated[b]	347	0.4	1.0	1.5	2.1	3.7	6.6	399.5	2.5 (2.3–2.7)
Prenatal Overall	609	0.1	1.0	1.4	2.1	3.8	6.6	399.5	2.4 (2.3–2.6)
Child Measured	546	0.5	3.6	5.5	9.4	15.1	25.6	173.1	9.5 (8.9–10.1)

[a] Includes n=57 values back-extrapolated via regression models based on maternal serum concentrations at delivery.

[b] Values were back-extrapolated via SuperLearner models based on maternal serum concentrations at child age 9 years.

Table 3

Change in child attention scores at age 9 and 12 years per 10-fold increase in prenatal and child ΣPBDE (−47, −99,−100,−153) concentration (ng/g, lipid-adjusted) using linear regression models[a] in the CHAMACOS cohort.

			Prenatal ΣPBDE overall[c]		Prenatal ΣPBDE measured		Child ΣPBDE	
Outcome	**mean (SD)**	**orientation[b]**	**n**	**β (95% CI)**	**n**	**β (95% CI)**	**n**	**β (95% CI)**
9-year assessment								
Conners' Continuous Performance Test II (CPT II) (T-scores)								
Errors of omission	58.8 (18.2)	(+)	588	3.9 (−0.6, 8.3)	246	4.0 (−2.0, 10.0)	541	−1.1 (−5.8, 3.6)
Errors of commission	49.8 (9.2)	(+)	588	0.6 (−1.6, 2.9)	246	0.1 (−3.2, 3.3)	541	0.5 (−1.8, 2.7)
Hit rate standard error (SE) overall	57.7 (10.4)	(+)	588	1.4 (−1.1, 3.9)	246	2.4 (−1.0, 5.7)	541	−0.9 (−3.5, 1.7)
Hit rate SE by block	50.8 (12.2)	(+)	588	2.7 (−0.3, 5.7)	246	3.4 (−0.8, 7.6)	541	0.3 (−2.9, 3.4)
Hit rate SE by inter-stimulus interval (ISI)	57.4 (10.9)	(+)	588	−0.1 (−2.7, 2.6)	246	0.7 (−2.9, 3.6)	541	−1.0 (−3.8, 1.7)
ADHD Confidence Index	54.7 (21.9)	(+)	588	2.2 (−2.9, 7.2)	247	3.9 (−3.0, 10.8)	541	−3.2 (−8.4, 1.9)
Conners ADHD/DSM-IV Scales (CADS) - Parent Version (T-score)								
ADHD Index	50.9 (9.1)	(+)	598	1.9 (−0.2, 3.9)	254	2.7 (−0.1, 5.5)	542	1.3 (−0.9, 3.5)
DSM-IV total scale	51.6 (9.1)	(+)	597	1.5 (−0.7, 3.7)	253	2.3 (−0.7, 5.3)	541	1.9 (−0.4, 4.3)
Inattentive subscale	49.7 (8.9)	(+)	597	1.7 (−0.3, 3.7)	253	2.6 (−0.1, 5.3)	541	1.3 (−0.8, 3.4)
Hyperactive/Impulsive subscale	53.6 (10.5)	(+)	597	1.0 (−1.5, 3.4)	253	1.5 (−1.9, 4.8)	541	2.2 (−0.3, 4.8)
10½ -yea r assessment								
Weschler Intelligence Scales for Children (WISC-IV)								
Processing Speed (standardized score)	98.3 (12.1)	(−)	580	−4.2 (−7.1, −1.3) **	243	−4.4 (−8.5, −0.3) *	531	−2.3 (−5.3, 0.8)
BASC-2-maternal report (*T*-score)								
Hyperactivity scale	46.5 (8.0)	(+)	574	−0.5 (−2.4, 1.4)	242	−1.0 (−3.4, 1.5)	525	0.3 (−1.8, 2.3)
Attention Problems scale	49.1 (10.3)	(+)	574	1.2 (−1.2, 3.7)	242	2.3 (−1.1, 5.7)	525	0.9 (−1.7, 3.5)
BASC-2-youth self-report (*T*-score)								
Hyperactivity scale	47.2 (9.3)	(+)	566	−0.1 (−2.3, 2.2)	237	−0.2 (−3.6, 3.3)	520	1.6 (−0.8, 4.0)
Attention Problems scale	50.0 (9.7)	(+)	558	0.3 (−2.1, 2.7)	230	−0.0 (−3.4, 3.3)	511	0.9 (−1.6, 3.4)
12-year assessment								
Conners' Continuous Performance Test II (CPT II) (T-scores)								
Errors of omission	48.8 (9.3)	(+)	567	2.2 (−0.2, 4.6)	242	2.1 (−1.7, 5.9)	525	1.3 (−1.3, 3.8)

