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Polybrominated diphenyl ether (PBDE) exposures and thyroid hormones in children at age 3 years

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Abstract

Background—Polybrominated diphenyl ethers (PBDEs) reduce serum thyroid hormone concentrations in animal studies, but few studies have examined the impact of early-life PBDE exposures on thyroid hormone disruption in childhood.

Methods—We used data from 162 mother-child pairs from the Health Outcomes and Measures of the Environment Study (2003–2006, Cincinnati, OH). We measured PBDEs in maternal serum at 16 ± 3 weeks gestation and in child serum at 1–3 years. Thyroid hormones were measured in serum at 3 years. We used multiple informant models to investigate associations between prenatal and early-life PBDE exposures and thyroid hormone levels at age 3 years.

Results—Prenatal PBDEs were associated with decreased thyroid stimulating hormone (TSH) levels at age 3 years. A 10-fold increase in prenatal ΣPBDEs (BDE-28, -47, -99, -100, and -153) was associated with a 27.6% decrease (95% CI −40.8%, −11.3%) in TSH. A ten-fold increase in prenatal ΣPBDEs was associated with a 0.25 pg/mL (0.07, 0.43) increase in free triiodothyronine

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Competing financial interest declaration

The authors declare they have no competing financial interests.

(FT_3). Child sex modified associations between prenatal PBDEs and thyroid hormones, with significant decrements in TSH among females and decreased free T_4 (FT_4) in males. Prenatal ΣPBDEs were not associated with TT_4, FT_4, or total T_3.

Conclusions—These findings suggest an inverse relationship between prenatal ΣPBDEs and TSH at 3 years. Associations may be sexually dimorphic, with an inverse relationship between prenatal BDE-47 and -99 and TSH in females and null associations among males.

Keywords

Polybrominated diphenyl ethers (PBDEs); Thyroid hormones; Epidemiology; Thyroid function; Brominated flame retardants; Endocrine disruption

1. Introduction

Polybrominated diphenyl ethers (PBDEs) are flame retardants that were used extensively in consumer products, such as furniture foam, textile fabrics, electrical equipment, and plastic materials. Historical use of PBDEs since the 1970s has resulted in widespread, persistent environmental contamination even though penta- and octa-brominated formulations were withdrawn from the market in 2004 (Hites, 2004; Linares et al., 2015). Epidemiological studies have reported that pre-natal and postnatal PBDE exposures are associated with cognitive deficits and increased ADHD-type behaviors (Braun et al., 2017b; Chen et al., 2014; Eskenazi et al., 2013; Herbstman et al., 2010; Sagiv et al., 2015; Shy et al., 2011; Vuong et al., 2017; Zhang et al., 2017).

One potential underlying mechanism for PBDE neurotoxicity may be due to interference of thyroid hormone action. Thyroid hormones are essential for brain development and regulates the genes involved in myelination and neuronal/glial cell differentiation (Bernal, 2000). PBDEs, which are structurally similar to thyroid hormones, have been observed to alter thyroid hormones in fish, rodents, birds, and felines (Czerska et al., 2013; Guigueno and Fernie, 2017; Walter et al., 2017; Yu et al., 2015). PBDEs may also interfere with thyroid hormone metabolic enzymes (Szabo et al., 2009; Yu et al., 2011; Zhou et al., 2001), competitively bind to thyroid hormone serum binding proteins and receptors (Hamers et al., 2006; Kojima et al., 2009; Marchesini et al., 2008; Meerts et al., 2000; Ren et al., 2013), and inhibit deiodinase enzymes (Marsan and Bayse, 2017; Roberts et al., 2015) and sulfo-transferase activity (Butt and Stapleton, 2013). Toxicological studies reported thyroid disruption, primarily decreased thyroxine, in offspring exposed to PBDEs during gestational (Kim et al., 2009; Kuriyama et al., 2007; Tseng et al., 2008), perinatal (Bansal et al., 2014; Bowers et al., 2015; Tung et al., 2016; Zhao et al., 2016), and postnatal development (Arkoosh et al., 2017; de-Miranda et al., 2016; Driscoll et al., 2009).

Studies investigating prenatal PBDEs and thyroid hormones have only examined associations with thyroid hormones in newborns (Chevrier et al., 2011; Herbstman et al., 2008). Thus, there is a critical need to expand thyroid hormone measurements to early childhood. In addition, most epidemiological studies examining childhood PBDEs and thyroid hormones have been cross-sectional, with varying ages of assessment, differing PBDE concentrations, and inconsistent results (Eggesbo et al., 2011; Gascon et al., 2011;

Jacobson et al., 2016; Kicinski et al., 2012; Leijs et al., 2012). Given the paucity of studies investigating prenatal PBDEs and thyroid hormones, as well as the inconsistency between studies of postnatal PBDEs, we examined prenatal and postnatal PBDEs' association with thyroid hormones in children at age 3 years.

