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Polybrominated Diphenyl Ether (PBDE) and Poly- and Perfluoroalkyl Substance (PFAS) Exposures During Pregnancy and Maternal Depression

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Polybrominated diphenyl ether (PBDE) and poly- and perfluoroalkyl substance (PFAS) exposures during pregnancy and maternal depression

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ABSTRACT

Background: Experimental studies in rodents suggest that polybrominated diphenyl ethers (PBDEs) and poly- and perfluoroalkyl substances (PFAS) may contribute to depressive symptoms. Few studies have examined the impact of these chemicals on depression in adults.

Objective:

To examine the associations between serum PBDE and PFAS concentrations during pregnancy and repeated measures of depressive symptoms in women assessed from pregnancy to 8 years postpartum.

Methods:

This study was based on 377 women from the Health Outcomes and Measures of the Environment Study, a birth cohort in Cincinnati, OH (USA). PBDEs (BDE-28, -47, -99, -100, -153, and ΣPBDEs) and PFAS (perfluorooctanoate [PFOA], perfluorooctane sulfonate [PFOS], perfluorohexane sulfonate [PFHxS], perfluorononanoate [PFNA]) were quantified in maternal serum at 16 ± 3 weeks gestation. Depressive symptoms were measured using the Beck Depression Inventory-II (BDI-II) at ~20 weeks gestation and up to seven times during postpartum visits (4 weeks, 1, 2, 3, 4, 5, and 8 years). We used linear mixed models to estimate covariate-adjusted associations between chemical concentrations and repeated measures of BDI-II. Multinomial logistic regression models were used to estimate the relative risk ratios of having a medium or high depression trajectory.

Results:

We found that a 10-fold increase in BDE-28 at 16 ± 3 weeks gestation was associated with significantly increased BDI-II scores (β = 2.5 points, 95% confidence interval [CI] 0.8, 4.2) from pregnancy to 8 years postpartum. Significant positive associations were also observed with BDE-47, -100, -153, and ΣPBDEs. A 10-fold increase in ΣPBDEs was associated with a 4.6-fold increased risk (95% CI 1.8, 11.8) of a high trajectory for BDI-II compared to a low trajectory. We observed no significant associations between PFAS and BDI-II scores.

Conclusion:

PBDEs during pregnancy were associated with more depressive symptoms among women in this cohort.

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1. Introduction

The prevalence of clinically significant depression in women, defined as severe symptoms affecting various aspects of daily life that persists for at least two weeks, ranges from 10 to 23% during pregnancy and postpartum (Bennett et al., 2004; Ertel et al., 2011; Mayberry et al., 2007). Women who experience symptoms of depression during this time may face many issues, including more sexual problems, deficient social support systems, increased risk of anemia, increased anxiety and fatigue, loss of sleep, and more harmful health behaviors, including alcohol and substance abuse (Asselmann et al., 2016a, 2016b; Kang et al., 2020; Zuckerman et al., 1989). Maternal depression is also associated with lower maternal functioning. Studies report that mothers with depression are less sensitive to child cues, provide less positive stimulation, have more parenting difficulties, and are less adherent to medical and preventive practices than their non-depressed counterparts (Coyl et al., 2002; Field, 2002; Leiferman, 2002; McLennan and Kotelchuck, 2000; Pelaez et al., 2008). Maternal depression has been documented to adversely affect offspring health, from infancy to adolescence (Campbell et al., 2009; Field et al., 2006; Goodman et al., 2011; Stewart, 2007). Children of depressed mothers are more likely to experience general psychopathology, exhibit more internalizing and externalizing problems, suffer from diminished cognitive functioning, and display suboptimal physical growth (Ertel et al., 2010; Goodman et al., 2011; Hay et al., 2008). Maternal depression during childhood is also associated with poorer academic performance (Murray et al., 2010). Adverse cognitive and behavioral outcomes in children may persist even after remission of maternal depression (Moehler et al., 2006; Murray, 1992; Murray et al., 1996), although some studies suggest psychotherapy and antidepressant treatment can improve outcomes for both women and their children (Goodman and Garber, 2017). Studies have found that alleviating maternal depression can improve children's mental health as well as reducing internalizing and externalizing behavioral problems (Cuijpers et al., 2015; Forman et al., 2007).

Depression is affected by alterations in the hypothalamic-pituitary-thyroid axis (Loh et al., 2019). In addition, dopamine dysfunction, particularly diminished dopaminergic neurotransmission, is involved in the pathophysiology of depression (Dunlop and Nemeroff, 2007). Reductions in dopamine release and impairments in signal transduction are potential underlying mechanisms contributing to depressive symptoms. Polybrominated diphenyl ethers (PBDEs) and poly- and perfluoroalkyl substances (PFAS) are endocrine disrupting chemicals that may play a role in the pathomechanism of depression by disrupting dopamine and thyroid function - similar to that observed for exposure to polychlorinated biphenyls (PCBs), which are structurally similar to PBDEs and share physiochemical properties (Gaum et al., 2019).