Outcome	mean (SD)	orientation[b]	Prenatal ΣPBDE overall[c] n	Prenatal ΣPBDE overall[c] β (95% CI)	Prenatal ΣPBDE measured n	Prenatal ΣPBDE measured β (95% CI)	Child ΣPBDE n	Child ΣPBDE β (95% CI)
Errors of commission	49.0 (10.4)	(+)	567	1.1 (−1.6, 3.7)	242	0.8 (−3.1, 4.7)	525	−0.5 (−3.2, 2.2)
Hit rate standard error (SE) overall	47.9 (9.1)	(+)	567	1.6 (−0.7, 3.8)	242	1.9 (−1.2, 5.0)	525	1.2 (−1.2, 3.6)
Hit rate SE by block	49.9 (9.6)	(+)	567	2.9 (0.5, 5.3) *	242	2.7 (−0.7, 6.1)	525	1.3 (−1.3, 3.8)
Hit rate SE by inter-stimulus interval	49.8 (9.4)	(+)	567	0.1 (−2.3, 2.4)	242	0.3 (−3.1, 3.7)	525	0.8 (−1.6, 3.2)
ADHD Confidence Index	46.7 (18.4)	(+)	567	3.3 (−1.1, 7.7)	242	3.9 (−2.2, 10.0)	525	3.1 (−1.4, 7.7)
Conners ADHD/DSM-IV Scales (CADS) - Parent Version (T-score)								
ADHD Index	49.8 (8.2)	(+)	546	0.1 (−1.9, 2.2)	230	0.4 (−2.4, 3.2)	499	0.3 (−1.9, 2.4)
DSM-IV total scale	49.9 (8.4)	(+)	546	−0.7 (−2.8, 1.4)	230	0.1 (−2.8, 3.0)	499	0.5 (−1.7, 2.8)
Inattentive subscale	48.3 (7.4)	(+)	546	−0.1 (−1.9, 1.7)	230	0.1 (−2.5, 2.6)	499	0.9 (−1.1, 2.8)
Hyperactive/Impulsive subscale	52.1 (9.2)	(+)	546	−1.3 (−3.7, 0.9)	230	−0.1 (−3.1, 3.0)	499	−0.2 (−2.7, 2.3)

[a] All models adjusted for child sex, parity, duration of breastfeeding, preschool attendance, and age at assessment; maternal age, education, IQ (PPVT score), and depression at child age 9; maternal prenatal smoking status; family structure (father present/absent) at time of assessment; household income; HOME score at child age 10½; and psychometrician or study interviewer who administered the task or rating scale. CPT II models also adjusted for time of day assessment occurred and child video game usage at age 9.

[b] (+) higher scores indicate poorer performance/more symptomatic behavior.

[c] Includes measured and back-extrapolated PBDE concentrations.

* p<0.05

** p<0.01

Table 4

Change in child 9 and/or 12-year attention scores per 10-fold increase in prenatal and child ΣPBDE (−47, −99,−100,−153) concentration (ng/g, lipid-adjusted) using GEE models[a] in the CHAMACOS cohort.

