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Gestational Exposure to Polybrominated Diphenyl Ethers and Social Skills and Problem Behaviors in Adolescents: The Home Study

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Gestational exposure to polybrominated diphenyl ethers and social skills and problem behaviors in adolescents: The HOME study

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ABSTRACT

Background: Polybrominated diphenyl ethers (PBDEs) are persistent environmental pollutants used as flame retardants. Gestational PBDE exposure has been associated with a variety of behavior problems in children, but little is known about its impact into adolescence, particularly on social skills, which are important for achieving social competence, establishing identity, and forming lasting relationships.

Objective: We investigated associations between gestational exposure to PBDEs and social skills and problem behaviors in early adolescence in a longitudinal pregnancy and birth cohort in Cincinnati, Ohio (recruited 2003–2006).

Methods: We measured maternal serum concentrations of five PBDE congeners during gestation. At age 12, we measured social skills and problem behaviors scores for 243 adolescents using self- and caregiver-report on the Social Skills Improvement System (SSIS). We used multivariable linear regression models to estimate associations between maternal PBDE concentrations and SSIS scores, controlling for potential covariates. We report associations for the five congeners and a summary exposure variable ($\sum_5\text{BDE}$: the sum of BDE- 28, 47, 99, 100, and 153, $n = 197$).

Results: We found sex-specific associations of $\sum_5\text{BDE}$ concentrations with adolescent-reported Problem Behaviors ($\sum_5\text{BDE} \times \text{sex } p_{\text{int}} = 0.02$) and caregiver-reported Social Skills ($\sum_5\text{BDE} \times \text{sex } p_{\text{int}} = 0.02$). In sex-stratified models, \log_{10} transformed data revealed increased maternal $\sum_5\text{BDE}$ concentration among males was associated with decreased caregiver-reported Social Skills composite score ($\beta = -10.2$, 95% CI: $-19.5, -1.0$), increased adolescent-reported Problem Behaviors composite score ($\beta = 12.1$, 95% CI: $5.4, 18.8$), and increased caregiver-reported Problem Behaviors composite score ($\beta = 6.2$, 95% CI: $0.7, 11.7$). Further analysis on SSIS subscales revealed similar patterns in significant associations among males. There were no statistically significant associations in stratified models among females despite higher $\sum_5\text{BDE}$ exposure (Female GM=40.15 ng/g lipid, GSE=1.10; Male GM=35.30 ng/g lipid, GSE=1.09).

Discussion: We found gestational PBDE exposure in males was associated with poorer behavioral outcomes, extending previous findings among this cohort into early adolescence.

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1. Introduction

Polybrominated diphenyl ethers (PBDEs) are a family of chemicals sharing a common molecular structure with 209 potential variants, or congeners. In the 1960s, PBDEs were introduced to the manufacture of household, office, and automotive products due to their ability to reduce flammability and extend burning time, a safety feature increasing time for escape in case of fire (Siddiqi et al., 2003; U.S. Environmental Protection Agency, 2009). In 2004, the US began voluntary phase-out of two of three commercial PBDE mixtures (octaBDE and pentaBDE) (U.S. Environmental Protection Agency, 2009). US discontinuation of the third commercial PBDE mixture (decaBDE) occurred in 2013 (Linares et al., 2015).

Despite the elimination of PBDEs from manufacturing in the US, exposure continues due to the stability of these chemicals and their persistence in the environment (Siddiqi et al., 2003). Continued exposure to PBDEs may occur through inhalation, ingestion, or dermal absorption. PBDEs are universally detected in the blood, tissue, and breastmilk of humans (Agency for Toxic Substances and Disease Registry, 2017). PBDEs are also transmitted from mother to fetus during gestation (Zhao et al., 2013).

Research on the consequences of prenatal PBDE exposures to child neurobehavior suggests associations with reduced intelligence (Braun et al., 2017b; Eskenazi et al., 2013; Lam et al., 2017) decreased motor skills (Eskenazi et al., 2013; Kicinski et al., 2012), increased hyperactivity (Chen et al., 2014; de Cock et al., 2012), impaired attention (Eskenazi et al., 2013; Roze et al., 2009) and increased externalizing behaviors (Braun et al., 2017b; de Cock et al., 2012). Three literature reviews have indicated that gestational PBDE exposure is negatively associated with child neurodevelopment (Berghuis et al., 2015; Gibson et al., 2018) and associated with impaired executive function and poorer attention control in youth (Berghuis et al., 2015; Vuong et al., 2018). Those reviews include recommendations for further exploration of the potential neurotoxic effects in adolescents (Vuong et al., 2018) and possible sex-dependent effects (Gibson et al., 2018; Vuong et al., 2018).