2. Methods

2.1. Study participants

Participants included in the present study are from the Health Outcomes and Measures of the Environment (HOME) Study, located in the greater Cincinnati, Ohio area (2003–2006). Details regarding inclusion and exclusion criteria, recruitment, and follow-up have been described by Braun et al. (2017a). Briefly, women were enrolled in the study if they were at least 18 years, at 16 ± 3 weeks of gestation, living in a home that was built before 1978, receiving prenatal care and planning to deliver at one of the nine collaborating obstetric practices, HIV negative, and not taking medications related to seizures, thyroid disorders, or chemotherapy/radiation treatment. Of the 390 women who delivered live singleton infants, 162 were included in the present study based on availability of at least one measurement of PBDEs (in maternal serum assessed at study enrollment or in child serum at ages 1, 2, or 3 years) and thyroid hormones measured in children at age 3 years. This study was approved by the institutional review board at the Cincinnati Children's Hospital Medical Center. The Centers for Disease Control and Prevention (CDC) relied on the IRB at Cincinnati Children's Hospital Medical Center.

2.2. Polybrominated diphenyl ethers (PBDEs)

Maternal serum was collected at 16 ± 3 weeks of gestation. Children provided serum samples at ages 1, 2, and 3 years during scheduled follow-ups. Of the 390 singleton children in the HOME Study, 336, 276, and 256 had follow-up visits at 1, 2, and 3 years. However, 72–77% did not have a sufficient quantity of serum to measure PBDEs at ages 1–3 years. Thus, PBDE measurements from ages 1–3 years were only available for 44–48% of the 162 children due to limited serum (Supplemental Table S1). Details regarding the measurement of PBDEs have been described in detail previously (Vuong et al., 2017). PBDE concentrations less than the limit of detection (LOD) were substituted with LOD/√2 (Hornung and Reed, 1990). Percent detection for PBDE congeners -28, -47, -99, -100, and -153 for 16 weeks gestation, 1 year, 2 years, and 3 years were > 80% at all time points (Table 1). Thus, we included these congeners and the sum of their concentrations (ΣPBDEs: BDE-28, -47, -99, -100, and -153) in our analysis. PBDEs were lipid-adjusted (ng/g lipid) (Phillips et al., 1989) and $\log_{10}$-transformed to achieve normality.

2.3. Thyroid hormones

Child serum was separated from whole blood samples collected at age 3 years and stored at −80 °C until analysis by the Department of Laboratory Medicine of the University of Washington. Upon thawing, thyroid hormones (thyroid-stimulating hormone [TSH], total and free thyroxine [TT_4 and FT_4], total and free triiodothyronine [TT_3 and FT_3]) were quantified using a UniCel DxI 800 automated clinical immunoassay analyzer by Beckman Coulter, Inc. (Fullerton, CA). For quality control, BioRad Liquicheck or BioRad

Immunoassay Plus, was used with each assay every day ($n = 22$). Coefficients of variation (CVs) for inter-assay variability ranged from 2.0–9.6%. Blinded quality control samples were also included and had low CVs (≤8.5%). A second technologist double-checked the results to reduce any potential transcription errors.

2.4. Statistical analyses

We used multiple informant models to estimate βs and 95% confidence intervals (CIs) for the associations between prenatal and childhood PBDEs measured at ages 1–3 years with thyroid hormones at age 3 years. These models are non-standard versions of generalized estimating equations that allow for repeated measures of PBDE exposures (Sanchez et al., 2011). They allow for more flexible repeated measures, with no requirement of the same number of PBDE measurements between participants, and consideration of correlations for PBDE measurements at various time points. To assess whether associations of PBDEs with thyroid hormones differed by each window of exposure, we included interaction terms between PBDEs (continuous) and child age (categorical), with p-values < 0.10 considered statistically significant. We determined whether child sex modified the association between prenatal PBDEs and thyroid hormones by including an interaction term between prenatal PBDEs (continuous) and child sex ($p < 0.10$) in multiple linear regression models. Effect measure modification analyses were restricted to prenatal PBDE concentrations due to the limited sample size of children with postnatal PBDE concentrations. All models were adjusted for baseline measures of maternal age, race/ethnicity, education, smoking status, alcohol consumption, vitamin use, maternal BMI, serum polychlorinated biphenyls (ΣPCBs: CB-28, 74, 99, 105, 118, 146, 153, 156, 170, 180, 183, 187, 194, 199, and 206; $\log_{10}$-transformed), parity, and child sex based on a review of the literature and bivariate analyses ($p < 0.10$), as categorized in Table 2. Percent changes for thyroid hormones were calculated by dividing the βs by the mean thyroid hormone concentration in the study sample for total and free T_4 and T_3 (Table 3). Percent change was determined using: $(e^{\beta}-1) \times 100$ for TSH, because TSH was ln-transformed given its skewed distribution.

We performed four sensitivity analyses. First, to test whether our results were similar using different lipid adjustment methods, we followed recommendations of O'Brien et al. (2016) and modeled PBDEs on a volume basis (pg/g serum) with serum lipids as a covariate; and standardized PBDEs (ng/g lipid) with serum lipids as a covariate. Second, we also excluded children with clinically elevated TSH levels (> 5 μIU/mL; $n = 2$) in a separate sensitivity analysis (Kliegman et al., 2007). Third, we performed multiple informant models for associations between PBDE concentrations from prenatal to age 3 years and thyroid hormones using multiple imputations of exposure to alleviate concerns regarding the small sample size of postnatal PBDE concentrations. Detailed procedures for multiple imputation, including selection of auxiliary variables, number of imputations, and convergence assessment of imputation models have been described previously (Vuong et al., 2017). Fourth, we additionally adjusted by organochlorines, including dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE), which have been reported to disrupt thyroid hormone homeostasis (Alvarez-Pedrerol et al., 2008; Liu et al., 2011; Picchietti et al., 2009), to determine whether the observed

associations in the present study were impacted by these chemicals. Lastly, we adjusted for potential selection bias using inverse probability weights.