Outcome (assessed at 9 and/or 12 year visits)	orientation[b]	Prenatal ΣPBDE overall[c] β (95% CI)	Prenatal ΣPBDE measured β (95% CI)	Child ΣPBDE β (95% CI)
Conners' Continuous Performance Test II (CPT II) (T-scores)				
Errors of omission	(+)	3.1 (0.3, 5.8)*	3.0 (−0.6, 6.5)	0.3 (−2.6, 3.1)
Errors of commission	(+)	0.8 (−1.1, 2.8)	0.4 (−2.4, 3.1)	0.1 (−1.9, 2.1)
Hit rate standard error (SE) overall	(+)	1.5 (−0.5, 3.5)	2.1 (−0.6, 4.7)	0.4 (−1.7, 2.4)
Hit rate SE by block	(+)	2.9 (0.9, 4.8)**	3.0 (0.4, 5.7)*	0.8 (−1.3, 2.9)
Hit rate SE by inter-stimulus interval (ISI)	(+)	0.1 (−1.9, 2.0)	0.3 (−2.3, 2.8)	−0.1 (−2.1, 1.9)
ADHD Confidence Index	(+)	2.8 (−0.9, 6.6)	3.9 (−1.2, 8.8)	0.2 (−3.6, 4.1)
Conners ADHD/DSM-IV Scales (CADS) - Parent Version (T-score)				
ADHD Index	(+)	1.3 (−0.5, 3.0)	2.1 (−0.3, 4.4)	1.0 (−0.9, 2.9)
DSM-IV total scale	(+)	0.9 (−1.0, 2.7)	1.8 (−0.6, 4.2)	1.5 (−0.5, 3.4)
Inattentive subscale	(+)	1.2 (−0.5, 2.8)	1.9 (−0.2, 4.1)	1.3 (−0.5, 3.0)
Hyperactive/Impulsive subscale	(+)	0.3 (−1.7, 2.3)	1.3 (−1.3, 3.9)	1.2 (−1.0, 3.4)

[a] All models adjusted for child sex, parity, duration of breastfeeding, preschool attendance, and age at assessment; maternal age, education, IQ (PPVT score), and depression at child age 9; maternal prenatal smoking status; family structure (father present/absent) at time of assessment; household income; HOME score at child age 10½; and psychometrician or study interviewer who administered the task or rating scale. CPT II models also adjusted for time of day assessment occurred and child video game usage at age 9.

[b] (+) higher scores indicate poorer performance/more symptomatic behavior.

[c] Includes measured and back-extrapolated PBDE concentrations.

* $p<0.05$

** $p<0.01$

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Table 5

Change in child executive function scores at age 9 and 12 years per 10-fold increase in prenatal and child ΣPBDE (−47, −99,−100,−153) concentration (ng/g, lipid-adjusted) using linear regression models[a] in the CHAMACOS cohort.

			Prenatal ΣPBDE overall[c]		Prenatal ΣPBDE measured		Child ΣPBDE	
Outcome	**mean (SD)**	**orientation[b]**	**n**	**β (95% CI)**	**n**	**β (95% CI)**	**n**	**β (95% CI)**
9-year assessment								
Wisconsin Card Sort Test (WCST)								
Categories completed (raw score)	2.4 (1.2)	(−)	589	−0.3 (−0.6, 0.0)	246	−0.4 (−0.7, 0.0)	542	0.1 (−0.2, 0.4)
Failure to maintain set (raw score)	0.7 (0.9)	(+)	589	−0.1 (−0.3, 0.1)	246	−0.1 (−0.4, 0.2)	542	−0.1 (−0.3, 0.2)
Errors (*T*-score)	48.0 (10.8)	(−)	587	−2.6 (−5.3, 0.0)	246	−4.2 (−7.9, −0.6) *	540	0.4 (−2.3, 3.2)
Perseverative errors (*T*-score)	51.8 (14.3)	(−)	587	−2.7 (−6.3, 0.8)	246	−5.6 (−10.5, −0.7) *	540	−0.5 (−4.2, 3.2)
NEPSY Tower (scaled score)	9.7 (2.8)	(−)	593	0.3 (−0.4, 1.0)	248	0.4 (−0.6, 1.3)	545	−0.4 (−1.1, 0.4)
Balloon Analogue Risk Test (raw scores)								
Number of pumps	536.3 (315.7)	(+)	569	−68.1 (−147.2, 11.0)	229	−60.6 (−174.2, 53.0)	525	25.7 (−56.4, 107.8)
Adjusted number of pumps	423.7 (212.0)	(+)	569	−49.8 (−103.3, 3.8)	229	−16.0 (−89.5, 57.6)	525	2.2 (−53.1, 57.6)
Number of explosions	4.4 (3.4)	(+)	555	−0.3 (−1.2, 0.6)	226	−0.6 (−1.9, 0.7)	512	0.1 (−0.8, 1.0)
Behavior Rating Inventory of Executive Function (BRIEF) (*T*-score)								
Inhibit Scale	50.5 (9.4)	(+)	599	−0.7 (−2.8, 1.4)	255	0.9 (−1.9, 3.6)	543	1.8 (−0.4, 4.1)
Shift Scale	50.88 (10.2)	(+)	599	0.0 (−2.25, 2.3)	255	1.8 (−1.1,4.8)	543	−1.0 (−3.4, 1.4)
Emotional Control Scale	50.0 (10.0)	(+)	599	1.8 (−0.4, 4.1)	255	3.7 (0.7, 6.6) *	543	1.0 (−1.4, 3.4)
Behavior Regulation Index	50.5 (10.2)	(+)	599	0.5 (−1.7, 2.8)	255	2.5 (−0.5, 5.5)	543	0.9 (−1.5, 3.3)
Initiate Scale	48.9 (9.5)	(+)	599	1.1 (−1.1, 3.2)	255	1.8 (−1.1, 4.6)	543	1.7 (−0.5, 4.0)
Working Memory Scale	50.8 (9.9)	(+)	599	2.6 (0.4, 4.8) *	255	4.5 (1.7, 7.4) **	543	0.5 (−1.9, 2.9)
Planning Scale	48.3 (9.8)	(+)	599	1.4 (−0.8, 3.5)	255	2.8 (0.0, 5.7)	543	1.2 (−1.1, 3.4)
Organization of Materials Scale	47.1 (10.0)	(+)	599	0.3 (−2.0, 2.5)	255	2.0 (−1.0, 5.0)	543	2.3 (−0.1, 4.7)
Monitor Scale	46.2 (9.9)	(+)	599	0.8 (−1.4, 3.0)	255	2.5 (−0.3, 5.4)	543	1.8 (−0.5, 4.2)
Metacognition Index	48.2 (10.2)	(+)	599	1.6 (−0.7, 3.8)	255	3.3 (0.4, 6.3) *	543	1.6 (−0.8, 4.0)
Global Executive Composite	49.0 (10.3)	(+)	599	1.2 (−1.1, 3.4)	255	3.1 (0.2, 6.04) *	543	1.4 (−1.0, 3.7)
10½-year assessment								
Luria (raw scores; sequences completed)								