Social skills, generally the set of tools used for interpersonal interaction, are important for social competence and academic achievement (Elliott and Gresham, 1987) and the ability to form lasting relationships and participate within a community (Cacioppo, 2002). Disruptions to development of these skills can negatively affect quality of life, inducing psychological distress, social isolation, and reduced self-esteem (Beauchamp and Anderson, 2010). Ding et al. (2015) examined gestational exposure and child development at 12 and 24 months and found diminished social development with higher BDE-47 exposure at 24 months. Gascon et al. (2011) found postnatal BDE-47 exposure was associated with a higher risk of poor social competence at age 4 years. Lipscomb et al. (2017) reported an association between concurrent flame-retardant exposures (including PBDEs and organophosphate-based flame retardants) and deficits in social skills among preschool children.

The development of adequate social skills and the ability to interact successfully with adults and peers, is a critical aspect of development (Gresham, 2001) that becomes more salient during adolescence as children become more independent. To date, investigations of the relationship between gestational PBDE exposure and social development have not extended beyond childhood. The purpose of this study was to investigate the association between exposure to PBDEs during gestation, a critical neurodevelopmental period, and social skills and problem behaviors in early adolescence among a longitudinal pregnancy and birth cohort.

2. Materials and methods

2.1. Study participants

The Health Outcomes and Measures of the Environment (HOME)

Study is a longitudinal pregnancy and birth cohort in Cincinnati, Ohio, US (Braun et al., 2017a). Eligible pregnant women (N = 468) were 1) age ≥ 18 years, 2) 13–19 weeks gestation, 3) residing in a home built before 1978, 4) not taking medication for thyroid or seizure disorders, 5) not diagnosed with bipolar disorder, schizophrenia, diabetes, or cancer requiring radiation or chemotherapy, 6) fluent in English, 7) not planning to move from the area (Braun et al., 2020). Children participated in up to nine follow-up study visits beginning shortly after birth and ending most recently with a visit at age 12 years. For the age 12 visit, we attempted to contact 431 caregivers of 441 adolescents (10 twin sets), not contacting those with a deceased child, who did not provide a biological specimen during pregnancy, who previously refused any future participation, or who were unable to be located.

The institutional review boards at Cincinnati Children's Hospital Medical Center (CCHMC) and the enrolling delivery hospitals approved this study. The Centers for Disease Control and Prevention (CDC) role did not require IRB review. Mothers provided informed consent for their own participation as well as their child. Adolescents provided assent at age 12 years.

2.2. Maternal serum PBDE

We collected serum samples from pregnant mothers at the 16th and 26th weeks' gestation. Samples from the 16th week were used for analysis in all except for two mothers for whom samples were insufficient at the 16th week, so samples from the 26th week were used. As described by Vuong et al. (2015), concentrations of BDE-17, -28, -47, -66, -85, -99, -100, -153, -154, and -183 were quantified in serum (ng/g lipid) via gas chromatography/isotope dilution high-resolution mass spectrometry at the CDC (Sjödin et al., 2004). Total lipids were determined based on serum measurements of triglycerides and total cholesterol using standard enzymatic methods (Phillips et al., 1989). Analysis included five congeners with detection rates $\geq 85\%$ (BDE-28, -47, -99, -100, and -153; Supplement Table 1). Concentrations less than the limit of detection (LOD) were imputed with $\text{LOD}/\sqrt{2}$ (Hornung and Reed, 1990). The LOD was defined as three times the standard deviation of the method blank samples analyzed in parallel with the study samples in the absence of a detectable blank as 5 pg/mL (Vuong et al., 2015). Additionally, a summary exposure measure was created from the sum of the five congeners (\sum_5 BDE), with all five congeners available for 197 of 243 participants.

2.3. Outcome measurement

The Social Skills Improvement System (SSiS) (Gresham and Elliot, 2008) is a validated, broad, multi-rater measure of social skills and problem behaviors valid with youth aged 3 to 18 years. The instrument was completed by adolescents (via self-report on the student form) and their caregivers (via the parent form) during the age 12 study visit. Raw scores were converted to age-standardized composite scores using a population mean = 100 and standard deviation = 15. A composite score beyond one standard deviation from the mean (<85 or >115) is considered below or above average, respectively. The instrument provides two composite scores: Social Skills, with higher scores indicating better social skills, and Problem Behaviors, with higher scores indicating more problem behaviors. Social Skills subscales assess Communication, Cooperation, Assertion, Responsibility, Empathy, Engagement, and Self-control; Problem Behavior subscales assess Externalizing, Bullying, Hyperactivity/Inattention, Internalizing, and Autism Spectrum (caregiver form only). Standardized scores are not available for the SSiS subscales so raw scores were analyzed.

