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Exploring autism spectrum disorder (ASD) and attention deficit disorder (ADD/ADHD) in children exposed to polybrominated biphenyl

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Background: Although the causes of attention-deficit/hyperactivity disorder (ADHD) and autism have not been identified, exposure to endocrine-disrupting chemicals, such as polybrominated biphenyl (PBB), during fetal development and early life has been suspected to impact neurological development. This study aims to investigate the association between prenatal and early life exposure to PBB and the development of ADHD and autism later in life.

Methods: Data from the Michigan PBB Registry, a cohort of Michigan residents who had been exposed to PBB in a mass contamination event in 1973, was leveraged for this nested case-control analysis among two distinct samples: (1) Those who self-reported ADHD or autism diagnosis, and (2) mothers who reported their child's ADHD or autism diagnosis. PBB exposure was measured in participants of the PBB Registry, and the mother's PBB level was used in mother-reported analyses. Cases were matched with controls by sex and year of birth. Conditional logistic regression models were used to estimate the association between PBB level and case status.

Results: PBB levels were higher among those who were exposed in early life compared with those exposed in utero (geometric mean: 0.300 ng/ml vs. 0.016 ng/ml). Among women in this cohort, a higher than expected proportion of self-reported ADHD diagnosis (11.11%), compared with population estimates. PBB was not associated with ADHD or autism in either self-reported or mother-reported analyses.

Conclusions: This study adds to the sparse literature about prenatal and early life exposure to PBB-153 and ADHD and autism. Future studies should examine potential effect modification by sex.

Keywords: Endocrine-disrupting chemicals; Attention-deficit/hyperactivity disorder (ADHD); Autism; Polybrominated biphenyl

Introduction

Diagnoses of mental health and behavioral disorders such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) have been increasing in the past couple of decades. As of 2016, 6.1 million children in the United States had been diagnosed with ADHD, and ASD surveillance indicates that 1 in 54 children have ASD.[1,2] These disorders can occur together. In fact, the Centers for Disease Control and Prevention estimates that nearly two-thirds of children with ADHD have another mental or developmental disorder such as depression, anxiety, or ASD.[1] Both disorders can drastically impact the quality of life for the affected child and symptoms continue throughout adulthood.

Although nongenetic causes of these disorders have not been identified, exposure to endocrine-disrupting chemicals (EDCs) during fetal development and early life has been suspected to impact neurological development and increase the risk of developing neurological disorders.[3] EDCs can disrupt or dysregulate normal hormone signaling pathways, which can induce neurological and behavioral effects, including ASD and ADHD.[4–8] However, epidemiological evidence for the effect of individual EDCs on neurological development is limited.

Michigan residents exposed to the EDC polybrominated biphenyl (PBB) in a mass contamination event have expressed concern regarding ADHD and ASD. Briefly, in 1973 a flame-retardant mixture of PBB (FireMaster) was accidentally added to livestock feed in place of a nutritional supplement (NurtiMaster) and was sent to farms throughout Michigan. The PBB-contaminated farm products (e.g., meat, milk, cheese, and

What this study adds:
This study adds to sparse literature about in utero and early life exposure to polybrominated biphenyl-153 and child developmental disorders like attention-deficit/hyperactivity disorder and autism spectrum disorder. We also add evidence to the literature on possible effect modification by sex in this association, which should be studied further.

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eggs) were distributed throughout the state, exposing millions of people to PBB.[9] Residents born after 1973 were exposed to PBB in utero and through breastmilk, PBB has been shown to cross the placenta.[10]

Though there are no epidemiologic studies on developmental exposure to PBB and ADHD, another group of brominated flame retardants, polybrominated diphenyl ethers (PBDEs), have been studied. One meta-analysis of developmental PBDE exposure found sufficient evidence of toxicity associated with decreased IQ score, but only found limited evidence of toxicity associated with ADHD and attention-related behaviors.[11] Another study examined pre- and postnatal exposure to PBDEs and found postnatal exposure was significantly associated with increased attention-related symptoms, but not hyperactivity-related symptoms at 4 years old. This study did not find significant associations between PBDE level at birth and any ADHD-related outcome.[12] Prenatal and early life exposure to polychlorinated biphenyls (PCBs), a heavily studied EDC, has not been associated with diagnosis of ADHD.[13,14] However in a study among frequent fish consumers in Michigan, prenatal PCB exposure was associated with increased impulsivity, decreased concentration, and working memory, but not with hyperactivity.[15]