Outcome	mean (SD)	orientation[b]	Prenatal ΣPBDE overall[c] n	Prenatal ΣPBDE overall[c] β (95% CI)	Prenatal ΣPBDE measured n	Prenatal ΣPBDE measured β (95% CI)	Child ΣPBDE n	Child ΣPBDE β (95% CI)
Hand-fist-palm dominant hand	4.0 (1.5)	(−)	581	0.0 (−0.4, 0.4)	243	0.3 (−0.2, 0.8)	532	0.1 (−0.3,0.4)
Hand-fist-palm non-dominant hand	4.6 (1.4)	(−)	581	−0.1 (−0.5, 0.2)	243	−0.1 (−0.6, 0.4)	532	0.2 (−0.2,0.5)
Oral sequence	2.8 (1.08)	(−)	575	0.2 (−0.1, 0.4)	241	0.2 (−0.2, 0.6)	527	0.1 (−0.2, 0.4)
Weschler Intelligence Scales for Children (WISC-IV)								
Working Memory (standardized)	96.2 (11.0)	(−)	581	−1.6 (−4.3, 1.1)	243	−2.0 (−5.5, 1.6)	532	−0.1 (−3.0, 27)
Longest Digit Span reverse span achieved (raw)	3.5 (0.8)	(−)	581	−0.1 (−0.3, 0.1)	243	−0.2 (−0.5, 0.1)	532	−0.1 (−0.3, 0.1)
Difference between longest Digit								
Span reverse and forward spans (raw)	1.37 (1.1)	(+)	581	0.1 (−0.1, 0.4)	243	0.3 (−0.1, 0.6)	532	0.3 (−0.0, 0.5)
Longest Letter-Number Sequence span achieved (raw)	3.4 (0.8)	(−)	581	−0.2 (−0.5, 0.0)	243	−0.2 (−0.5, 0.1)	532	−0.1 (−0.3, 0.1)
12-year assessment								
Wisconsin Card Sort Test (WCST)								
Categories completed (raw)	3.1 (1.2)	(−)	564	−0.1 (−0.4, 0.2)	241	−0.2 (−0.6, 0.2)	523	−0.3 (−0.6, 0.0)
Failure to maintain set (raw)	0.5 (0.7)	(+)	564	−0.1 (−0.3, 0.1)	241	−0.2 (−0.4, 0.1)	523	0.1 (−0.1, 0.3)
Errors (*T*-score)	52.7 (11.2)	(−)	560	−2.5 (−5.3, 0.3)	240	−3.7 (−7.7, 0.3)	519	−2.8 (−5.8, 0.1)
Perseverative errors (*T*-score)	56.5 (14.2)	(−)	560	−2.3 (−5.9, 1.3)	240	−5.3 (−10.2, −0.4) *	519	−0.7 (−4.5, 3.2)
Balloon Analogue Risk Test (raw)								
Number of pumps	666.3 (321.3)	(+)	563	−51.0 (−132.6, 30.6)	238	−18.0 (−121.5, 85.6)	521	42.9 (−43.2, 129.0)
Adjusted number of pumps	525.0 (210.3)	(+)	563	−25.4 (−78.7, 27.9)	238	−6.2 (−75.9, 63.6)	521	16.6 (−39.2,72.5)
Number of explosions	5.4 (3.3)	(+)	557	−0.4 (−1.3, 0.4)	237	−0.2 (−1.3, 0.9)	515	0.4 (−0.5,1.3)
Behavior Rating Inventory of Executive Function (BRIEF) (*T*-score)								
Inhibit Scale	51.7 (9.4)	(+)	545	−2.4 (−4.7, −0.1) *	229	−0.3 (−3.3, 2.8)	498	−0.6 (−3.1, 1.8)
Shift Scale	51.1 (10.2)	(+)	545	−0.4 (−2.9, 2.1)	229	−0.5 (−4.1, 3.0)	498	−1.8 (−4.5, 0.8)
Emotional Control Scale	50.5 (10.5)	(+)	544	0.7 (−1.9, 3.2)	229	2.7 (−0.9, 6.2)	497	0.0 (−2.7, 2.7)
Behavior Regulation Index	51.3 (10.6)	(+)	544	−0.9 (−3.4, 1.7)	229	0.8 (−2.7, 4.2)	497	−0.8 (−3.5, 1.9)
Initiate Scale	48.0 (9.0)	(+)	545	0.7 (−1.6, 2.9)	229	0.8 (−2.3, 4.0)	498	0.0 (−2.4, 2.3)
Working Memory Scale	50.8 (9.4)	(+)	545	1.6 (−0.7, 3.9)	229	1.1 (−2.2, 4.4)	498	0.3 (−2.2, 2.7)
Planning Scale	48.5 (8.7)	(+)	543	0.5 (−1.6, 2.7)	229	1.1 (−2.1, 4.2)	496	0.2 (−2.0, 2.5)
Organization of Materials Scale	46.8 (9.2)	(+)	545	−1.0 (−3.3, 1.3)	229	−0.3 (−3.4, 2.8)	498	1.1 (−1.4, 3.5)
Monitor Scale	48.0 (8.9)	(+)	545	−0.3 (−2.5, 1.9)	229	0.5 (−2.6, 3.6)	498	0.7 (−1.7, 3.0)
Metacognition Index	48.3 (9.0)	(+)	544	0.4 (−1.8, 2.6)	229	0.8 (−2.3, 3.9)	497	0.4 (−1.9, 2.8)