3. Results

3.1. Study participants

Children excluded from the present study due to missing information had mothers who were more likely to be younger, non-Hispanic black or others, a smoker or exposed to environmental tobacco smoke during pregnancy, and have higher blood lead levels (Supplemental Table S2). They were also less likely to have at least some college education and take daily vitamin supplementation during pregnancy.

3.2. Description of PBDE concentrations and thyroid hormone levels

BDE-47 was the most abundant congener, with the highest geometric mean (GM) concentration at age 1 year (Table 2). Prenatal BDE-47 concentrations were significantly higher among females and children whose mothers were non-Hispanic black or others, had lower education, were active smokers during pregnancy, and were obese. The GM of TSH levels at age 3 years was 2.0 μIU/mL (Table 3). Mean total and free T_4 levels were 8.8 μg/dL and 0.9 ng/dL, respectively.

3.3. Prenatal PBDEs and thyroid hormones

Several interaction terms between PBDEs (continuous) and child age (categorical) had a $p < 0.10$, thus βs are presented for each exposure window. After adjusting for potential confounders, a 10-fold increase in prenatal BDE-47 was associated with a 0.21 decrease in ln-TSH (95% CI −0.40, −0.03) at 3 years, which corresponds to a decrement of 19.2% (95% CI −32.7%, −3.1%) (Fig. 1). Prenatal ΣPBDEs was also inversely associated with ln-TSH at age 3 years (β = −0.32, 95% CI −0.53, −0.12), corresponding to a decrease of 27.6% (−40.8%, −11.3%). We observed significant positive associations of prenatal BDE-99 (β = 0.26 pg/mL, 95% CI 0.06, 0.45) and ΣPBDEs (β = 0.25 pg/mL, 95% CI 0.07, 0.43) with FT_3 levels (Supplemental Table S3). No statistically significant associations were observed between prenatal PBDEs and TT_4, FT_4, or TT_3 at age 3 years.

3.3.1. Effect measure modification by child sex—We observed significant decreases in TSH of ~35% for a 10-fold increase in prenatal BDE-47 and -99 concentrations in females, while null associations were noted among males ($p_{\text{interaction for BDE-47}} = 0.064$; $p_{\text{interaction for BDE-99}} = 0.013$) (Fig. 2). In contrast, increased concentrations of several PBDEs, were associated with significantly lower FT_4 in males, whereas positive, but not statistically significant associations were observed in females ($p_{\text{interaction}} < 0.08$). In particular, a 10-fold increase in prenatal BDE-47 concentrations was associated with significantly decreased FT_4 (−0.08 ng/dL, 95% CI −0.15, −0.01) in males, but increased FT_4 levels in females (β = 0.04 ng/dL, 95% CI −0.02, 0.11), which corresponds to an 8.9% decrease (−16.7%, −1.1%) in FT_4 among males and an increase of 4.4% (−2.2%, 12.2%) among females. No evidence of effect measure modification by child sex was noted for associations between prenatal PBDEs and TT_4, TT_3, or FT_3.

3.4. Postnatal PBDEs and thyroid hormones

Postnatal PBDE exposures were also associated with altered thyroid hormones at age 3 years (Fig. 1). We observed a 39% to 50% increase in TSH with a 10-fold increase in BDE-47 and -99 at age 2 years. Specifically, 10-fold increases in BDE-47 and -99 were associated with a ln-TSH increase of 0.40 (95% CI 0.04, 0.76) and 0.33 (95% CI 0.01, 0.65), respectively. Significant positive associations were present between all individual PBDE congeners and ΣPBDE concentrations at age 2 years with TT_4 levels, corresponding to an 11% to 23% increase from the mean TT_4. Concurrent concentrations of BDE-100 and -153 were also positively associated with TT_4 levels at age 3 years. No relationship was noted between postnatal PBDEs and FT_4, TT_3, or FT_3.

3.5. Sensitivity analyses

Examining PBDEs on a volume basis (pg/g serum) with additional adjustment of lipid levels, and standardizing PBDEs (ng/g lipid) while including total lipids in the models, resulted in similar findings (results not shown). Excluding children who had serum TSH concentrations > 5 μIU/mL did not change the pattern of our results (results not shown). However, associations between BDE-47 and -99 at 2 years and TSH at 3 years were only marginally significant. Effect measure modification by child sex remained between several prenatal PBDEs and FT_4 and prenatal BDE-99 and TSH. Third, when we examined the associations between PBDEs and thyroid hormones using imputed data, we continued to observe several statistically significant inverse associations between prenatal PBDE concentrations and TSH levels at age 3 years (Supplemental Table S4). In addition, marginally significant positive associations were noted between prenatal BDE-99 (β = 0.18 pg/mL, 95% CI −0.02, 0.38) and ΣPBDE concentrations (β = 0.14 pg/mL, 95% CI −0.08, 0.36) and FT_3 levels. However, previously observed significant associations between PBDE concentrations at age 2 years and TSH and TT_4 levels became non-significant. There were no differences in results when we additionally adjusted for maternal concentrations of DDT or DDE. Lastly, applying weights to the models equal to the inverse probability of being observed still resulted in inverse associations between prenatal PBDEs and TSH, though associations were only marginally statistically significant (*e.g.*, ΣPBDEs: β = −0.23 μIU/mL, 95% CI −0.48, 0.01). Associations between PBDEs at age 3 years and TT_4 were no longer significant.