PBDEs are flame retardants that were used in polyurethane foam for furniture and carpet padding and in the hard plastic casings in appliances and electronics. Despite the phase out of Penta- and OctaBDE in 2004 and DecaBDE subsequently in 2013 (Linares et al., 2015), BDE-28, -47, -99, -100, and -153 were still detected in > 90% of the general U.S. population in the National Health and Nutrition Examination Survey (NHANES) for the years 2005/2006 through 2013/2014 (Sjodin et al., 2019). Interest in PBDEs as potential chemicals of concern for depression stem from their similar structure and toxicological properties to PCBs, which have been documented to interfere with the dopamine system by disrupting tyrosine hydroxylase activity, disturbing dopamine transport, and affecting dopamine metabolism (Choksi et al., 1997; Fonnum and Mariussen, 2009; Putschogl et al., 2015; Seegal et al., 2010). PBDEs have also been reported to disrupt the dopaminergic system (Bradner et al., 2013; Slotkin et al., 2013; Wang et al., 2015). PFAS may play a role in the etiology of neuropsychiatric disorders by altering dopaminergic synapses, disturbing dopaminergic gene transcription, modifying neuronal activity, and inhibiting gene and protein expression of dopamine receptors (Hallgren and Viberg, 2016; Patel et al., 2016; Salgado et al., 2016). Both PBDEs and PFAS have been identified to disrupt thyroid hormones in humans (Ballesteros et al., 2017; Czerska et al., 2013; Herbstman and Mall, 2014; Kim et al., 2018). PBDEs may disrupt thyroid hormone homeostasis via competitive binding to thyroid hormone receptors and thyroid transport protein transthyretin as well as inducing thyroxine glucuronidation, thereby increasing thyroxine clearance (Meerts et al., 2000; Richardson et al., 2008; Zhou et al., 2002). Reductions in thyroxine observed with PFAS exposure may be due to increased metabolism from upregulating hepatic transport proteins, increased glucuronidation, upregulated deiodinase enzyme DIO1, and displaced thyroxine-bound receptors (Chang et al., 2008; Weiss et al., 2009; Yu et al., 2009; Yu et al., 2011). Hypothyroidism and subclinical hypothyroidism have been associated with depressive symptoms (Hage and Azar, 2012; Loh et al., 2019).

No study has examined PBDEs or PFAS during pregnancy and maternal depression. Given the potential for PBDEs and PFAS to contribute to the pathophysiology of depression based on mechanisms demonstrated by PCBs as well as the relatively long half-lives of these compounds in the human body, we investigated the relationship between serum concentrations of PBDEs and PFAS among women in their early second trimester of pregnancy and depressive symptoms from pregnancy to 8 years postpartum. In addition to analysis of outcome at an individual time point, we examined the trajectories of depressive symptoms to reflect patterns of symptom change during this period. We hypothesize that PBDE and PFAS concentrations during pregnancy are associated with more depressive symptoms in women as well as a trajectory of depression throughout the period.

2. Methods

2.1. Study design and cohort

The Health Outcomes and Measures of the Environment (HOME) Study is an ongoing prospective pregnancy and birth cohort of mother-child dyads in the greater Cincinnati area (Braun et al., 2017a). Pregnant women were recruited from March 2003 to February 2006 from nine prenatal clinics if they met the following inclusion criteria: (1) 18 years of age; (2) 16 ± 3 weeks of gestation; (3) residing in housing constructed before 1978; (4) receiving and planning to continue prenatal care and deliver at one of the collaborating obstetric practices; (5) HIV- status; and (6) not taking any medications related to seizures, thyroid disorders, or chemotherapy/radiation. Of the 1263 eligible women identified via clinical records and phone interviews, there were 468 women who enrolled and 390 who subsequently delivered liveborn singletons. Follow-up visits consisted of home visits, telephone interviews, and clinic visits. Participants missing a particular follow-up visit (e.g., 2 year postpartum) were not excluded from the study and might complete a subsequent follow-up visit (e.g., 5 years postpartum). The availability of at least one assessment of depressive symptoms was a requirement to be included in the present study, as a longitudinal mixed model was employed. A total of 377 had at least one assessment of depressive symptoms from baseline to 8 years postpartum and a measurement of either PBDEs or PFAS quantified at enrollment. Of these women, biomonitoring was completed during pregnancy for the following: 96% (n = 361) for PBDEs, 94% (n = 360) for PFAS, and 90% (n = 339) for both chemical classes. The study protocol was approved by the Institutional Review Board (IRB) at the Cincinnati Children's Hospital Medical Center (CCHMC). The Centers for Disease Control and Prevention (CDC) deferred to CCHMC IRB as the IRB of record.

2.2. Concentrations of PBDEs and PFAS

Maternal blood samples were collected at ~16 ± 3 weeks gestation. Serum was separated and stored at −70 °C until analysis. Details regarding quality assurance, quantification procedures, and lipid

adjustment have been described previously (Vuong et al., 2016). Briefly, gas chromatography/isotope dilution high-resolution mass spectrometry was used to quantify PBDE congeners -17, -28, -47, -66, -85, -99, -100, -153, -154, and -183 (Jones et al., 2012; Sjodin et al., 2004). For the present study, we focused on PBDE congeners BDE-28, -47, -99, -100, and -153, as well as their sum (ΣPBDEs), which had detection frequencies > 87% (see Supplemental Table S1). Because detection frequencies were high and percentages of PBDE measurements below the limit of detection (LOD) were low, we substituted values < LOD with LOD/√2 as recommended by Hornung and Reed (1990).