Outcome	mean (SD)	orientation[b]	Prenatal ΣPBDE overall[c] n	Prenatal ΣPBDE overall[c] β (95% CI)	Prenatal ΣPBDE measured n	Prenatal ΣPBDE measured β (95% CI)	Child ΣPBDE n	Child ΣPBDE β (95% CI)
Global Executive Composite	49.3 (9.8)	(+)	545	0.0 (−2.3, 2.4)	229	0.9 (−2.3, 4.2)	498	−0.2 (−2.7, 2.3)

[a] All models adjusted for child sex, parity, duration of breastfeeding, preschool attendance, and age at assessment; maternal age, education, IQ (PPVT score), and depression at child age 9; maternal prenatal smoking status; family structure (father present/absent) at time of assessment; household income; HOME score at child age 10½; and psychometrician or study interviewer who administered the task or rating scale. CPT II models also adjusted for time of day assessment occurred and child video game usage at age 9.

[b] (+) higher scores indicate poorer performance/more symptomatic behavior.

[c] Includes measured and back-extrapolated PBDE concentrations.

* p<0.05

** p<0.01

Table 6

Change in child 9 and/or 12-year executive function scores per 10-fold increase in prenatal and child ΣPBDE (−47,−99,−100,−153) concentration (ng/g, lipid-adjusted) using GEE models[a] in the CHAMACOS cohort.