Similar to ADHD, there is limited evidence of an association between ASD and PBB; however, there is one epidemiologic study investigating the association between PBB and ASD, directly. A population-based case-control study found increased PBB-153 level in the second trimester of pregnancy was not associated with ASD diagnosis.[16] Though, they did find PBDE exposure (PBDE-47, PBDE-99, PBDE-100, and PBDE-153) during pregnancy was protective of ASD diagnosis in boys, but found no association in girls.[16] Another study investigated autistic behaviors, measured using the social responsive scale (SRS), and PBB-153 and PBDE exposure during pregnancy. They found no association between PBB-153 and SRS score, but found a significantly protective effect of PBDE-85 on SRS score which indicates fewer autistic behaviors. Other PBDEs were not significantly associated with SRS score.[17] Both of these studies had PBB-153 levels that were lower than are found among Michigan residents.[16–18]

This article aims to estimate the effect of in utero and early life PBB exposure on diagnosis of ADHD and ASD in a highly exposed cohort from Michigan.[18] This study uses data from the Michigan PBB Registry, a cohort of individuals exposed to PBB during this contamination event and their children and grandchildren who were exposed in utero.

Methods

Data source

The Michigan PBB Registry is a cohort of Michigan residents created to study the health effects of PBB exposure after the mass contamination event in 1973.[9] In 1976 the Michigan Department of Health and Human Services, formally known as the Michigan Department of Public Health, created a cohort of exposed farmers, chemical plant workers, family members, and residents to study the effects of PBB exposure. Studies using data from this cohort are ongoing and are currently led by the PBB leadership team, consisting of academic scientists at Emory University, the PBB Citizens Advisory Board, the Pine River Superfund Citizens Task Force, and the Mid-Michigan District Health Department. Multiple questionnaires have been administered throughout the years to collect data from the PBB Registry members. This study uses questionnaire data collected during two phases: 2012–2015 and 2017–2019. During both time periods, individuals were recruited through community meetings conducted throughout the state advertised in the local press and online.[19] Many individuals belonged to the original PBB Registry created in 1976 by the Michigan Department of Health and Human Services and received postcard invitations to community meetings. Additional participants who attended community meetings were eligible for the study if they lived in Michigan during the contamination period (1973–1974) or were offspring of those who lived in the state at that time.

Informed consent was obtained from study participants and the study protocol was approved and overseen by Emory University's Institutional Review Board (protocol # CR003-IRB00045959).

Study populations

We conducted a nested case-control study that examines two distinct samples: (1) Adults who self-reported ADHD or ASD diagnosis and (2) mother-reported ADHD or ASD diagnosis of their child(ren). To be included in the self-reported ADHD analysis, participants were born after 1963 and had PBB measurements. The year 1963 was chosen as the cutoff to include participants who were exposed to PBB in their early childhood (<10 years old) while their brains were still developing. Self-reported participants born after 1973 are assumed to have been exposed in utero. Reports from mothers regarding their children's diagnoses were only available in the 2017–2019 data collection phase. To be included in the mother-reported ADHD and ASD analyses, participants were mothers with PBB measurements who had children born after 1973 and were therefore exposed in utero. Due to the long half-life of PBB, estimated to be between 10 and 15 years, women who were exposed during the 1973–1974 contamination event can expose their children to PBB in utero even when the children were conceived much later.[20–23]

Exposure assessment

Serum was collected from nonfasting Michigan PBB Registry participants around the time they completed the health questionnaires. Blood samples were collected via venipuncture and serum was isolated and stored at −80°C until analysis. Serum samples were analyzed for PBB-153, and PCB congeners (138, 153, and 180) using gas chromatography-tandem mass spectrometry (Agilent Technologies; Agilent 7890A gas chromatograph coupled to an Agilent 7000B tandem mass spectrometer) at the Laboratory for Exposure Assessment and Method Development in Environmental Research at Emory University's Rollins School of Public Health. Laboratory methods have been described in detail previously.[24]

Participants were exposed to a mixture of PBBs with PBB-153 as the predominant congener,[24] thus, PBB-153 was used as a marker of exposure to the PBB mixture. PBB and PCB serum analyses methods were the same for both study phases, though detection limits differ. Limits of detection (LOD) for 2012–2015 range from 0.001 to 0.006 ng/ml for PBB-153, LOD for 2017–2019 ranges from 0.005 to 0.05 ng/ml for PBB-153 and PCBs. PBB-153 level below the LOD was imputed as LOD/$\sqrt{2}$. The imputed PBB-153 level was right-skewed and natural-log transformed (lnPBB) to be used in regression analyses. PCB 153, 138, and 180 were summed to create a ΣPCB measurement. Before summation, PCB level below LOD was imputed as LOD/$\sqrt{2}$. Spearman correlation was used to quantify the correlation between PBB and ΣPCB.