4. Discussion

Findings from the present study suggest that prenatal and postnatal PBDE exposures are associated with thyroid hormone concentrations in children at age 3 years. We observed decrements of 14–28% in TSH levels associated with a 10-fold increase in several PBDE congeners measured in maternal serum during pregnancy. There was a positive association between prenatal BDE-99 and ΣPBDEs and FT_3. No association was observed between prenatal PBDEs and TT_4, FT_4, or TT_3. We also found positive associations between all individual PBDE congeners and ΣPBDEs at age 2 years and BDE-100 and -153 at age 3 years with TT4. However, due to the small sample size for postnatal PBDEs and findings using imputed PBDE measurements, observed findings may not sufficiently support a relationship between postnatal PBDEs and thyroid hormones. However, given that previous

epidemiological studies examining postnatal PBDEs and thyroid hormones have mainly been cross-sectional and do not have repeated measures of PBDEs during childhood, the present study is able to provide new data on possible associations between postnatal PBDEs and thyroid hormone disruption with minimal concern for temporality. Therefore, our findings can only support that prenatal PBDEs may be associated with thyroid hormone disruption.

This study is one of the first to investigate the associations between prenatal PBDEs and childhood thyroid hormones. In previous studies, higher cord BDE-153 was associated with increased odds of having low TT_4 measured in neonatal blood spots measured < 2 days postpartum (Herbstman et al., 2008). In the Center for the Health Assessment of Mothers and Children of Salinas Study (CHAMACOS), no association was found between maternal serum PBDE concentrations (BDE-47, -85, -99, -100, and -153 or their sum) and TSH measured < 24 h postpartum (Chevrier et al., 2011). In the present study, we observed an inverse association between prenatal BDE-28, -47, -100, and ΣPBDE concentrations and TSH levels at age 3 years and a positive association with FT_3 and higher concentrations of prenatal BDE-99 and ΣPBDEs. Toxicological studies in which rodents were exposed to either BDE-99 or BDE-209 during fetal development indicate altered thyroid hormone levels during postnatal development. In contrast to our findings, reductions in postnatal T_4 and T_3 were observed in rats exposed to PBDEs during gestation (Kim et al., 2009; Kuriyama et al., 2007; Tseng et al., 2008).

Findings for postnatal PBDEs and thyroid hormones in epidemiological studies are conflicting. While null associations have been reported in a number of studies (Eggesbo et al., 2011; Gascon et al., 2011; Lignell et al., 2016; Xu et al., 2014b), some have observed positive associations between postnatal PBDEs and TSH. In a study of 80 children aged 1–5 years in southeastern United States, a 22% increase in TSH was observed with a log-unit increase in ΣPBDEs (BDE-47, -99, -100, and -153) (Jacobson et al., 2016). Studies examining children (4–8 years) in electronic waste recycling areas in China concluded a positive relationship between ΣPBDEs (BDE-28, -47, -99, -100, -153, -154, -183, and -209 in Guiyu and Shantou, China Study; BDE-8, -11, -12/13, -15, -28, -47, -99, -100, -116, -118, -119, -138, -153, -154, and -183 in Luqiao and Longyou, China Study) and TSH (Han et al., 2011; Xu et al., 2014a). Additionally, adolescents in Belgium with BDE-47 above the level of quantification had approximately a 10% increase in TSH (Kicinski et al., 2012). Findings for associations of postnatal PBDEs with T_3 and T_4 between studies are inconsistent. Compared to our null results between TT_3 and FT_3, two studies observed inverse associations between concurrent ΣPBDEs (BDE-8, -11, -12/13, -15, -28, -47, -99, -100, -116, -118, -119, -138, -153, -154, and -183) and FT_3 among 4 to 8-year old children in China (Xu et al., 2014a) and between concurrent concentrations of BDE-99 and -100 and FT_3 among adolescents in Belgium (Kicinski et al., 2012). In contrast, elevated levels of FT_3 were reported in US children age 1–5 years with higher concurrent PBDE concentrations (Jacobson et al., 2016). Leijs et al. (2012) similarly observed positive correlations between BDE-99 concentrations at age 14–18 years and concurrent T_3 and FT_4 levels.

Inconsistencies between studies may be due to differences in child age at the time of thyroid hormone assessment. Previous studies examining prenatal PBDEs and thyroid hormones

measured thyroid hormones in newborns and are not directly comparable to this present study. Thyroid hormone levels undergo a cascade of changes following birth that allow newborns to adapt to the extrauterine environment, with a spike in newborn TSH that declines within 2 days (Schmaltz, 2012). In addition, most studies examined concurrent PBDE exposures during childhood, whereas we examined repeated PBDE measures from *in utero* to age 3 years. Third, biological matrices in which postnatal PBDEs were measured differed across studies (breastmilk *vs.* child serum). Fourth, PBDE concentrations varied greatly between study populations. Concentrations of PBDEs found in the children of the HOME Study were much higher than studies examining thyroid hormones in children of similar ages in other countries. For instance, the median concentration of BDE-47 in our study was 36.7 ng/g lipid at age 3 years compared to 0.12 ng/g lipid at age 4 years in the Menorca cohort (Gascon et al., 2011). The GM of Σ_4PBDEs (BDE-28, -47, -99, and -153) in male children at age 3 years (65.2 ng/g lipid) in our study was higher than that of males aged 1–5 years in the Atlanta cohort (51 ng/g lipid) (Jacobson et al., 2016). However, GMs of Σ_4PBDEs were comparable in females (HOME Study: 74.6 ng/g lipid; Atlanta cohort: 77 ng/g lipid). Lastly, discrepant findings between studies could be due to differences in confounder adjustment and timing of blood draw during the day for thyroid hormone analysis.