Outcome (assessed a t 9 and/or 12 year visits)	orientation[b]	Prenatal ΣPBDE overall[c] β (95% CI)	Prenatal ΣPBDE measured β (95% CI)	Child ΣPBDE β (95% CI)
Wisconsin Card Sort Test (WCST)				
Categories completed (raw score)	(−)	−0.2 (−0.4, 0.0)	−0.3 (−0.6, 0.0)	−0.1 (−0.3, 0.1)
Failure to maintain set (raw score)	(+)	−0.1 (−0.2, 0.1)	−0.1 (−0.3, 0.1)	0.0 (−0.2, 0.2)
Errors (*T*−score)	(−)	−2.5 (−4.6, −0.5)	−3.9 (−6.8, −1.0) *	−1.2 (−3.4, 1.0)
Perseverative errors (*T*−score)	(−)	−2.5 (−5.1, 0.2)	−5.4 (−9.1, −1.8) *	−0.6 (−3.4, 2.2)
Balloon Analogue Risk Test (raw scores)				
Number of pumps	(+)	−56.7 (−117.0, 3.6)	−38.6 (−114.1, 37.0)	33.7 (−29.2, 96.5)
Adjusted number of pumps	(+)	−35.7 (−76.2, 4.8)	−10.3 (−61.9, 41.4)	8.5 (−33.5, 50.5)
Number of explosions	(+)	−0.3 (−1.0, 0.3)	−0.4 (−1.2, 0.4)	0.3 (−0.4, 1.0)
Behavior Rating Inventory of Executive Function (BRIEF) (*T*−score)				
Inhibit Scale	(+)	−1.2 (−3.0, 0.7)	0.8 (−1.5, 3.1)	0.7 (−1.3, 2.7)
Shift Scale	(+)	0.1 (−1.9, 2.1)	1.2 (−1.3, 3.7)	−1.3 (−3.4, 0.8)
Emotional Control Scale	(+)	1.6 (−0.5, 3.6)	3.5 (0.9, 6.1) *	0.6 (−1.5, 2.8)
Behavior Regulation Index	(+)	0.2 (−1.8, 2.3)	2.2 (−0.4, 4.7)	0.2 (−2.0, 2.4)
Initiate Scale	(+)	1.1 (−0.7, 3.0)	1.7 (−0.7, 4.1)	1.0 (−1.0, 2.9)
Working Memory Scale	(+)	2.5 (0.5, 4.4) *	3.5 (1.0, 6.0) *	0.6 (−1.5, 2.7)
Planning Scale	(+)	1.3 (−0.6, 3.1)	2.4 (0.0, 4.8)	0.9 (−1.0, 2.8)
Organization of Materials Scale	(+)	0.1 (−1.9, 2.0)	1.3 (−1.2, 3.8)	2.0 (−0.1, 4.1)
Monitor Scale	(+)	0.7 (−1.2, 2.5)	2.1 (−0.3, 4.4)	1.4 (−0.5, 3.4)
Metacognition Index	(+)	1.5 (−0.5, 3.4)	2.7 (0.2, 5.1)	1.3 (−0.8, 3.3)
Global Executive Composite	(+)	1.1 (−0.9, 3.0)	2.6 (0.1, 5.1)	0.8 (−1.3, 3.0)

[a] All models adjusted for child sex, parity, duration of breastfeeding, preschool attendance, and age at assessment; maternal age, education, IQ (PPVT score), and depression at child age 9; maternal prenatal smoking status; family structure (father present/absent) at time of assessment; household income; HOME score at child age 10½; and psychometrician or study interviewer who administered the task or rating scale. WCST models also adjusted for time of day assessment occurred and child video game usage at age 9.

[b] (+) higher scores indicate poorer performance/more symptomatic behavior.

[c] Includes measured and back-extrapolated PBDE concentrations.

* p<0.05

** p<0.01

Table 7

Change in child 9 and/or 12-year attention and executive function scores per 10-fold increase in child ΣPBDE (−47, −99,−100,−153) concentration (ng/g, lipid-adjusted) using GEE models[a] stratified by sex in the CHAMACOS cohort.