Lipid analyses

In addition to PBB and PCB, serum triglyceride content was measured using an Abnova Triglyceride Quantification Assay Kit (Abnova Corporation), and total cholesterol content was measured using a Cayman Cholesterol Assay Kit (Cayman Chemical Company) according to the manufacturers' instructions. Total lipid levels were calculated using traditional methods.[25]

Outcome assessment

Self-reported

In analyses using self-reported ADHD; PBB Registry data from 2012 to 2015 and 2017 to 2020 were queried for case status. Participants were asked "Has a doctor ever told you that you have [ADD/ADHD]?," cases were defined as those who answered yes (n = 46), while controls answered no (n = 362). One participant indicated they did not have ADHD, but was taking a medication used for the treatment of ADHD, this participant was treated as a case in analyses. Those who indicated that they "may have this condition but have not been diagnosed by a doctor" (n = 30) or did not respond (n = 8) were removed from analysis. There were too few self-reported ASD cases (n = 4) for regression analysis, therefore this analysis was not pursued further.

Mother-reported

In analyses using mother-reported ADHD, data were extracted from questionnaires administered from 2017 to 2019. Only singleton births were included in the query, because there were too few multiple gestation births to use in an analysis. Participants were asked "Has a doctor ever told you that your child has [ADD/ADHD]?," cases were defined as those who answered yes (n = 38), while controls answered no (n = 181). Those who did not respond were removed from analysis. In analyses using mother-reported ASD, participants were asked "Has a doctor ever told you that your child has [ASD]?," cases were defined as those who answered yes (n = 13), while controls answered no (n = 206). Those who did not respond were removed from analysis.

Selection of cases and controls

Self-reported ADHD

Using the matched case-control sampling procedure outlined elsewhere,[26] cases were matched to controls by questionnaire (phase 1, 2), sex, if they were born before or after 1973, and a 5-year range of birth year. Cases and controls were able to be matched without replacement in a 1:3 ratio.

Mother-reported ADHD among their children

A 1:3 ratio of cases and controls was unable to be reached using the without-replacement approach.[26] Therefore a sampling with replacement approach was taken, which is described elsewhere.[27] All cases and controls were from phase 2 (2017–2019) and were born after 1973, so cases and controls were matched on sex and a 5-year range of birth year. Each case was matched with three controls, leading to n = 38 cases and n = 56 controls. Children age 4+ at the time of the mother's survey were included. This was based on the American Academy of Pediatrics clinical practice guidelines, which state that children 4–17 may be evaluated for ADHD.[28]

Mother-reported ASD among their children

For analyses of mother-reported ASD (as with mother-reported ADHD), a 1:3 ratio was unable to be reached using sampling without replacement, so again the sampling with replacement method was used.[27] Cases and controls were matched by sex and a 5-year range of birth year. Each case was matched to three controls, leading to n = 13 cases and n = 30 controls. For mother-reported ASD, we did not restrict by a child's age at the time of the survey since the youngest case of ASD was born in 2011.

Statistical analysis

Conditional logistic regression models were used to estimate the association between PBB level and case status. In self-reported ADHD analyses, logistic regression models were additionally stratified by early life exposure (born 1963–1972) and in utero exposure (born after 1973) to PBB. Models were adjusted for preterm birth (born before 37 weeks gestation) and lipids. Adjusted models were only able to include participants from Phase 1 (n = 42) as questions about gestational age of the participant were not asked in Phase 2. Mother-reported ADHD analyses were adjusted for preterm birth, birthweight, ΣPCB quartile, lipids, and time since birth. Time since birth was calculated using child's birthdate and sample collection date. Time since birth was used to adjust for the elimination of PBB between the birth of the child and sample collection. Mother-reported ASD analyses were adjusted for birthweight, time since birth, and lipids. Preterm birth and ΣPCB quartile were not added to the adjusted models because of the small sample size and low power. All analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Self-reported ADHD