PFAS compounds, including perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA), were measured using on-line solid-phase extraction coupled to high-performance liquid chromatography-isotope dilution-tandem mass spectrometry (Kato et al., 2011). For women without PFAS measurements at 16 ± 3 weeks, we substituted measurements quantified at 26 weeks gestation (n = 35) or at parturition (n = 17). For those with > 1 measurement during pregnancy (n = 70), an average was used for prenatal PFAS. All PFAS compounds were detected in all serum samples (see Supplemental Table S1). PBDEs and PFAS concentrations were $\log_{10}$- and ln-transformed (due to a lower range of concentrations), respectively, to reduce the influence of outliers.

2.3. Maternal depression

Maternal depressive symptoms were measured using the Beck Depression Inventory-II (BDI-II) at ~20 weeks of gestation and seven postpartum visits, including 4 weeks, 1, 2, 3, 4, 5, and 8 years (Beck et al., 1996). For the majority of women, the BDI-II was self-administered. In a few cases when literacy was in question, it was administered orally by a research assistant. All research assistants were trained in proper administration and scoring of the measure by a developmental psychologist with over 25 years of experience in test administration, scoring, and interpretation. The 21-item questionnaire consisted of areas related to mental and somatic components of depression. Symptoms of depression may include feelings of hopelessness or irritability, and signs of depression may manifest physically, such as feeling fatigue, experiencing weight loss, or lacking interest in sex. Responses were rated on a 4-point Likert scale, from 0, "not at all," to 3, "severely." Total scores on the BDI-II ranged from 0 to 63, with scores ≤13 considered "minimally depressed," 14–19 considered "mildly depressed," 20–28 considered "moderately depressed," and > 28 considered "severely depressed." Because of the low percentages of HOME Study women who had BDI-II scores considered moderately, severely, or clinically depressed, we categorized BDI-II scores into > 13 as women exhibiting "some depressive symptoms," and ≤13 as women exhibiting "little to no depressive symptoms" (see Supplemental Table S2). Research coordinators executing the study visits did not have knowledge of the participants' previous responses on the measure. They also did not have information about specific exposures of interest at the time of the study visit. Protocols for explaining the BDI-II, providing instructions for its completion, review and tally of total scores according to the published manual, and delivery of intervention (as needed) were employed to ensure standardization of the process across all study participants.

2.4. Statistical methods

Intraclass correlation coefficients were calculated for BDI-II scores measured at 8 visits. We used linear mixed models to estimate βs and 95% confidence intervals (CIs) for individual PBDEs, ΣPBDEs, and the four individual PFAS in relation to repeated measurements of BDI-II scores assessed from ~20 weeks of gestation to 8 years postpartum. We only present overall estimates for repeated BDI-II scores rather than visit-specific estimates because the interaction terms between continuous measures of our exposure (PBDEs or PFAS) and visit (categorical) were not all statistically significant (see Supplemental Tables S3 and S4). We also examined whether higher concentrations of PBDEs or PFAS were associated with higher odds of having a score "at risk" of depression, defined in our study as a BDI-II score > 13, using generalized linear models.

We categorized women into three different groups according to their 9-year longitudinal trajectory of BDI-II score patterns from early second trimester of pregnancy to 8 years postpartum. The group-based trajectory modeling (GBTM) was performed using Stata/IC 12.1 procedure Traj to identify clusters of individuals with similar progressions of BDI-II scores using a zero-inflated Poisson model with a quadratic polynomial trajectory function that allows for an inflection point within the data (Jones and Nagin, 2013; Nagin et al., 2018). GBTM assumes that the population distribution of BDI-II trajectories arises from a finite mixture of unknown groups. It does not identify a true number of trajectory groups since there is no true number, but it distinguishes distinct features of the population with similar trajectories. Using a general quasi-Newton procedure, GBTM predicts each groups' trajectory, estimates the probability that an individual is within each group, and assigns an individual to the group that they have the highest probability to be in. Almost half of the women in the HOME Study had a BDI-II score trajectory that was categorized as low, 40% of women were categorized as medium, and about 10% had a high depression trajectory (Fig. 1). We used multinomial logistic regression models to estimate the excess relative risk of being in the medium or high BDI-II score trajectory relative to the low trajectory with increasing PBDE or PFAS concentrations, yielding relative risk ratios (RRRs) and 95% CIs. All models were adjusted for maternal age, race/ethnicity, household income at enrollment, self-reported marijuana use during pregnancy, serum cotinine as a measure of tobacco use or secondhand smoke exposure, serum ΣPCBs, maternal IQ, marital status, and parity based on a review of the literature and bivariate analysis with both exposure and outcome (p < 0.20).