Perturbations in thyroid hormone homeostasis puts into motion a series of feedback mechanisms to restore euthyroidism (Hoermann et al., 2015). While the molecular events involved in thyroid hormone homeostasis are not fully elucidated, it is recognized that maturation begins during the latter half of gestation and extends into the neonatal period (Fisher et al., 2000). However, additional adjustments to the homeostatic set point persist well into childhood and adolescence, indicating that there is progressive maturation that can be perturbed and modulated by various factors, including non-thyroidal illnesses, genetic polymorphisms, neuromodulators, epigenetics, and xenobiotics, that can potentially shift the regulatory control axis temporarily or permanently (Fisher et al., 2000; Hoermann et al., 2015). Prenatal PBDEs may play a role in the programing of the homeostatic set point during gestational development while continuous postnatal exposures could influence shifts in the axis during childhood. In rodents, prenatal programming of adult thyroid function is developmentally regulated by the maternal hormonal milieu *in utero*; rats had altered thyroid function in adulthood in the presence of maternal ethanol consumption and T_4 administration (Wilcoxon and Redei, 2004). Previously, in this cohort, we reported increased maternal serum T_4 at ~16 weeks gestation with higher BDE-28 and -47 concentrations and increased maternal levels of T_3 with increased BDE-47 (Vuong et al., 2015), suggesting that prenatal PBDEs may impact fetal thyroid homeostasis in pregnant women. Several studies of felines have also reported hyperthyroidism with PBDE exposure (Chow et al., 2015; Norrgran et al., 2015; Walter et al., 2017). A hyperthyroidism state may result from the down-regulation of transcription of alpha and beta forms of thyroid hormone receptors by PBDEs. Previously, BDE-99 was reported to directly down-regulate thyroid receptors alpha-1 and alpha-2 in rat cerebellar granular neurons (Blanco et al., 2011). In the present study, we observed thyroid hormone disruption of a hyperthyroid state with regard to prenatal PBDE exposure. However, several epidemiological studies have reported associations that suggests a hypothyroid association. It is unclear whether conflicting

findings are due to differences in concentrations, timing of measurement, study participant composition, or residual confounding.

In the present study we observed that higher prenatal BDE-47 and -99 were associated with significantly lower TSH in females, but not in males. In contrast, decrements in FT_4 levels were observed in males, but not in females. PBDE accumulation differs between the sexes, with male placentas having higher concentrations than females (Leonetti et al., 2016b). In addition, thyroid hormone sulfotransferase (SULT) activities differ between sexes with PBDE exposures (Leonetti et al., 2016a). PBDEs were positively associated with T3 SULT activity in males, but inverse associations were noted in females. SULT is a thyroid hormone metabolizing enzyme involved in sulfation and changes the rate of conversion from T_4 (Stanley et al., 2001). As such, significantly lower FT_4 in males with h igher PBDEs could be due to alterations in SULTactivity which has been previously reported in male placentas (Leonetti et al., 2016a).

This study had several strengths, including its prospective design and multiple PBDE measurements during both the prenatal and post-natal periods. We also incorporated repeated PBDE measurements into one model to identify windows of heightened vulnerability for thyroid hormone disruption at age 3 years. Third, we were able to adjust for several confounders, including sociodemographic and behavioral factors and maternal serum ΣPCBs. We also examined effect modification by child sex. Fourth, we utilized imputed measures of PBDEs to increase our power and precision and found similar findings with regard to prenatal PBDEs and thyroid hormones. In contrast, findings for post-natal PBDEs and thyroid hormones were no longer statistically significant. This may be due to higher concentrations of PBDEs at ages 2 and 3 years in the imputed datasets compared to the original dataset, which could have influenced the results by attenuating the β estimates. Lastly, we additionally adjusted for maternal concentrations of DDT or DDE in sensitivity analyses and observed congruent findings.

However, several limitations deserve mention. First, we lacked information on urinary iodine levels at age 3 years in children, which may be an effect modifier as it is an indispensable component of T_3 and T_4 and deficiencies interfere with thyroid hormone synthesis. For example, individuals with iodine deficiencies have higher levels of TSH due to low amounts of T_4. Thus, statistically significant positive associations between PBDEs and TSH may be due to low levels of iodine. However, we observed statistically significant inverse associations between pre-natal PBDEs and TSH. Therefore, while residual confounding may remain due to missing information on iodine status, the reported findings do not appear to be driven by iodine sufficiency. Second, selection bias is a potential concern given the significant differences in maternal characteristics between those included in the present study and those excluded due to missing PBDE measurements and/or thyroid hormones at age 3 years, including age, race/ethnicity, education, vitamin supplementation, smoking during pregnancy, and blood lead concentrations. Results from sensitivity analyses applying inverse probability weights indicates a pattern of inverse associations between prenatal PBDEs and TSH, though results were not statistically significant. Third, we measured thyroid hormones using immunoassays, which may have resulted in artefactual positive associations, because antibodies used to bind thyroid hormones may also bind with PBDEs