2.4. Covariates

Based on prior literature, we *a priori* selected covariates to be considered for inclusion in adjusted models (Chen et al., 2014; Vuong

et al., 2015) suggesting their potential roles as covariates of either PBDE exposure or adolescent behavior, and confounders of the relationship between PBDE exposure and adolescent behavior (Figure S1). These included adolescent sex and race (determined by self-report), maternal age at delivery; marital status, maternal education, household income, and maternal depression (measured with the Beck Depression Inventory-II, a self-report rating inventory measuring the characteristic attitudes and symptoms of depression) (Beck et al., 1996) at the age 12 study visit; maternal blood lead concentration ($\mu\text{g}/\text{dL}$) during pregnancy, and maternal serum cotinine (ng/mL) as a measure of tobacco exposure during pregnancy. At the age 12 visit, caregivers also completed the Parenting Relationship Questionnaire (PRQ) (Kamphaus and Reynolds, 2008). Based on our previous work with this measure (Volton et al., 2019), we examined the contribution from the Relational Frustration subscale that reflects the caregiver's level of stress/distress in relating to and controlling the behavior and emotions of the adolescent. We included maternal depression and relational frustration scores based on the premise that the caregiver's own mental health and perception of their relationship with their child may influence their assessment of their child's behavior as measured by the SSiS. We dichotomized continuous BDI-II scores as minimal depression (0–13) or greater than minimal depression (≥ 13). Women with elevated scores were offered support and resources related to depression prior to the completion of the study visit.

2.5. Statistical analysis

We first conducted univariate analyses on the PBDE concentrations, SSiS scores, and covariates, examining data distributions and patterns of missing information. We \log_{10} -transformed PBDE concentrations prior to further analysis to reduce the influence of outliers. We compared scores for adolescent- versus caregiver-report for composite scores and subscales with an equal number of test items using paired t-tests; we compared the mean of each participant's summed responses for subscales with differing numbers of test items between adolescent- and caregiver-report.

We examined associations between gestational PBDE concentrations and SSiS scores using multivariable linear regression models. In adjusted analysis, we included covariates described earlier in the full models. Using step-wise backward elimination, we retained covariates in the adjusted models if they were significantly ($p < 0.05$) associated with the outcome or if their removal resulted in over 10% change in the PBDE estimate. Final regression models retained the following covariates: adolescent sex and race; maternal age at delivery, maternal depression at age 12, gestational serum cotinine concentration, caregiver relationship frustration at age 12, and household income at age 12. We then evaluated the presence of the sex by PBDE interaction by including a sex \times PBDE product term in the regression models. We considered the interaction to be statistically significant if the p-value of the interaction term was < 0.10 . After noting the sex by PBDE interaction was significant for multiple congeners and composite SSiS scores, we completed multivariable regression analyses stratified by sex.

Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., 2013), and a two-sided significance level of 0.05 was used.

3. Results

3.1. Study participant characteristics

Serum PBDE was measured in the 16th week of gestation for 384 mothers of 394 children (10 twin sets) in the study. There were 441 adolescents of 431 mothers who were eligible for the age 12 study visit, with 256 adolescents (58%) completing the visit. Of these, 250 adolescents and 255 caregivers completed the SSiS. The final cohort of those with both available gestational PBDE concentrations and completed SSiS included 243 adolescents (7 twin sets) and 236 caregivers.

Fifty-six percent of adolescents were female and 58% were non-Hispanic white, while 86% of mothers attended at least some college, and mean household income at age 12 was \$86,512 USD (Table 1). Mean age of female participants was 12.3 years (range 11.0–14.2 years); mean age of male participants was 12.4 years (range 11.0–14.1 years). We compared demographics and covariates for caregivers and adolescents who participated in the age 12 visit compared with those from the original cohort who did not participate, finding no statistically significant differences between groups with the exception of higher mean maternal blood lead ($\mu\text{g}/\text{dL}$) in the those who did not participate (0.76 v. 0.69, $p = 0.03$). Caregivers indicated a diagnosis of Autism Spectrum Disorder in $< 2\%$ of participants ($n = 4$; Female = 1, Male = 3).