We conducted a sensitivity analysis using only PFAS concentrations measured at 16 ± 3 weeks of gestation, regardless of whether the participant had more than one measurement at multiple time points (n = 303) to address potential concerns of exposure misclassification bias. We also performed a number of sensitivity analyses with additional adjustment for pre-pregnancy body mass index (BMI), blood lead levels during pregnancy, if women breastfed (yes/no), alcohol consumption (never, < 1/month, > 1/month), and polyunsaturated fatty acid (PUFA) intake to alleviate concerns of residual confounding outside of the covariates included in our final model. PUFA levels were

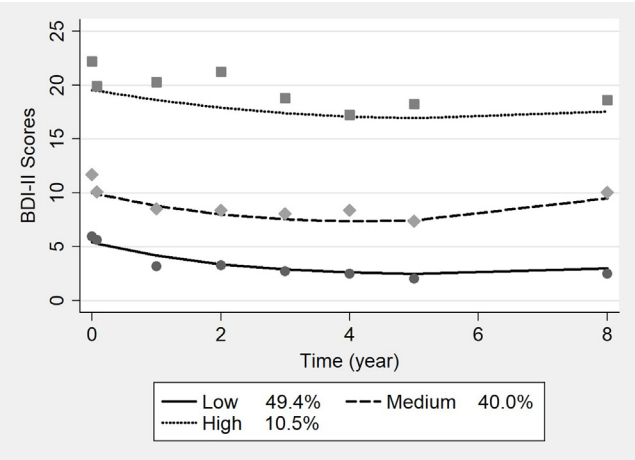

Fig. 1. Trajectories of BDI-II scores from pregnancy to 8 years postpartum, HOME Study.

calculated based on reported total intake of fish consumption (types, frequency) during pregnancy using data from the USDA National Nutrient Database. We also adjusted for time varying covariates, including household income, marital status, paternal education, perceived social support, and neighborhood quality, to take into account changes that may have occurred following baseline which may have resulted in information bias. Social support was categorized into high, moderate, and low based on participant responses to questions inquiring about help received from family and friends living nearby. It was measured by two questions inquiring about family and friends, which asked, "How much help would you expect to get from [FAMILY/FRIENDS] living nearby?" Neighborhood quality was determined based on two sets of questions. First, regarding the likelihood of participants' neighbors getting involved in various scenarios involving their children, the neighborhood, and the community. The first set of questions for neighborhood involvement contained five questions asking, "How likely would your neighbors intervene if…": (1) "children were skipping school and hanging out on a street corner?"; (2) "if children were spray-painting graffiti on a local building?"; (3) "if children were showing disrespect to an adult?"; (4) "a fight broke out in front of their house?"; and (5) "the fire station closest to their house was threatened with budget cuts?" Second, participants were asked to agree with statements inquiring about the willingness of neighbors to help others, the level of familiarity within the neighborhood, trustworthiness, and the ability of neighbors to get along. The set of five statements consisted of the following: (1) "People around my home are willing to help their neighbors"; (2) "I live in a close-knit neighborhood"; (3) "People in my neighborhood can be trusted"; (4) People in my neighborhood generally don't get along with each other"; and (5) "People in my neighborhood do not share the same values."

3. Results

3.1. Study participants

The mean age at baseline was 29.4 years, with 61.8% of the women identifying as non-Hispanic white and 50% having a Bachelor's degree or higher. Approximately 60% had an annual household income at baseline ≥$40,000, and 79% were married or living with a partner. Concentrations of ΣPBDEs during pregnancy were lower among older women, non-Hispanic whites, those with higher education and income, and among women who were married/living with a partner (Table 1). PFOA and PFOS concentrations were higher among non-Hispanic whites and among women who were nulliparous. Lower BDI-II scores during pregnancy and at 8 years postpartum were observed among women who were non-Hispanic white, married or living with a partner, more educated, had a higher household income, and non-marijuana users.

3.2. Longitudinal trends of maternal depression

The intraclass correlation coefficient for BDI-II scores was 0.58, indicating good reproducibility between BDI-II assessments across time. BDI-II scores were highest during pregnancy, with a mean of 10.0 ± 7.0 (see Supplemental Table S2). Scores declined after delivery, with the lowest mean of 5.5 ± 6.0 at 5 years postpartum. However, at 8 years postpartum, the mean of BDI-II scores increased to 7.4 ± 7.3. The percentage of women exhibiting some depressive symptoms (BDI-II scores > 13) was highest during pregnancy (22.3%) followed by 8 years postpartum (18.4%). Moderately and severely depressed women, defined as individuals with a BDI-II score ≥20, were observed in less than 10% of the HOME Study women at every time point.

3.3. Serum PBDEs and PFAS during pregnancy and maternal depression

BDI-II scores were positively associated with concentrations of PBDEs during pregnancy after covariate adjustment (Fig. 2). Aside from BDE-99, all PBDE congeners and ΣPBDEs were significantly positively associated with BDI-II scores. A 10-fold increase in BDE-28 concentrations at 16 ± 3 weeks gestation was associated with a 2.5-point increase (95% CI 0.8, 4.2) in BDI-II scores from pregnancy to 8 years postpartum. We observed similar statistically significant positive associations between BDI-II and BDE-47, -100, -153, and ΣPBDEs. Higher odds of having a BDI-II score > 13 from pregnancy to 8 years postpartum was observed among women with higher concentrations of BDE-28, -47, -100, -153, and ΣPBDEs (see Supplemental Table S5). A 10-fold increase in ΣPBDEs during the early second trimester of pregnancy was significantly associated with approximately a 2-fold risk (95% CI 1.4, 4.2) of having a BDI-II score that would indicate potential depressive symptoms from pregnancy to 8 years postpartum.