(Chevrier, 2013). However, Leonetti et al. (2014) reported a positive association between PBDEs and T_3 levels in placentas that were measured using liquid chromatography-tandem mass spectrometry. Thus, the positive associations observed in the present study may not be due to measurement error of thyroid hormones. We were also unable to examine PBDE metabolites (OH-PBDEs), which have a higher affinity to thyroid hormone serum binding proteins and may increase deiodination of T_4 (Marchesini et al., 2008; Meerts et al., 2000; Stapleton et al., 2009). In addition, higher brominated PBDEs, including BDE-209, were not examined. It is plausible that the relationship between PBDEs and thyroid response varies depending on the structure of PBDEs. Multiple comparisons is also a concern. However, we utilized multiple informant models rather than linear regression models, which greatly reduced the total number of models in the main analyses from 120 to 30.While there is no reduction in type 1 error, because we did not assume equal associations over time, multiple informant models are able to produce more precise confidence intervals. Sixth, PBDE congeners are highly correlated and thus it is difficult to estimate congener-specific associations that do not overlap with associations from other BDE congeners (Vuong et al., 2017). Lastly, the sample sizes for PBDE measures at age 1–3 years were modest and lower than prenatal measures, which reduced our statistical power and precision to estimate associations.

5. Conclusions

In this cohort, decrements in TSH concentrations at age 3 years were observed with increased prenatal BDE-28, -47, -100, and ΣPBDEs. In addition, higher TT_4 levels were observed with all individual PBDE congeners at age 2 and with BDE-100 and -153 at age 3 years. However, due to our limited sample size and results using imputed data, associations between postnatal PBDEs and thyroid hormones in children should be interpreted cautiously and findings need to be verified with other cohorts in future investigations. Child sex modified the associations between prenatal BDE-47 and -99 and thyroid hormones, with decreased TSH among females with higher prenatal BDE-47 and -99 while there were null associations with TSH among males. Future investigations need to integrate BDE-209 and OH-PBDEs in their examination of PBDEs as several toxicological studies indicate potential thyroid hormone disruption by these contaminants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.05.019.

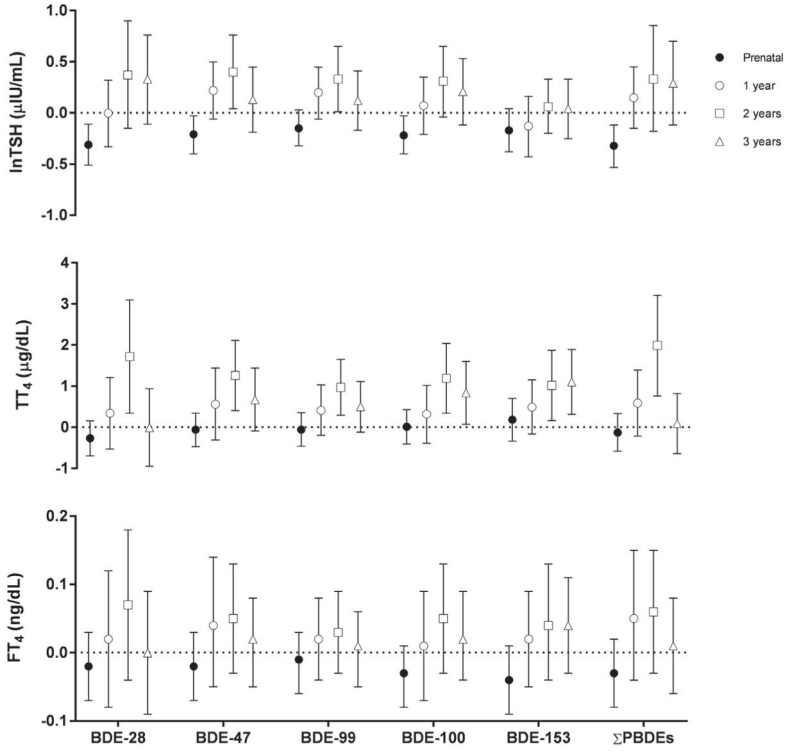

Fig. 1.

β-coefficients and 95% CIs from multiple informant models for associations of PBDEs (ng/g lipid) and thyroid hormones at age 3 years. Adjusted by maternal age, race/ethnicity, education, smoking status during pregnancy, alcohol consumption during pregnancy, vitamin use, maternal BMI, parity, maternal serum ΣPCBs, and child sex.