3.2. Maternal serum PBDE

Compared with a national cohort of pregnant women (Woodruff et al., 2011), mothers in this study had modestly lower GM serum concentrations for all PBDE congeners (Table 2). The geometric mean (GM) of \sum_5 BDE in maternal serum was 38.0 ng/g lipid, and geometric standard error (GSE) was 1.07 among all participants. BDE-47 (GM = 20.5, GSE = 1.06) was the largest contributor to the summary measure. Stratified by sex, gestational \sum_5 BDE concentrations and composite scores for Social Skills and Problem Behaviors were similar among males and females (Table 3).

3.3. SSiS

Among adolescent participants, 17% scored lower than average (< 85) for Social Skills and 7% scored higher than average (> 115) for Problem Behaviors. Among caregivers, 18% reported lower than average (< 85) Social Skills and 8% reported higher than average (> 115)

Table 1
Selected characteristics of HOME Study participants included in the analysis.

	n (%)
Total Cohort	243 (100)
Adolescent Sex	
Female	135 (56)
Male	108 (44)
Adolescent Race	
Non-Hispanic White	141 (58)
Non-Hispanic Black	87 (36)
Hispanic	5 (2)
Asian/Pacific Islander	8 (3)
Native American	2 (1)
Maternal Age at Delivery (years)	
< 25	57 (23)
25–34	153 (63)
≥ 35	33 (14)
Maternal Marital Status	
Married or living with partner	185 (76)
Not married and living alone	58 (24)
Maternal Education	
High school or less	34 (14)
Some college or 2-year degree	75 (31)
Bachelor's degree	71 (29)
Graduate or professional	63 (26)
Maternal Depression (BDI-II)	
Minimal (0–13)	209 (86)
Mild, Moderate, or Severe (> 13)	34 (14)
	M \pm SD
Household Income in USD	86,512 \pm 52,016
PRQ: Relational Frustration	48.14 \pm 9.08
Maternal gestational blood lead ($\mu\text{g}/\text{dL}$)	0.69 \pm 0.28
	GM (GSD)
Maternal gestational serum cotinine (ng/dL)	0.08 (16.34)

Abbreviations: BDI-II, Beck Depression Inventory-II; GM, geometric mean; GSD, geometric standard deviation; M, Mean; PRQ, Parenting Relationship Questionnaire; SD, standard deviation; USD, United States Dollar.

Table 2
Gestational PBDE concentrations (ng/g lipid) by congener.

PBDE Congener	N (% male)	Percentage of Samples \geq LOD	Min	25th	50th	75th	95th	Max	GM (GSE) ^a	NHANES ^b GM (GSE)
BDE-28	197 (42%)	89%	0.3	0.6	1.0	1.7	4.6	16.7	1.1 (1.06)	NA
BDE-47	243 (44%)	99%	2.2	10.6	19.6	34.8	92.2	539.0	20.5 (1.06)	23.9 (2.2)
BDE-99	234 (44%)	99%	0.6	2.4	4.5	7.9	29.9	193.0	4.8 (1.07)	5.5 (0.8)
BDE-100	233 (44%)	96%	0.4	2.0	3.6	6.8	20.0	107.0	3.9 (1.07)	6.1 (0.9)
BDE-153	237 (44%)	95%	0.6	2.5	4.2	8.4	36.3	152.0	4.8 (1.07)	9.9 (3.0)
\sum_5 BDE	197 (42%)	NA	5.2	19.8	35.5	66.7	213.7	905.8	38.0 (1.07)	NA

Abbreviations: LOD, Limit of Detection; GM, Geometric Mean (ng/g lipid); GSE, Geometric Standard Error; N, number of samples with quantity sufficient for analysis; NA, Not available; PBDE, Polybrominated Diphenyl Ether; \sum_5 BDE, sum of Polybrominated Diphenyl Ether congeners BDE-28, -47, -99, -100, and -153.

^a Geometric Mean includes imputed values (LOD/ $\sqrt{2}$) for results less than the limit of detection.

^b Serum concentrations in NHANES (National Health and Nutrition Examination Survey) 2003–2004 pregnant women (Woodruff et al., 2011).

Table 3
 \sum_5 BDE concentrations and SSiS composite scores by sex. Higher score indicates better social skills and more problem behaviors.