When we examined trajectories of maternal depressive symptoms, we observed significantly higher risk of having a high BDI-II score trajectory with 10-fold increases in several PBDE congeners and ΣPBDEs compared to a low BDI-II score trajectory (Table 2). Both BDE-47 and BDE-99 had statistically significant RRRs for medium and high BDI-II score trajectories. A 10-fold increase in ΣPBDEs was associated with a 4.6 increase in risk (95% CI 1.8, 11.8) of having a high BDI-II trajectory compared to a low trajectory.

Serum concentrations of PFAS during pregnancy were not associated with BDI-II scores measured from pregnancy to 8 years postpartum (Fig. 2). In addition, no relationship was noted between PFAS and higher odds of having an "at risk" BDI-II score (see Supplemental Table S5).

3.4. Sensitivity analyses

Examination of PFAS measured only at 16 weeks gestation did not yield findings that were discordant from our original results (Supplemental Table S6). Additional adjustment for perceived social support and neighborhood quality, pre-pregnancy BMI, blood lead levels during pregnancy, breastfeeding, alcohol consumption, and PUFA levels did not change our results (see Supplemental Table S7). After including paternal education at baseline as well as a time-varying paternal education variable in two separate sensitivity analyses, we no longer observed a significant association between BDE-100 and BDI-II scores (see Supplemental Table S8). However, all other significant positive associations between BDE-28, -47, -153, and ΣPBDEs remained.

4. Discussion

In the HOME Study, we found that PBDE concentrations during pregnancy were significantly associated with higher depressive symptoms in women. Several PBDE congeners as well as ΣPBDEs had statistically significant positive associations with BDI-II scores, suggesting that PBDEs may play a role in the pathogenesis of depression. In contrast, there was no evidence to indicate that serum concentrations of PFAS during pregnancy are related to maternal depressive symptoms.

Some studies have examined PBDEs and internalizing behaviors in children. While most reported null associations (Braun et al., 2017b; Chen et al., 2014; Gump et al., 2014; Hoffman et al., 2012), higher PBDE concentrations have been associated with improvement in internalizing behaviors in some studies (Adgent et al., 2014; Roze et al., 2009) and worsening of internalizing behaviors in others (Lipscomb et al., 2017). Because no studies have examined PBDEs and depression in adults, studies investigating PCBs and depression in adults may serve as a comparison as PBDEs are structurally similar and have analogous toxicological properties (Costa et al., 2014). In a longitudinal study, individuals with a higher PCB burden had increased risk of developing depressive symptoms (Gaum et al., 2014). PCBs were also positively

Table 1
Serum concentrations of ΣPBDEs (ng/g lipid), PFOA and PFOS (both in ng/mL), and BDI-II scores by maternal characteristics, HOME Study.[a]