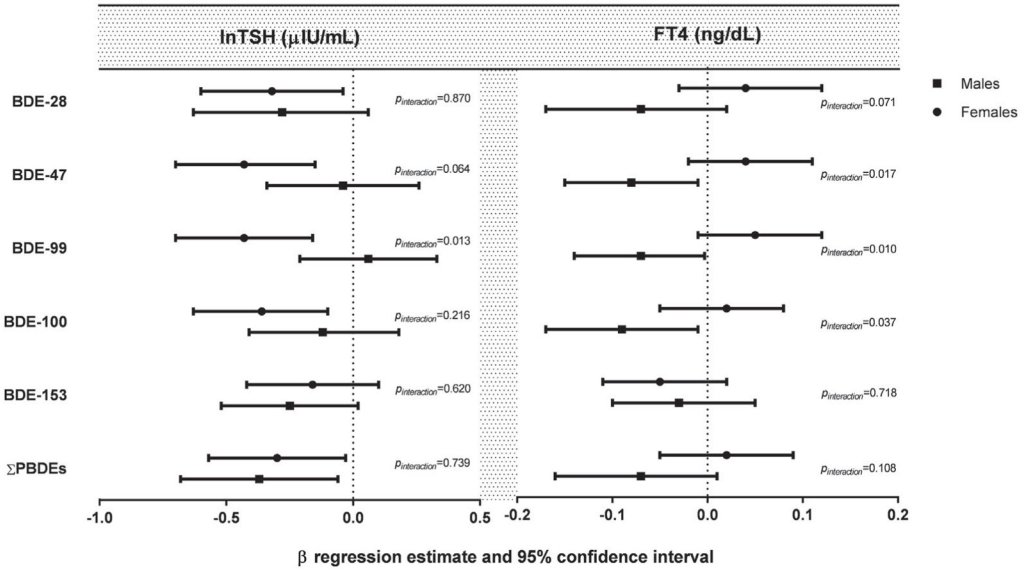

Fig. 2.

β-coefficients and 95% CIs from linear regression models for associations of prenatal PBDEs (ng/g lipid) and thyroid hormones at 3 years by child sex. Adjusted by maternal age, race/ethnicity, education, smoking status during pregnancy, alcohol consumption during pregnancy, vitamin use, maternal BMI, parity, maternal serum ΣPCBs, and child sex.

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Table 1

Serum concentrations of PBDEs (ng/g lipid), HOME Study.

			Percent detection	Percentile					Max	GM (GSD)
	n	LOD		Min	25th	50th	75th	95th		
Prenatal										
BDE-28	127	0.2–0.8	81.9	0.2	0.5	1.1	1.8	6.6	31.4	1.1 (2.6)
BDE-47	158	0.3–8.2	100	2.4	10.8	19.5	34.2	159.0	1290	21.1 (2.8)
BDE-99	158	0.2–3.1	98.7	0.6	2.4	4.4	7.6	34.3	465	4.8 (2.9)
BDE-100	156	0.2–2.8	96.2	0.1	2.0	3.3	6.9	27.6	172	3.9 (2.8)
BDE-153	158	0.2–3.1	96.2	0.6	2.4	4.2	8.7	39.1	152	5.2 (2.9)
ΣPBDEs	127	–	100	5.2	19.0	34.5	78.0	234.2	2046.9	39.6 (2.8)
1 *Year*										
BDE-28	56	0.2–0.8	91.1	0.3	1.1	2.0	3.4	7.7	82.3	2.1 (2.5)
BDE-47	77	0.3–5.8	100	6.4	36.0	72.2	106.2	218.3	383.2	61.0 (2.4)
BDE-99	76	0.3–2.9	100	1.7	8.5	18.7	34.1	78.9	87.9	16.8 (2.7)
BDE-100	76	0.3–2.9	100	1.1	5.5	11.7	19.1	42.7	76.0	10.2 (2.6)
BDE-153	76	0.3–2.9	100	0.9	3.4	7.6	12.0	31.3	112.1	7.0 (2.7)
ΣPBDEs	56	–	100	11.5	46.7	105.8	157.7	358.7	411.4	90.0 (2.5)
2 *Years*										
BDE-28	39	0.4–0.9	87.2	0.5	1.0	1.7	2.9	5.4	6.2	1.6 (2.0)
BDE-47	71	0.4–3.4	100	7.6	30.4	58.6	109.2	182.4	223	54.0 (2.2)
BDE-99	70	0.4–2.9	100	1.1	6.4	11.9	26.1	47.8	91.4	12.5 (2.5)
BDE-100	70	0.4–2.9	100	1.9	6.1	11.3	20.9	35.7	88.2	10.8 (2.3)
BDE-153	71	0.4–3.4	100	1.5	5.1	8.5	14.8	31.4	83.1	8.7 (2.3)
ΣPBDEs	39	–	100	19.3	41.6	86.0	166.2	296.2	324.3	82.2 (2.2)
3 *Years*										
BDE-28	47	0.4–0.9	80.9	0.5	0.9	1.5	2.5	4.7	5.1	1.5 (2.1)
BDE-47	71	0.4–2.2	100	6.1	18.5	36.7	78.3	154.2	194.7	40.3 (2.3)
BDE-99	71	0.4–2.2	100	0.8	4.1	8.2	19.8	42.5	65.6	8.8 (2.6)
BDE-100	71	0.4–2.2	100	1.7	4.4	10.2	15.9	35.1	49.0	9.1 (2.3)
BDE-153	71	0.4–2.2	100	1.6	4.7	9.0	15.9	33.0	58.8	8.8 (2.3)

			Percent detection	Percentile					Max	GM (GSD)
	n	LOD		Min	25th	50th	75th	95th		
ΣPBDEs	47	–	100	11.5	44.0	74.2	118.6	244.1	338.6	72.3 (2.2)

Abbreviations: GM, geometric mean; GSD, geometric standard deviation.

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Table 2

Maternal and child serum BDE-47 concentrations (ng/g lipid) by demographic characteristics, HOME Study (n = 162).