		Child ΣPBDE		
Outcome (assessed at 9 and/or 12 year visits)	**orientation[b]**	**Boys β (95% CI)**	**Girls β (95% CI)**	***p*-value interaction**
Attention				
Conners' Continuous Performance Test II (CPT II) (*T*-scores)				
Errors of omission	(+)	−1.0 (−5.2, 3.3)	2.1 (− 1.7, 5.9)	0.49
Errors of commission	(+)	−0.1 (−2.8, 2.7)	−0.2 (−3.1, 2.7)	0.78
Hit rate standard error (SE) overall	(+)	−0.1 (−2,9, 2.6)	1.3 (−1.7, 4.3)	0.59
Hit rate SE by block	(+)	1.7 (−1.2, 4.6)	−0.7 (−3.7, 2.4)	0.42
Hit rate SE by inter-stimulus interval (ISI)	(+)	−1.2 (−3.8, 1.5)	1.0 (−2.0, 3.9)	0.24
ADHD Confidence Index	(+)	−0.1 (−5.3, 5.2)	1.5 (−4.2, 7.2)	0.80
Conners rating scales(CADS)- maternal report (*T*-score)				
ADHD Index	(+)	−0.2 (−2.3, 2.0)	2.2 (−0.9, 5.3)	0.18
DSM-IV total scale	(+)	0.0 (−2.3, 2.3)	3.0 (−0.2, 6.1)	0.11
Inattentive subscale	(+)	0.3 (−1.7, 2.2)	2.3 (−0.6, 5.1)	0.20
Hyperactive/Impulsive subscale	(+)	−0.6 (−3.3, 2.2)	3.1 (−0.1, 6.3)	0.07
Executive Function				
Wisconsin Card Sort Test (WCST)				
Categories completed (raw score)	(−)	−0.1 (− 0.4, 0.2)	−0.1 (−0.4, 0.2)	0.93
Failure to maintain set (raw score)	(+)	0.0 (−0.2, 0.2)	0.1 (−0.1, 0.3)	0.80
Errors (*T*-score)	(−)	−1.0 (−4.0, 2.0)	−1.7 (−4.8, 1.4)	0.58
Perseverative errors (*T*-score)	(−)	1.1 (−2.7, 3.0)	−2.7 (−6.7, 1.3)	0.13
Balloon Analogue Risk Test (raw scores)				
Number of pumps	(+)	85.9 (−0.3, 172.0)	−22.0 (−111.0, 66.9)	0.07
Adjusted number of pumps	(+)	31.7 (−24.9, 88.4)	−18.7 (−79.0, 41.7)	0.24
Number of explosions	(+)	0.7 (−0.2, 1.7)	−0.1 (−1.1, 0.9)	0.14
Behavior Rating Inventory of Executive Function (BRIEF) (*T*-score)				
Inhibit Scale	(+)	−0.4 (−3.2, 2.5)	1.5 (−1.2, 4.2)	0.21
Shift Scale	(+)	−2.8 (−5.9, 0.3)	0.2 (−2.6, 3.0)	0.09
Emotional Control Scale	(+)	−0.2 (−3.3, 2.8)	1.3 (−1.7, 4.3)	0.30
Behavior Regulation Index	(+)	−1.1 (−4.3, 2.1)	1.4 (−1.6, 4.3)	0.15
Working Memory Scale	(+)	−0.7 (−3.5, 2.1)	1.8 (−1.3, 4.9)	0.22
Planning Scale	(+)	−0.5 (−3.1, 2.1)	2.2 (−0.6, 4.9)	0.10
Organization of Materials Scale	(+)	0.4 (−2.4, 3.2)	3.6 (0.6, 6.6)*	0.10
Monitor Scale	(+)	0.6 (−2.2, 3.3)	2.5 (−0.2, 5.2)	0.22
Metacognition Index	(+)	−0.1 (−2.9, 2.6)	2.6 (−0.3, 5.6)	0.13
Global Executive Composite	(+)	−0.7 (−3.6, 2.3)	2.3 (−0.7, 5.2)	0.11

[a] All models adjusted for child sex, parity, duration of breastfeeding, preschool attendance, and age at assessment; maternal age, education, IQ (PPVT score), and depression at child age 9; maternal prenatal smoking status; family structure (father present/absent) at time of assessment; household income; HOME score at child age 10½; and psychometrician or study interviewer who administered the task or rating scale. CPT II and WCST models also adjusted for time of day assessment occurred and child video game usage at age 9.

[b] (+) higher scores indicate poorer performance/more symptomatic behavior.

[c] Includes measured and back-extrapolated PBDE concentrations.

* $p<0.05$

** $p<0.01$