	ΣPBDEs		PFOA		PFOS		BDI-II: Baseline		BDI-II: 8 years	
	n	GM ± GSD	n	GM ± GSD	n	GM ± GSD	n	GM ± GSD	n	GM ± GSD
Age, years										
< 25	74	47.5 ± 2.2*	87	5.5 ± 1.8	87	12.2 ± 1.9	87	13.7 ± 8.4*	59	8.9 ± 7.5
25–34	179	39.6 ± 2.7	210	5.1 ± 1.7	210	12.7 ± 1.6	226	8.8 ± 6.1	131	6.8 ± 7.1
≥35	47	29.4 ± 2.5	57	5.9 ± 1.8	57	14.1 ± 1.6	60	8.8 ± 6.4	32	7.3 ± 7.5
Race/ethnicity										
Non-Hispanic White	183	32.5 ± 2.5*	216	5.6 ± 1.7*	216	13.9 ± 1.6*	231	7.9 ± 5.6*	135	6.0 ± 6.6*
Non-Hispanic Black and Others	118	53.1 ± 2.6	139	4.8 ± 1.7	139	11.1 ± 1.8	142	13.2 ± 7.9	88	9.6 ± 7.7
Education										
High school or less	83	56.4 ± 2.4*	94	5.2 ± 1.8	94	11.3 ± 1.9	97	14.5 ± 9.1*	61	9.8 ± 7.5*
Some college/2 yr degree	72	40.5 ± 2.3	86	5.4 ± 1.7	86	12.9 ± 1.8	88	11.1 ± 6.3	57	9.2 ± 7.9
Bachelor's	88	34.1 ± 2.5	105	5.5 ± 1.8	105	13.4 ± 1.5	109	7.4 ± 4.3	65	5.2 ± 6.7
Graduate or professional	57	28.7 ± 3.1	69	5.1 ± 1.7	69	13.7 ± 1.6	79	6.7 ± 4.2	39	5.0 ± 4.7
Family Income										
< $40,000	123	49.3 ± 2.6*	145	4.9 ± 1.8	145	11.2 ± 1.9*	147	13.4 ± 8.5*	92	9.7 ± 7.6*
$40,000–$79,999	97	37.8 ± 2.6	113	5.5 ± 1.7	113	13.3 ± 1.6	123	8.3 ± 5.0	73	5.4 ± 6.9
≥$80,000	81	29.5 ± 2.4	97	5.7 ± 1.8	97	14.7 ± 1.6	103	7.1 ± 4.4	58	6.3 ± 6.1
Marijuana Use										
Yes	277	38.5 ± 2.6	329	5.3 ± 1.7	329	13.1 ± 1.7*	344	9.4 ± 6.6*	207	7.0 ± 7.0*
No	23	54.5 ± 2.2	25	5.0 ± 1.8	25	9.0 ± 1.9	29	16.4 ± 8.7	15	13.7 ± 8.6
Parity										
Nulliparous	132	35.2 ± 2.6	153	6.5 ± 1.7*	153	14.7 ± 1.7*	166	9.2 ± 5.8	103	6.7 ± 7.2*
Primiparous	90	41.6 ± 2.4	110	4.4 ± 1.6	110	11.9 ± 1.7	115	10.0 ± 8.5	65	6.3 ± 5.7
Multiparous	76	44.4 ± 2.7	89	4.7 ± 1.7	89	10.9 ± 1.6	90	11.3 ± 6.9	54	10.1 ± 8.4
Marital status										
Married/living with partner	236	35.7 ± 2.7*	278	5.3 ± 1.8	278	13.0 ± 1.7	296	8.9 ± 6.5*	165	6.4 ± 6.8*
Not married, living alone	64	57.6 ± 2.1	76	5.3 ± 1.6	76	11.9 ± 1.8	77	13.9 ± 7.8	57	10.3 ± 7.9
Child Sex										
Male	138	34.8 ± 2.5*	166	5.2 ± 1.7	166	12.6 ± 1.7	172	9.0 ± 6.4*	99	6.8 ± 6.1
Female	162	44.1 ± 2.7	188	5.4 ± 1.7	188	12.9 ± 1.8	201	10.8 ± 7.5	123	8.0 ± 8.0
Breastfed current child										
No	53	46.3 ± 2.2	66	5.5 ± 1.6	66	12.2 ± 1.6	67	12.1 ± 7.9*	45	7.5 ± 6.6
Yes	236	38.0 ± 2.6	277	5.3 ± 1.8	277	13.1 ± 1.7	295	9.3 ± 6.6	176	7.3 ± 7.3

Abbreviations: GM, geometric mean; GSD, geometric standard deviation; SD, standard deviation.
$p < 0.05$ for two-sided p values using ANOVA.
[a] Frequencies may not add to the total number of participants because of missing values.

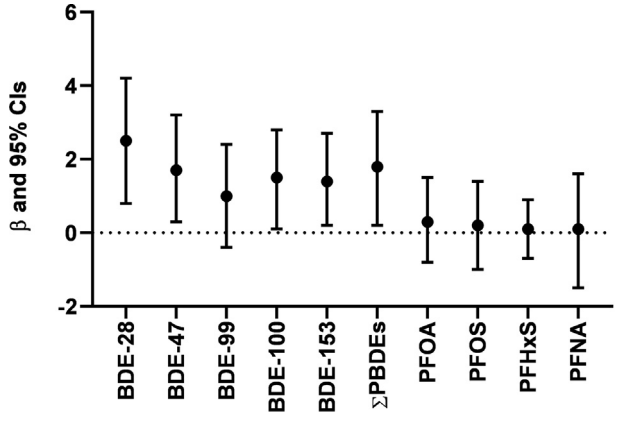

Fig. 2. Estimated score differences and 95% confidence intervals in BDI-II scores from the early second trimester of pregnancy to 8 years postpartum by a 10-fold increase in serum PBDE concentrations (ng/g lipid) or 1-ln unit increase in serum PFAS concentrations (ng/mL) during pregnancy, HOME Study. Adjusted by age, race/ethnicity, household income, maternal marijuana use, serum cotinine and ΣPCBs, IQ, marital status, and parity.

associated with depressive symptoms among occupationally exposed workers and their relatives in the German Health Effects in high Level exposure to PCB (HELPcB) surveillance program (Gaum et al., 2017). The authors noted that depressive symptoms might be mediated by

Table 2
Relative risk ratios (RRRs) and 95% confidence intervals of having a medium or high BDI-II score trajectory by a 10-fold increase in serum PBDE concentrations (ng/g lipid) or 1-ln unit increase in serum PFAS concentrations (ng/mL) during pregnancy, HOME Study.