	Male		Female	
	M (SD)	n (%)	M (SD)	n (%)
Problem Behaviors Composite Score – Caregiver report	95.9 (11.6)	108 (44%)	97.2 (12.7)	135 (56%)
Problem Behaviors Composite Score – Adolescent Report	95.2 (11.6)	105 (44%)	95.0 (12.8)	134 (56%)
Social Skills Composite Score – Caregiver Report	97.8 (13.6)	108 (44%)	100.1 (16.3)	135 (56%)
Social Skills Composite Score – Adolescent Report	97.2 (17.6)	105 (44%)	101.0 (16.2)	134 (56%)
	GM (GSE)	n (%)	GM (GSE)	n (%)
\sum_5 BDE	35.30 (1.09)	83 (42%)	40.15 (1.10)	114 (58%)

Abbreviations: GM, Geometric Mean (ng/g lipid); GSE, Geometric Standard Error; M, Mean; SD, Standard Deviation; \sum_5 BDE, sum of Polybrominated Diphenyl Ether congeners BDE-28, -47, -99, -100, and -153.

Problem Behaviors in their adolescent. Standardized composite SSiS scores for adolescent self-report (Social Skills: M = 99, SD = 15; Problem Behaviors: M = 97, SD = 12) and caregiver report (Social Skills: M = 99, SD = 17; Problem Behaviors: M = 95, SD = 12) were moderately correlated (Social Skills: $r = 0.3$, $p < 0.001$; Problem Behaviors: $r = 0.4$, $p < 0.001$). Adolescents reported significantly higher scores than their caregivers reported on composite Problem Behaviors (Mean difference = 1.7, 95% CI: 0.0, 3.3) and Externalizing, Bullying, Hyperactivity/Inattention, Internalizing, and Self-Control subscales, while reporting significantly lower scores on the Assertion and Communication subscales for Social Skills (Supplement Table 2).

In unadjusted analyses, we found each ten-fold increase in gestational BDE-47 concentration was associated with lower caregiver-reported composite Social Skills scores, such that as maternal PBDE concentrations during pregnancy increased, caregivers reported poorer social skills among their children. We also found a ten-fold increase in gestational BDE-28, -47, -99, and \sum_5 BDE concentration was associated with higher adolescent-reported composite Problem Behavior scores (Supplement Table 3), such that as maternal PBDE concentrations increased, adolescent report of problem behaviors increased.

In adjusted analyses, we found the presence of significant PBDE by sex interaction. For example, the PBDE \times sex interaction terms were significant in the associations of \sum_5 BDE concentrations with adolescent-reported Problem Behaviors ($p_{\text{int}} = 0.02$) and with caregiver-reported Social Skills ($p_{\text{int}} = 0.02$). Therefore, we conducted sex-stratified analyses for all models. In the adjusted models stratified by sex, we found no significant association between maternal serum PBDE and SSiS scores among female adolescents. In contrast, among male adolescents, higher PBDE concentrations were significantly associated with decreased caregiver-reported Social Skills (BDE-47, -99, -100, -153, and \sum_5), and increased adolescent- and caregiver-reported Problem Behaviors (BDE-28, -47, -99, -100, and \sum_5 and BDE-28, -47, and \sum_5 , respectively) (Table 4). For example, among male adolescents, \log_{10} transformed data revealed that with each 10-fold increase in maternal \sum_5 BDE concentration, there was a 10.2 point decrease (95%CI: -19.5, -1.0) in caregiver-reported Social Skills composite scores, a 12.1 point (95%CI: 5.4, 18.8) increase in adolescent-reported

Problem Behaviors composite scores, and a 6.2 point (95%CI: 0.7, 11.7) increase in caregiver-reported Problem Behaviors composite scores. Additional associations are presented in Table 4.

When we further examined SSiS subscales for the male adolescents, in Social Skills subscales, we found a 10-fold increase in maternal \sum_5 BDE concentration was significantly associated with lower scores for caregiver report on Cooperation ($\beta = -2.1$, 95%CI: -4.0, -0.3) and Responsibility ($\beta = -2.8$, 95%CI: -4.7, -0.8). For Problem Behavior subscales, we found significantly higher scores for caregiver report on Externalizing ($\beta = 2.8$, 95%CI: 0.9, 4.7) and Hyperactivity/Inattention ($\beta = 2.5$, 95%CI: 0.6, 4.4), and significantly higher scores for adolescent-report on Externalizing ($\beta = 4.2$, 95%CI: 1.6, 6.9), Bullying ($\beta = 1.2$, 95%CI: 0.3, 2.1), Hyperactivity/Inattention ($\beta = 3.6$, 95%CI: 1.1, 6.1), and Internalizing ($\beta = 4.4$, 95%CI: 1.7, 7.1) (Table 5).