Forty-six ADHD cases were self-reported, of which, 76% (n = 35) were exposed to PBB in utero, and the other 24% (n = 11) were exposed in early life. A majority of cases were female (n = 30, 65.22%) and from phase 1 questionnaires (n = 29, 63.05%) (Table 1). A majority of phase 1 and 2 participants were female (66.18%), among all women eligible for inclusion in the self-reported ADHD analysis sample 11.11% reported having ADHD. This is very similar to the percentage among men (11.59%) (Supplemental Table 1; http://links.lww.com/EE/A268). Among those exposed in utero, the mean birth year was 1982, which was the same for cases and controls. For those exposed in early life, the mean birth year was 1968, which was again the same for cases and controls. Few participants were born preterm (6.45%, n = 1 case, n = 6 controls). PBB levels were higher among those exposed in early life than those exposed in utero. Among those that were exposed to PBB in early life, the geometric mean PBB-153 level of cases was 0.302 ng/ml (SD 0.108), and the mean of controls was 0.299 ng/ml (SD 0.083). The geometric mean for those exposed in utero was lower than for those exposed in early life. Cases had a slightly higher geometric mean PBB level (0.02 ng/ml, SD 0.005) than controls (0.015 ng/ml, SD 0.003).

In conditional logistic regression modeling, adjusted models showed null results (odds ratio [OR] = 1.02; 95% confidence interval [CI] = 0.72, 1.43) for the association between PBB and ADHD (Figure 1, Table 2). In models stratified by exposure period (in utero vs. early life), unadjusted in utero effect estimates were similar to overall (OR = 1.06; 95% CI = 0.79, 1.41), while unadjusted early life models had a higher effect estimate, but more uncertainty (OR = 1.26; 95% CI = 0.47, 3.38). Adjusted in utero models were also similar to overall models (OR = 1.05; 95% CI = 0.74, 1.48). In supplemental analyses participant age was added as an additional confounder, effect estimates did not differ after the addition of participant age to the model (Supplemental Table 1; http://links.lww.com/EE/A268).

Mother-reported ADHD among their children

Thirty-eight ADHD cases were mother-reported with a majority male (n = 25, 65.76%) (Table 3, Supplemental Table 2; http://links.lww.com/EE/A268). The mean year born for cases was 1990, while the mean for controls was 1989. Birthweight and number of preterm births were similar between cases and controls. The geometric mean PBB level was higher in controls (0.246 ng/ml, SD = 0.061) than cases (0.210, SD = 0.059). More

Table 1.
Descriptive statistics for self-reported ADHD sample from the Michigan PBB Registry (n = 184) (2012–2019)

		In utero exposure			Early life exposure			
		Cases[c]	Controls[c]	Total[d]	Cases[c]	Controls[c]	Total[d]	Overall total
n		35	105	140	11	33	44	184
Sex	Male (n [%])	12 (34.29)	36 (34.29)	48 (34.29)	4 (36.36)	12 (36.36)	16 (36.36)	64 (34.78)
	Female (n [%])	23 (65.71)	69 (65.71)	92 (65.71)	7 (63.64)	21 (63.64)	28 (63.64)	120 (65.22)
Questionnaire	Phase 1 (2012–2015)	25 (71.42)	75 (71.42)	100 (71.42)	4 (36.36)	12 (36.36)	16 (36.36)	116 (63.05)
	Phase 2 (2017–2019)	10 (28.57)	30 (28.57)	40 (28.57)	7 (63.64)	21 (63.64)	28 (63.64)	68 (36.96)
Birth year (mean [SD])		1982 (6.97)	1982 (6.73)	1982 (6.76)	1968 (3.30)	1968 (2.68)	1968 (2.81)	1978 (8.62)
Preterm (n [%])[a]		1 (4.00)	6 (8.70)	7 (7.45)	0 (0.00)	0 (0.00)	0 (0.00)	7 (6.54)
PBB 153[b] (ng/ml) (mean (SD))		0.020 (0.005)	0.015 (0.003)	0.016 (0.002)	0.302 (0.108)	0.299 (0.083)	0.300 (0.067)	0.033 (0.005)

[a]Available in phase 1 only.
[b]Imputed LOD/sqrt(2), geometric mean.
[c]Column %.
[d]Row %.

controls were in the highest quartile of ΣPCB exposure (n = 16, 28.57%) compared with cases (n = 6, 15.79%). PBB-153 and ΣPCB levels were not correlated (ρ = 0.07, *P* = 0.49).