		BDI-II score trajectory		
		Low	Medium	High
	n	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
PBDEs				
BDE-28	276	Referent	1.9 (0.9, 4.0)	6.1 (2.2, 17.1)
BDE-47	312	Referent	1.8 (1.0, 3.3)	5.5 (2.3, 13.1)
BDE-99	312	Referent	1.9 (1.1, 3.4)	4.5 (2.0, 10.1)
BDE-100	312	Referent	1.5 (0.9, 2.6)	3.9 (1.7, 8.9)
BDE-153	311	Referent	1.2 (0.7, 2.0)	1.9 (0.9, 4.1)
ΣPBDEs	275	Referent	1.6 (0.9, 3.1)	4.6 (1.8, 11.8)
PFAS				
PFOA	300	Referent	1.3 (0.8, 2.0)	0.9 (0.5, 1.9)
PFOS	300	Referent	0.9 (0.6, 1.5)	0.6 (0.3, 1.2)
PFHxS	300	Referent	1.0 (0.7, 1.3)	0.6 (0.4, 1.0)
PFNA	300	Referent	0.8 (0.4, 1.5)	0.7 (0.3, 1.8)

[a]Adjusted by age, race/ethnicity, household income, maternal marijuana use, serum cotinine and ΣPCBs, IQ, marital status, and parity.

altered dopamine metabolism, specifically reporting that there was significant mediation for lower-chlorinated, higher-chlorinated, and dioxin-like PCBs. Among older residents residing along the upper contaminated portions of the Hudson River in New York, Fitzgerald et al., (2008) reported significantly higher BDI-II scores of ~19% with an increase in serum PCBs from 250 to 500 ppb. In contrast, some studies have observed null associations between PCBs and adult depression (Kilburn et al., 1989; Lin et al., 2008; Peper et al., 2005; Seegal et al., 2013). To our knowledge, only one study has examined PFAS and adult depression. In contrast with our study, Berk et al. (2014) found that several PFAS were inversely associated with depression prevalence, using the NHANES data from 2005 to 2010. Divergent findings may be related to differences in study design, depression assessment tools, sample characteristics, and PFAS concentrations.

Our finding that PBDEs are associated with higher depressive symptoms in women have several possible explanations. First, animal studies have consistently reported that PBDEs reduce blood levels of thyroid hormones (Darnerud, 2008), suggesting a hypothyroxinemic or hypothyroid effect. Overt and subclinical hypothyroidism have been linked to an increased risk of depression in humans (Constant et al., 2006; Larisch et al., 2004; Loh et al., 2019). In a pooled analysis of over 12,000 individuals, those with subclinical hypothyroidism had 2-fold greater risk for depression compared to euthyroid controls (Loh et al., 2019). PBDEs' role and impact in the disruption of the hypothalamic-pituitary-thyroid axis in humans is described in the medical literature (Albert et al., 2018; Byrne et al., 2018; Chen et al., 2018; Czerska et al., 2013).

Second, PBDEs can disrupt the dopaminergic system, which plays a major role in depression. Dopamine is involved in the regulation of several prominent features of depression, including motivation, psychomotor speed, concentration, and the ability to experience pleasure (Dunlop and Nemeroff, 2007). Impaired function of the mesolimbic dopamine system has been reported in rodent models of depression, suggesting that there is diminished dopamine release and lower dopamine receptor binding (Neill et al., 2002; Papp et al., 1994; Salamone et al., 1999). DE-71 significantly reduces striatal dopamine, dopamine handling, and dopamine transporters *in vivo*, demonstrating that PBDEs disrupt the nigrostriatal dopamine system (Bradner et al., 2013), which is involved in motivated behaviors (Smillie and Wacker, 2014). BDE-99 also suppresses neurodifferentiation into dopamine phenotypes in PC12 cells (Slotkin et al., 2013). In zebrafish larvae, PBDE exposure reduced whole-body dopamine, its metabolite, and dopamine transporter protein, indicating dopamine synthesis and transport dysregulation (Wang et al., 2015).

Third, the biological mechanism of action for PBDEs and depression may involve affecting neuroplasticity, whose functional aspects include long-term potentiation and depression (Wang et al., 1997). BDE-99 exposure altered levels of key proteins involved in synaptic plasticity, including Gap-43/neuromodulin and stathmin, in the striatum region of the mouse brain (Alm et al., 2006). While we did not observe a significant linear association between BDE-99 and BDI-II scores, there was a statistically significant positive association with moderate and high score trajectories. PBDEs also disrupt Ca^{2+} signaling, because they are potent modulators of ryanodine receptors, which play a role in neurotransmission and synaptic plasticity (Kim et al., 2011). Because PBDE exposure can be reduced, it can be considered a modifiable risk factor for depression during and after pregnancy. While PBDEs are ubiquitous, exposure can be limited with behavior modification, including replacement of PBDE-laden products, regularly vacuuming with a HEPA filtered vacuum, and frequent handwashing.