4. Discussion

In this longitudinal cohort study, we found that higher gestational PBDE exposure was associated with poorer social skills and more problem behaviors in males. For caregiver report, we found that higher PBDE exposure was associated with poorer overall social skills in males, especially for cooperation and responsibility. For both adolescent self-report and caregiver-report, we found higher PBDE exposure was associated with increased problem behaviors in males, especially for increased externalizing behaviors such as bullying, hyperactivity, and inattention. Importantly, significant associations emerged only upon stratification by sex and were not detected in females.

Previous studies from this cohort at earlier ages (1 to 8 years) have found gestational exposure to PBDEs within the cohort to be associated with behavioral outcomes including more externalizing problems at ages 1 to 8 years (Braun et al., 2017a, 2017b; Chen et al., 2014; Zhang et al., 2017), increased hyperactivity at ages 2–5 years (Chen et al., 2014), and poorer behavioral regulation at ages 1–8 years (Vuong et al., 2016). No significant associations have been found in this cohort between PBDE exposure and measures of inattention or impulsivity at age 8 years (Vuong et al., 2017), or adaptive skills and internalizing problems at ages 2 to 5 years (Chen et al., 2014). The findings from this study

Table 4

Estimated score differences and 95% confidence intervals in adolescent- and caregiver-reported SSIS composite scale standardized scores at age 12 years by a 10-fold increase in maternal PBDE concentrations, stratified by sex. Higher score indicates better social skills and more problem behaviors.

	Social Skills Scale					
	Adolescent-reported			Caregiver-reported		
	Female	Male	P _{int}	Female	Male	P _{int}
BDE-28	-4.1 (-12.1, 4.0)	-3.6 (-13.2, 6.1)	0.95	0.8 (-6.0, 7.5)	-10.1 (-20.4, 0.2)	0.01
BDE-47	-2.0 (-8.4, 4.5)	0.3 (-7.1, 7.7)	0.38	1.08 (-4.4, 6.3)	-11.2 (-19.1, -3.4)*	0.03
BDE-99	-2.3 (-8.7, 4.2)	-0.8 (-8.5, 6.8)	0.49	0.8 (-4.5, 6.1)	-10.6 (-18.8, -2.5)*	0.07
BDE-100	-1.8 (-8.1, 4.5)	3.4 (-4.0, 10.8)	0.11	2.6 (-2.6, 7.8)	-9.1 (-17.0, -1.1)*	0.11
BDE-153	-0.9 (-7.3, 5.5)	2.2 (-4.1, 8.5)	0.28	1.8 (-3.5, 7.0)	-7.4 (-14.2, -0.6)*	0.14
Σ₅ BDE	-2.7 (-10.2, 4.8)	0.5 (-8.3, 9.4)	0.37	2.4 (-3.8, 8.7)	-10.2 (-19.5, -1.0)*	0.02

	Problem Behaviors Scale					
	Adolescent-reported			Caregiver-reported		
	Female	Male	P _{int}	Female	Male	P _{int}
BDE-28	1.4 (-4.5, 7.4)	14.6 (7.3, 21.8)*	0.09	0.4 (-4.4, 5.2)	6.6 (0.5, 12.6)*	0.09
BDE-47	1.4 (-3.4, 6.1)	10.1 (4.0, 16.3)*	0.01	-0.7 (-4.4, 2.9)	6.2 (1.2, 11.2)*	0.09
BDE-99	2.5 (-2.3, 7.2)	9.6 (3.2, 15.9)*	0.02	0.7 (-3.0, 4.4)	5.0 (-0.2, 10.3)	0.21
BDE-100	0.7 (-4.0, 5.4)	7.6 (1.3, 13.9)*	0.01	-0.1 (-3.7, 3.5)	4.2 (-0.9, 9.3)	0.27
BDE-153	-0.8 (-5.6, 3.9)	5.1 (-0.3, 10.6)	0.04	-0.1 (-3.7, 3.6)	4.0 (-0.3, 8.3)	0.27
Σ₅ BDE	1.0 (-4.5, 6.6)	12.1 (5.4, 18.8)*	0.02	-0.2 (-4.7, 4.3)	6.2 (0.7, 11.7)*	0.08

All reported as β (95% CI); * p < 0.05; pint = p-value for interaction term for child sex by PBDE.