In conditional logistic regression analyses, unadjusted models showed for every ln(1)-ng/ml increase in PBB-153, the odds of ADHD decrease by 13% (OR = 0.87; 95% CI = 0.65, 1.17) (Figure 2, Table 4). Though once adjusted for preterm birth, birthweight, time since birth, ΣPCB, and lipids, the OR was attenuated to 0.92 (95% CI = 0.55, 1.54). In supplemental analyses maternal age was added as an additional confounder, the OR was further attenuated to 0.97 (95% CI = 0.55, 1.70) (Supplemental Table 2; http://links.lww.com/EE/A268).

Mother-reported ASD among their children

Thirteen ASD cases were mother-reported with a majority male (69.23%). The average year born for cases was 1995, while controls was 1994 (Table 3, Supplemental Table 2; http://links.lww.com/EE/A268). Cases also had a larger percentage born preterm (n = 3, 23.08%) than controls (n = 4, 13.00%). Cases also had a lower birthweight (113. Oz, SD = 27.51) than controls (124.51 oz, SD = 20.38). The geometric mean PBB-153 level was higher in controls (0.309 ng/ml, SD = 0.072) than cases (0.289, SD = 0.164). More controls were in the highest ΣPCB quartile, 33.33% of controls compared with 7.69% of cases. PBB-153 and ΣPCB levels were not correlated (ρ = 0.14, *P* = 0.38).

Unadjusted models showed for every ln(1)-ng/ml increase in PBB-153, the odds of ASD decreased by 35% (OR = 0.65; 95% CI = 0.3, 1.41) (Figure 2, Table 4). After adjustment for birthweight, time since birth, and lipids, the odds of ASD decrease further by 54% for every 1-ng/ml increase in PBB-153 (OR = 0.46; 95% CI = 0.09, 2.32).

Discussion

In self-reported ADHD analyses, this study compared in utero and early life exposure to PBB-153 among cases and controls. This is the first study investigating the association between PBB-153 and ADHD. Nonsignificant findings for both time periods may be due to small sample size, but is consistent with other studies that have found nonsignificant associations between other flame retardants and ADHD.[11] The effect estimate for early life PBB exposure and ADHD was larger than for in utero PBB exposure. This aligns with the one other study that measured both prenatal and postnatal (age 4) PBDE measurements and found age 4 PBDE-47 levels were significantly associated with ADHD symptoms and poor social competence, but prenatal PBDE-47 levels were not associated with these outcomes.[12] These studies indicate that early life may be a particularly sensitive period of exposure to brominated flame retardants in the development of ADHD. Future studies should examine both periods because important brain development occurs postnatally.[29,30] In our sample, two-thirds of self-identified ADHD cases were female, similar to their proportion of the respondents indicating a 1:1 ratio of cases among males and females. This is contrary to prevalence estimates that show a male-to-female ratio of 4:1 in community samples.[31] PBB is an EDC and has been shown to act similarly to estrogen in previous research.[32] Although this study did not find an association between PBB and ADHD, there may be sex differences that we are underpowered to detect. Future studies with larger sample sizes are needed to explore differences in the relationship between PBB and ADHD by sex.

Similar to the self-reported ADHD analyses, in utero PBB-153 was not significantly associated with mother-reported ADHD diagnosis, but had a slightly protective association. The null findings could be due to exposure misclassification by using mother's PBB-153 measurement instead of the individual's PBB-153 measurement. As discussed previously, no other studies have examined PBB-153 in relation to ADHD. Previous studies measuring