One strength of our study is that we used data from the HOME Study, an ongoing prospective, birth cohort that is rich with covariate information. This allowed us to adjust for important confounders, including socioeconomic factors, marital status, and parity. We were also able to adjust for PUFA intake in sensitivity analyses as fish consumption has been reported to protect against perinatal depression (Hamazaki et al., 2018; Lin et al., 2017). We additionally adjusted for perceived social support from family and friends, paternal education, and alcohol consumption. A second strength of this study is that we took into account co-exposures to tobacco smoke and PCBs. PCBs and PBDEs potentially share similar pathological mechanisms for depression, because of their structural similarities. A third strength is that we had up to 8 repeated measures of BDI-II from pregnancy to 8 years postpartum. Using linear mixed models increased our power to detect associations between serum PBDEs and PFAS and changes in BDI-II scores, and we were able to examine trajectories of maternal depression. Further, yearly time intervals may reduce a possible bias due to childrearing responsibilities as well as seasonal influences on depressive symptoms. Last, we utilized BDI-II to assess depressive symptoms in the HOME Study women. This instrument has been extensively validated and is reliable, performing well in diverse cohorts and ethnic groups (Beck et al., 1996; Dadfar and Kalibatseva, 2016; Gregory, 2007; Lee et al., 2017; Wiebe and Penley, 2005).

This study has some limitations. First, while we adjusted for parity, we did not have information on subsequent births that may have occurred after the index pregnancy. Maternal depression is associated with interpregnancy intervals < 24 months (Gurel and Gurel, 2000; Patchen and Lanzi, 2013). According to the U.S. Department of Health and Human Services, a third of all pregnancies in the USA from 2006 to 2010 occurred less than 18 months after the prior live birth (2010). Therefore, it is likely that a portion of HOME Study women may have had a subsequent birth within 2 years after the index pregnancy, which may have contributed to depressive symptoms. However, Schetter et al., (2016) noted that most women (75%) had interpersonal stability in their depressive symptoms from one postpartum period to the next. We also did not take into account maternal stress, history of depression, and antidepressant use. Since history of depression is a major risk factor for perinatal depression, lack of adjustment could have inflated the point estimates. For instance, if women who reported perinatal depressive symptoms had a history of depression prior to conception, then the associations observed between PBDEs during pregnancy and perinatal depressive symptoms may not reflect a true relationship as depression was already present prior to PBDE measurement. Further, without history of depression, it is unclear whether outcome may have influenced exposure concentrations. Women experiencing depression prior to pregnancy may engage in less cleaning and hygiene behaviors, which could have influenced their concentrations of PBDEs as one of the major routes of exposure is through ingestion and dermal absorption of house dust. Lack of antidepressant use may have biased the estimates toward the null. If HOME Study women were taking antidepressants then this would lower the depressive symptoms reported by the participants. In addition, because few HOME Study women had moderate or severe depression, we could not determine the potential impact of PBDE or PFAS exposures on severe depressive phenotypes. Third, we utilized BDI-II to assess depressive symptoms among HOME Study women, which may have resulted in an overestimation of severity as it includes somatic items as a measure of depression. The perinatal period involves physiological and psychosocial changes that may manifest as somatic symptoms (e.g., changes in appetite, sleep, energy, mood, sexual interest, etc.) normally characteristic of depression, but are normal among women adjusting to pregnancy and infant care (O'Hara and Wisner, 2014; Stewart, 2005). Therefore, including somatic items to assess perinatal depression may overstate the level of depression severity (Pereira et al., 2014) and could have biased estimates away from the null. However, since we only found statistically significant associations between PBDE concentrations and maternal depression and not with PFAS concentrations, the identified association may be reflective of a true relationship. Fourth, selection bias may also be a concern. However, women included in this analysis comprised of ~97% of the 390 women who delivered singletons. Thus, there was very little attrition pertaining to the present study. We additionally utilized an average of PFAS concentrations for 70 women who had > 1

measurement during pregnancy. However, sensitivity analyses examining only PFAS concentrations at 16 ± 3 weeks gestation were concordant with our study's conclusions. Last, the HOME Study is based on only one study site, which affects our finding's generalizability, and we were limited by a modest sample size.

Serum PBDE concentrations during pregnancy were associated with higher depressive symptom scores in an 8-year follow-up of women. In contrast, we found no evidence that PFAS are involved in the development of maternal depressive symptoms to support our hypothesis. Additional research is necessary to confirm our findings on PBDE exposure and better understand whether the associations persist over time and whether they are present in other study populations. Future research should consider important factors that were not taken into account in the present study with regard to the association between PBDEs and PFAS during pregnancy and maternal depression, including history of depression as well as antidepressant usage. Measures of PBDE and PFAS concentrations postpartum should also be considered to identify susceptible windows of exposure to these endocrine disruptors in the pathophysiology of depression.

CRediT authorship contribution statement

Ann M. Vuong: Conceptualization, Methodology, Formal analysis, Writing - original draft, Visualization. **Kimberly Yolton:** Investigation, Writing - review & editing, Project administration, Funding acquisition. **Joseph M. Braun:** Investigation, Writing - review & editing, Project administration, Funding acquisition. **Andreas Sjodin:** Resources, Writing - review & editing. **Antonia M. Calafat:** Resources, Writing - review & editing. **Yingying Xu:** Data curation, Software, Writing - review & editing, Project administration. **Kim N. Dietrich:** Writing - review & editing. **Bruce P. Lanphear:** Investigation, Writing - review & editing, Project administration, Funding acquisition. **Aimin Chen:** Conceptualization, Methodology, Investigation, Supervision, Writing - review & editing, Project administration, Funding acquisition.

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Appendix A. Supplementary material

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