Adjusted by adolescent race, maternal age at delivery, household income at 12 years, maternal Beck Depression Inventory-II score at the age 12 years visit, Parenting Relationship Questionnaire relational frustration score at the age 12 years visit, and maternal serum cotinine.

Table 5

Estimated score differences and 95% confidence intervals in adolescent- and caregiver-reported SSIS subscale raw scores at age 12 years by a 10-fold increase in maternal Σ₅ BDE concentration. Higher score indicates better social skills and more problem behaviors.

Social Skills Subscale	Adolescent-reported		Caregiver-reported	
	Female	Male	Female	Male
Communication	-0.1 (-1.8, 1.5)	-0.7 (-2.5, 1.2)	0.7 (-0.6, 2.0)	-0.7 (-2.7, 1.3)
Cooperation	-0.1 (-1.9, 1.7)	-0.9 (-3.3, 1.5)	0.0 (-1.2, 1.3)	-2.1 (-4.0, -0.3)*
Assertion	-0.0 (-2.0, 2.0)	0.4 (-1.9, 2.6)	0.9 (-0.6, 2.3)	-1.8 (-3.8, 0.2)
Responsibility	-0.1 (-1.8, 1.5)	-0.6 (-2.8, 1.6)	0.1 (-1.3, 1.5)	-2.7 (-4.7, -0.8)*
Empathy	-0.9 (-2.3, 0.5)	0.9 (-1.1, 2.9)	0.9 (-0.6, 2.3)	-1.5 (-3.7, 0.7)
Engagement	-1.0 (-3.0, 1.0)	0.8 (-1.6, 3.2)	-0.2 (-1.6, 1.3)	-1.4 (-3.8, 1.0)
Self-Control	-0.6 (-2.3, 1.1)	0.4 (-1.5, 2.3)	-0.2 (-1.9, 1.4)	-1.7 (-4.1, 0.6)

Problem Behaviors Subscale	Adolescent-reported		Caregiver-reported	
	Female	Male	Female	Male
Externalizing	-0.6 (-3.1, 1.9)	4.2 (1.6, 6.9)*	0.6 (-0.9, 2.1)	2.8 (0.9, 4.7)*
Bullying	-0.1 (-1.0, 0.9)	1.2 (0.3, 2.1)*	-0.2 (-0.7, 0.3)	0.3 (-0.3, 0.9)
Hyperactivity/Inattention	0.6 (-1.4, 2.5)	3.6 (1.1, 6.1)*	0.0 (-1.1, 1.2)	2.5 (0.5, 4.4)*
Internalizing	1.3 (-0.6, 3.3)	4.4 (1.6, 7.1)*	0.3 (-1.3, 2.0)	0.9 (-0.8, 2.5)
Autism Spectrum	-	-	-0.2 (-2.1, 1.6)	1.6 (-1.5, 4.8)

All reported as β (95% CI).

Adjusted by adolescent race, maternal age at delivery, household income at 12 years, maternal depression at 12 years, Parenting Relationship Questionnaire relational frustration score at 12 years, and maternal serum cotinine.

* p < 0.05.

further corroborated the potential adverse impact of gestational exposure to PBDEs on several problem behaviors and extended the prior findings into early adolescence.

Very few studies have investigated the relationship between PBDE exposures and social skills. Gascon et al. (2011) found a statistically significant association between BDE-47 exposure at age 4 years and concurrently higher risk of poor social competence. Ding et al. (2015) found increased gestational BDE-47 exposure was associated with a decrease in the social domain developmental quotient in children at age two years. Hoffman et al. (2012) found lactational exposure to BDE-47, -99, and -100 was associated with increased externalizing behavior problems at the age of 30 months. Roze et al. (2009) reported mixed results among school-age children, with better behavior but poorer attention correlated with prenatal PBDE concentrations. Eskenazi et al. (2013) similarly found prenatal PBDE concentrations were associated

with impaired attention among school-aged children. Lipscomb et al. (2017) found a cross-sectional relationship between PBDE exposure over a 7-day period and concurrent teacher-reported SSIS scores in children ages 3 to 5 years, such that increased PBDE exposure was associated with lower scores in the Assertion sub-scale. Although the child age group, exposure windows, and reporter differ between our study and Lipscomb et al. (2017), we also found PBDE exposure was significantly associated with lower caregiver-reported scores on the Assertion sub-scale among adolescent males. Importantly, while previous investigations of gestational PBDE exposure examined effects in childhood, ours is the first to examine these associations into adolescence.