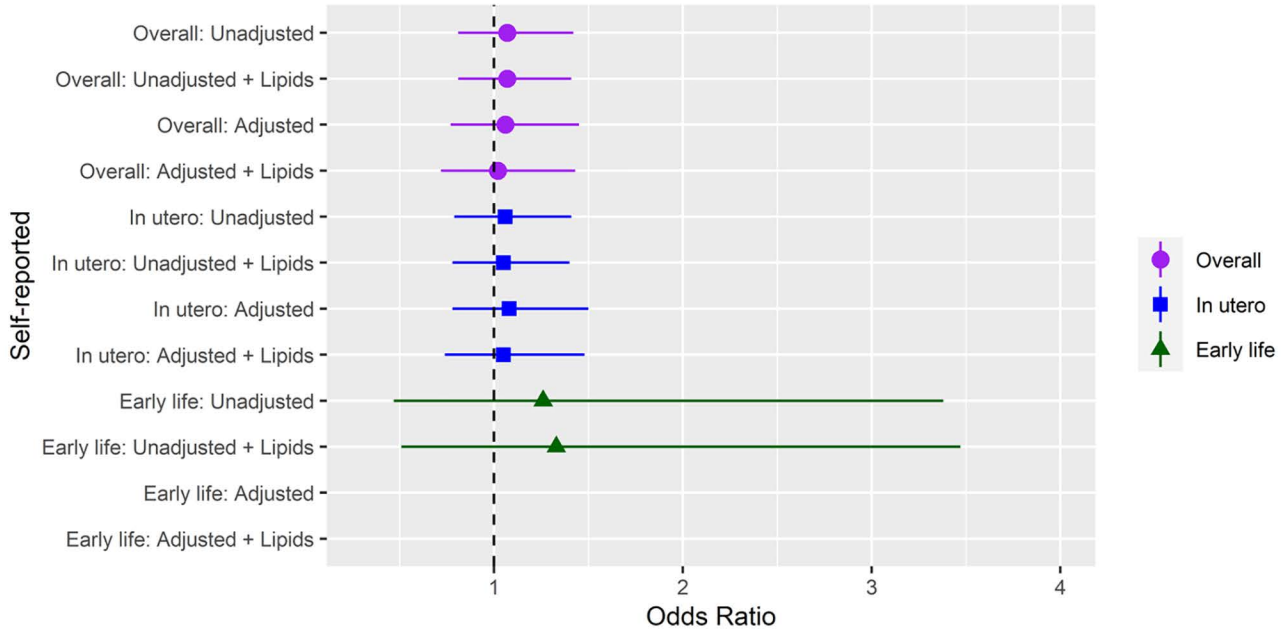

Figure 1. Conditional logistic regression modeling the association between serum PBB levels and self-reported ADHD from the Michigan PBB Registry (n = 184) stratified by exposure timing.

Table 2.

Conditional logistic regression modeling the association between serum PBB levels and self-reported ADHD from the Michigan PBB Registry (n = 184) stratified by exposure timing

	Overall					In utero exposure					Early life exposure				
	n	Cases	Controls	OR	95% CI	n	Cases	Controls	OR	95% CI	n	Cases	Controls	OR	95% CI
Unadjusted	184	46	138	1.07	0.81, 1.42	140	35	105	1.06	0.79, 1.41	44	11	33	1.26	0.47, 3.38
Unadjusted + Lipids	183	46	137	1.07	0.81, 1.41	139	35	104	1.05	0.78, 1.40	44	11	33	1.33	0.51, 3.47
Adjusted[a]	107	29	78	1.06	0.77, 1.45	94	25	69	1.08	0.78, 1.50	13	4	9	–	–
Adjusted + Lipids[a]	107	29	78	1.02	0.72, 1.43	94	25	69	1.05	0.74, 1.48	13	4	9	–	–

[a]Adjusted with preterm birth, only available in phase 1.
95% CI indicates Confidence interval; OR, odds ratio.

Table 3.

Descriptive statistics for mother-reported sample for ADHD (n = 94) and ASD (n = 43) from the Michigan PBB Registry (2017–2019)