		BDE-47 GM (GSD)			
	Overall *n* (%)	**Prenatal (*n* = 158)**	**1 year (*n* = 77)**	**2 years (*n* = 71)**	**3 years (*n* = 71)**
Overall		21.1 (2.8)	61.0 (2.4)	54.0 (2.2)	40.3 (2.3)
Age, years					
< 25	28 (17.3)	27.8 (2.3)	46.2 (2.4)	63.8 (1.7)	38.6 (2.0)
25–34	108 (66.7)	21.5 (2.9)	66.6 (2.5)	54.6 (2.4)	43.2 (2.5)
≤35	26 (16.1)	14.8 (2.6)	51.8 (1.7)	40.0 (1.9)	27.2 (1.7)
Race/ethnicity					
Non-Hispanic White	115 (71.0)	18.3 (2.7) *	67.7 (2.3) *	53.4 (2.3)	40.5 (2.3)
Non-Hispanic Black and Others	47 (29.0)	30.2 (2.7)	41.1 (2.7)	56.5 (2.1)	39.7 (2.3)
Education					
High school or less	32 (19.8)	30.8 (2.4) *	59.0 (3.1)	65.1 (1.5)	39.9 (2.1)
Some college or 2 year degree	33 (20.4)	25.7 (2.5)	67.3 (1.9)	54.5 (1.9)	37.9 (2.0)
Bachelor's	60 (37.0)	17.2 (2.7)	62.9 (2.5)	57.7 (2.5)	48.0 (2.6)
Graduate or professional	37 (22.8)	18.0 (3.3)	54.3 (2.6)	44.4 (2.3)	32.8 (2.3)
Parity					
Nulliparous	75 (46.3)	19.8 (2.7)	51.5 (2.6)	49.9 (2.5)	38.4 (2.6)
Primiparous	53 (32.7)	19.2 (2.4)	73.9 (2.3)	67.5 (1.9)	47.1 (2.2)
Multiparous	34 (21.0)	28.2 (3.3)	64.0 (2.2)	38.5 (2.0)	31.2 (1.7)
Maternal Vitamin Use					
Daily	135 (83.3)	20.0 (2.7)	61.0 (2.4)	53.2 (2.2)	40.2 (2.3) *
< Daily	20 (12.4)	25.0 (3.0)	54.2 (2.9)	61.0 (2.3)	41.7 (2.5)
Never	7 (4.3)	36.8 (2.5)	101.0 (1.1)	–	–
Smoking Status during pregnancy					
No	142 (87.7)	19.4 (2.7) *	58.5 (2.4)	53.2 (2.3)	40.2 (2.3)
Environmental Tobacco Smoke	8 (4.9)	28.3 (2.8)	104.2 (1.4)	82.7 (2.1)	79.9 (1.3)
Active	12 (7.4)	52.8 (2.3)	72.4 (3.4)	54.9 (1.6)	32.1 (1.9)
Alcohol consumption during pregnancy					
Never	84 (51.9)	21.9 (2.8)	62.7 (2.3)	58.7 (2.2)	38.2 (2.3)

		BDE-47 GM (GSD)			
	Overall *n* (%)	**Prenatal (*n* = 158)**	**1 year (*n* = 77)**	**2 years (*n* = 71)**	**3 years (*n* = 71)**
< 1 Drink/Month	54 (33.3)	20.1 (2.8)	68.1 (2.1)	55.6 (2.1)	47.0 (2.3)
> 1 Drink/Month	24 (14.8)	20.9 (2.9)	40.3 (4.0)	35.9 (2.4)	30.8 (2.4)
Maternal BMI					
Underweight/Normal	68 (42.0)	18.4 (2.7)*	69.8 (2.3)	57.9 (2.2)	47.3 (2.2)
Overweight	57 (35.2)	19.8 (2.5)	51.7 (2.6)	48.2 (2.5)	36.1 (2.4)
Obese	37 (22.8)	30.4 (3.1)	59.5 (2.6)	56.3 (1.8)	32.5 (2.4)
Child sex					
Male	76 (46.9)	17.4 (2.6)*	70.2 (2.5)	55.9 (2.2)	36.2 (2.5)
Female	86 (53.1)	25.2 (2.9)	52.5 (2.4)	51.9 (2.2)	45.6 (2.0)
Preterm birth					
No	150 (92.6)	21.2 (2.8)	60.5 (2.5)	53.6 (2.2)	40.2 (2.3)
Yes	12 (7.4)	21.0 (2.6)	76.0 (1.8)	64.6 (2.5)	44.7 (3.2)
		Pearson r	Pearson r	Pearson r	Pearson r
Maternal Serum ΣPCBs (ng/g lipid)					
Mean ± SD: 53.0 ± 30.3		−0.08	0.12	−0.16	−0.07

Abbreviations: GM, geometric mean; GSD, geometric standard deviation.

*$p < 0.05$.

Table 3

Child thyroid hormone levels at age 3 years (n = 162), HOME Study.

Thyroid hormones	*n*	Min	Max	Mean(SD)
TSH[a]	158	0.5	5.6	2.0 (1.6)
TT_4	130	5.4	12.7	8.8 (1.2)
TT_3	95	96	212	148.8 (25.1)
FT_4	142	0.7	1.3	0.9 (0.1)
FT_3	77	0.5	3.3	4.3 (0.5)

Abbreviations: SD, standard deviation.

Units: TSH (uIU/mL), TT_4 (μg/dL), TT_3 and FT_4 (ng/dL), FT_3 (pg/mL).

[a]Geometric mean (GSD).