A strong body of evidence supports the increased vulnerability of male fetuses to environmental toxicants including lead (Wang et al., 2017), maternal substance use (DiPietro and Voegtline, 2017), and pesticides (DiPietro and Voegtline, 2017), among others. The

associations between PBDEs and neurodevelopmental outcomes are also proposed to differ by sex (Gibson et al., 2018). Sagiv et al. (2015) found child PBDE levels were associated with poorer caregiver-reported attention and executive function for females at age 9 years but not males, and an isolated finding of prenatal PBDE exposure and significantly higher errors of omission on the Connors' Continuous Performance Test II (CPT II) for males than females. Similarly, Vuong et al. (2017) found associations with concurrent PBDE exposure such that 8-year-old males performed more poorly on inattention measures than females with regard to omission errors and measures of reaction times. Thus, our finding of significant associations of gestational PBDE exposure and increased problem behaviors and decreased social skills in males at age 12 supports previous findings of both social deficits related to PBDE exposure, and sex differences in those relationships. It was first suggested that the nervous system of developing males is more vulnerable to exposures than females over three decades ago, and this suggestion has subsequently been supported (DiPietro and Voegtline, 2017). However, although the relationship between child sex and neurodevelopment has been long-studied, mechanisms remain largely unknown. As efforts will undoubtedly continue toward discovering mechanisms for the increased vulnerability of male fetuses to environmental toxicants, precision medicine may offer the best opportunity to discern differences in susceptibility by sex (Torres-Rojas and Jones, 2018).

Measurement of social skills by both self-report and caregiver-report strengthened the study; single-reporter outcomes may fail to fully assess internalizing and externalizing behaviors, especially among adolescents. It has previously been reported that caregivers and their offspring frequently report psychiatric symptoms differently, with children and adolescents reporting more severe symptoms than their caregivers, possibly due to caregivers' unawareness of symptom severity (Moretti et al., 1985; Stanger and Lewis, 1993). By definition, internalizing symptoms are more difficult for others to detect, whereas externalizing symptoms, including many social skills and problem behaviors, project outward and are more evident to others. While we found moderate correlation between adolescent report and caregiver report for both Social Skills and Problem Behaviors composite scores, we found significantly different mean values between adolescent-report and caregiver-report for four of the seven Social Skills subscales, the Problem Behaviors composite scores, and all Problem Behavior subscales. Interestingly, adolescents reported generally poorer social skills and generally higher problem behaviors than their caregivers reported, indicating adolescents are perhaps more critical of their own social skills than are their caregivers, or perhaps caregivers are not accurate assessors of adolescent social skills. Our findings support future studies using self-report for investigating effects on adolescent social skills.

Study strengths include longitudinal data from a pregnancy and birth cohort, allowing examination of the relationship between gestational PBDE exposures and outcomes in adolescence. Additionally, we had the ability to measure multiple potential covariates including maternal blood lead and serum cotinine levels and concurrent demographic variables. While previous studies have focused on postnatal and sometimes concurrent exposure with measurement of social skills, our investigation of gestational exposure shows stronger associations and may allude to sensitive periods of exposure.

There are some limitations to this study. Although we have included comprehensive potential covariates and confounders based on known and theorized relationships between PBDE exposure and social skills, as with all observational studies, the possibility of residual confounding cannot be ruled out. Future analyses may benefit from the incorporation of a directed acyclic graph (DAG) for determining adjustment sets *a priori*. We examined ten PBDE congeners, focusing our analysis on the five congeners with the highest detection rates. While we expect our summary PBDE metric to encompass the preponderance of gestational PBDE exposure, there may be differences in participant exposure postnatally. The relatively high socioeconomic status of the cohort and

higher concentrations of PBDE in the US compared with other countries may limit global generalizability of these findings.

5. Conclusion

Social skills in adolescence are important for achieving social competence, establishing identity, and forming lasting relationships. We found exposure to PBDEs during gestation was associated with decreased social skills and increased problem behaviors among males in early adolescence. Demonstrating poorer social skills and more problem behaviors may inhibit the formation of healthy interpersonal relationships and negatively affect identity formation during this critical developmental stage. Importantly, this study expanded on previous studies to examine the effects of prenatal exposure to PBDEs, finding continued consequences into adolescence. Additionally, our findings underscore that the effects of PBDE exposure may vary by sex, adding to the body of evidence supporting the increased vulnerability of male fetuses to environmental toxicants.

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The authors declare they have no actual or potential competing financial interests.

7. Data sharing

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2021.107036>.

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