		Mother-reported ADHD			Mother-reported ASD		
		Cases[b]	Controls[b]	Total[c]	Cases[b]	Controls[b]	Total[c]
N		38	56	94	13	30	43
Sex	Male (n [%])	25 (65.76)	31 (55.36)	56 (59.57)	9 (69.23)	18 (60.00)	27 (62.79)
	Female (n [%])	13 (34.21)	25 (44.64)	38 (40.43)	4 (30.77)	12 (40.00)	16 (37.21)
Year born (mean [SD])		1990 (9.75)	1989 (9.71)	1990 (9.67)	1995 (5.44)	1994 (6.85)	1994 (6.4)
Preterm (n [%])		7 (18.42)	9 (16.07)	16 (17.02)	3 (23.08)	4 (13.00)	7 (16.28)
Birthweight (oz) (mean [SD])		120.21 (19.94)	120.98 (19.19)	120.66 (19.4)	113.69 (27.51)	124.51 (20.38)	121.17 (23.04)
PBB 153[a] (ng/ml) (mean [SD])		0.210 (0.059)	0.246 (0.061)	0.231 (0.043)	0.289 (0.164)	0.309 (0.072)	0.302 (0.070)
ΣPCB Quartiles	1 (Lowest)	8 (21.05)	14 (25.0)	22 (23.4)	3 (23.08)	7 (23.33)	10 (23.26)
	2	10 (26.32)	15 (26.79)	25 (26.6)	4 (30.77)	7 (23.33)	11 (25.58)
	3	14 (36.84)	11 (19.64)	25 (26.6)	5 (38.48)	6 (20.00)	11 (25.58)
	4 (Highest)	6 (15.79)	16 (28.57)	22 (23.4)	1 (7.69)	10 (33.33)	11 (25.58)

[a]Imputed LOD/sqrt(2), geometric mean.
[b]Column %.
[c]Row %.

other brominated flame retardants (PBDEs) have found mixed results in association with ADHD.[11] Roze et al,[33] found in utero exposure to PBDE-47 was significantly associated with lower attention sustained childhood behavior checklist score at 5–6 years old. Another study found in utero exposure to PBDE-47 was significantly associated with increased odds of ADHD at 5–7 years old.[34] Though yet another study found a nonsignificant protective association between PBDE-47 and ADHD childhood behavior checklist at 3–7 years.[35] Future studies should examine exposure to brominated flame retardants in utero and in early life to examine sensitive periods of exposure and elucidate the relationship between these chemicals and ADHD.

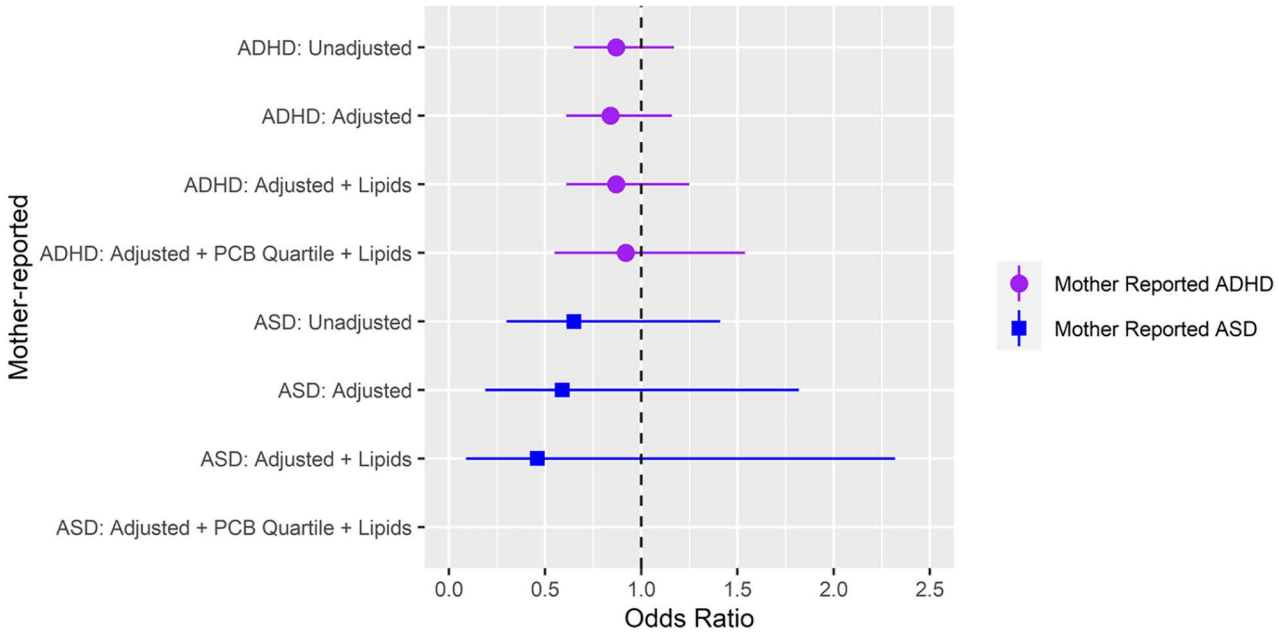

Figure 2. Conditional logistic regression modeling the association between maternal PBB levels and mother-reported ADHD (n = 94) and ASD (n = 43) from the Michigan PBB Registry.

Table 4.

Conditional logistic regression modeling the association between maternal PBB levels and mother-reported ADHD (n = 94) and ASD (n = 43) from the Michigan PBB Registry

	Mother-reported ADHD					Mother-reported ASD				
	N	Case	Control	OR	95% CI	N	Case	Control	OR	95% CI
Unadjusted	94	38	56	0.87	0.65, 1.17	43	13	30	0.65	0.30, 1.41
Adjusted	92	38	54	0.84	0.61, 1.16	42	13	29	0.59	0.19, 1.82
Adjusted + Lipids	90	36	54	0.87	0.61, 1.25	42	13	29	0.46	0.09, 2.32
Adjusted + PCB Quartile + Lipids	90	36	54	0.92	0.55, 1.54	–			–	–

Mother-reported ADHD adjusted for preterm, birthweight, and time since birth. Mother-reported ASD adjusted for birthweight, and time since birth.

Similar to the mother-reported ADHD analysis, the mother-reported ASD analyses suffer from possible exposure misclassification from using mother's PBB-153 level as opposed to the individual's PBB-153 level. There may also be residual confounding because the small sample size did not have adequate power to include certain covariates (e.g., preterm birth and ΣPCB quartile). This study found a nonsignificant protective association between in utero PBB-153 exposure and ASD. Although the literature is sparse, another study found nonsignificant protective association with SRS score-measuring behaviors associated with autism.[17] Braun et al,[17] also found a statistically significant protective association between PBDE-85 and SRS score, while other brominated flame retardants had mixed protective and harmful nonsignificant associations. Another study found PBDE-47, PBDE-99, PBDE-100, PBDE-135, and a sum measurement of all brominated flame retardants (including PBB-153) to be significantly associated with the odds of ASD diagnosis (Lyall et al[16]). Though, PBB-153, by itself, was not significantly associated with ASD diagnosis. More research is needed in this area to examine the effects of prenatal exposure to brominated flame retardants on ASD. Additionally, the use of different measures, for example, ASD diagnosis versus behaviors associated with ASD, may be adding to the mixed results seen in the literature.

The Michigan PBB Registry is a unique cohort that has been extremely useful for studying the health effects of human exposure to brominated flame retardants since 1975. One of the goals of the registry is to listen to the concerns of the community affected by this mass contamination effect and study the health effects that are of concern to them. This population continues to have higher PBB and other persistent organic pollutants levels than the general population.[18] Many in the exposed community perceived an increase in developmental disorders associated with PBB exposure and this study was undertaken to address that question. This study adds to sparse literature about in utero and early life exposure to PBB-153 and child developmental disorders like ADHD and ASD. This study is limited by small sample sizes, residual confounding, and possible exposure misclassification. The small number of cases limits the inference of these analyzes, as we could not adjust for certain confounding variables. However, our use of conditional logistic regression models better controls for confounding though matching with these small samples. The results of this study may not be generalizable to the general population as this population was highly exposed to PBB. Another limitation of this study is the variation of limit of detection values for PBB samples analyzed in different time periods. This may limit describe the effect of PBB at low levels. However, this is a highly exposed population and all PBB samples were analyzed using the same method.[18] This study is also limited by a self-reported (or mother-reported) diagnosis of ADHD or autism, as opposed to a diagnosis as reported by a health care provider. To reduce bias from outcome misclassification we did not include participants who were unsure of their diagnosis. Validity measures for self-reported ADHD and

autism are still needed and would greatly improve observational research into these conditions.[36] Although PBB level was assessed after ADHD or ASD diagnosis, PBB has a long half-life[20,22,23] and exposure only occurred during the contamination event in 1973–1974, which allows for interpretation of these results.

Conclusions

In this cohort, serum PBB levels were higher among those exposed in early life compared with those exposed in utero. The sex ratio of self-reported ADHD was 1:1 in this population, and the proportion of women self-reporting ADHD was higher than in the general population. However, PBB levels were not associated with self-reported ADHD or autism diagnosis. Mothers' PBB levels were also not associated with ADHD or autism diagnosis among their children.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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