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Prenatal PBDE Exposure and Neurodevelopment in Children 7 Years Old or Younger: a Systematic Review and Meta-analysis

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Abstract

Purpose of Review Evidence suggests prenatal polybrominated diphenyl ethers (PBDE) exposure effects on human neurodevelopment, but this is controversial due to conflicting research results. We conducted a systematic review and meta-analysis to summarize available peer-reviewed data of prenatal PBDE exposure effects on cognitive function, motor function, and behavior problems in children.

Recent Findings Eligible birth cohort studies (January 1996–February 2017) were located through PubMed®, Web of Science®, or Google Scholar® and reported PBDE concentration in cord blood, maternal blood, or colostrum, as well as neurodevelopment assessment scores in children. Comprehensive meta-analysis (v.3.3.070, November 20, 2014) was used to calculate summary effect. Covariates are child age category (≤ 2, 3–5 and 6–7 years), location, and time period.

Summary Six studies were included in meta-analysis. We found that prenatal PBDE exposure significantly correlated with decreased cognitive function ($n_{pooled} = 804$; $k = 6$; $r = -0.237$; 95% CI −0.441, −0.010; $p = 0.041$), decreased motor function ($n_{pooled} = 794$; $k = 5$; $r = -0.350$; 95% CI −0.610, −0.022; $p = 0.037$), and increased behavior problems ($n_{pooled} = 307$; $k = 3$; $r = 0.393$; 95% CI 0.133, 0.602; $p = 0.004$). Child age category was a significant covariate. The largest summary effect by child age category was ≤ 2 years for cognitive function and 6–7 years for behavior problems. Biomarker type was also a significant covariate. PBDEs measured in colostrum had a similar neurodevelopment effect size to cord blood, but PBDEs measured in maternal blood had a smaller effect size, relative to cord blood. The effect of prenatal PBDE exposure on behavior may be underestimated because only maternal blood was used as the exposure biomarker in eligible behavior assessments. Our study suggests that prenatal PBDE exposure adversely affects neurodevelopment. This study was underpowered due to the low number of available studies meeting eligibility criteria, although the use of pooled data analysis helped to offset the underpowered meta-analysis.

Keywords PBDE · Neurodevelopment · Prenatal · Biomarker · Systematic review · Meta-analysis

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Introduction

Background

Polybrominated diphenyl ether (PBDE) flame retardants are persistent organic pollutants commonly found in the environment [1–4]. Predominantly used in polyurethane foam and plastics for consumer products, PBDEs entered the commercial market in the 1970s, driven by demand created by California Technical Bulletin 117 (1975) that required certain consumer products sold in California be able to withstand direct contact with an open flame for 12 s without sustaining combustion [2, 5–7]. The size of the California consumer market made the flame-resistant standard a de facto requirement for rest of the USA [7].

Theoretically, there are 209 PBDE congeners with one to ten bromine atoms attached to the diphenyl ether substrate; however, only three congeners were commercially produced: pentabromodiphenyl ether (pentaBDE), octabromodiphenyl ether (octaBDE), and decabromodiphenyl ether (decaBDE) [2, 3]. Billions of pounds of PBDEs were incorporated into consumer goods, such as furniture, electronics, textiles, carpet padding, plastics, vehicle seats and car seats, and placed on the market, primarily in the USA [8, 9]. PBDEs are additive flame retardants—they are not covalently bonded to foam or a plastic polymer matrix—so they volatilize or leach into the environment and potentially bioaccumulate [3, 10, 11].

Regulatory Response

Concern regarding persistence, bioaccumulation, and toxicity of some PBDE congeners led to regulatory restrictions and phaseout of most PBDEs by 2014. Regulatory remedies restricting environmental release of PBDEs to reduce human exposure were initiated by the European Union (EU) Commission in 2001 over concerns of bioaccumulation after research detected pentaBDE derivatives in human breast milk [12, 13]. The European Union (EU) subsequently banned pentaBDE and OctaBDE in consumer products in 2004 [14]. The US Environmental Protection Agency (US EPA) implemented a voluntary production phaseout of pentaBDE and octaBDE [8, 15, 16]. By 2008, the EU restricted all commercially produced PBDEs to less than 0.1% by weight in most electronic or electrical devices [17, 18]. In 2009, tetra-, penta-, hexa-, hepta-, and octaBDE were added to the Stockholm Convention on Persistent Organic Pollutants (POPs) [1, 19]. In 2012, the US EPA proposed a Significant New Use Rule (SNUR) for six common PBDE congeners, effectively limiting their continued use in US commerce [20]. This initiated a voluntary production phaseout of decaBDE by the last two manufacturers of the chemical in the USA by December 31, 2013 [20]. California Technical Bulletin 117 was changed to allow furniture manufactures an option of not using flame retardants if their products would not combust when in contact with a *smoldering* ignition source, rather than an *open flame* ignition source specified under the 1975 version [7].

Regulatory action has reduced PBDEs detected in the environment and in humans [21, 22•, 23, 24]. However, PBDEs are still detected in house dust, food, animal tissue, and humans, particularly in adipose tissue, breast milk, and blood lipids [5, 8, 25–27]. This is due in part to continued use of furniture containing PBDEs and from the environmental persistence and bioaccumulation of several PBDE congeners [3, 5]. In 2002, US adult PBDE sera levels were ten times the levels found in their European or Asian counterparts, but until recently, there were few research studies on human health effects of PBDE exposure [8, 27, 28].

PBDE Fate and Transport, Routes of Human Exposure

PBDEs are lipophilic and have a moderate to high octanol-water partition coefficient, depending on amount of bromination [8]. Partitioning coefficient estimates the environmental fate of a chemical regarding how likely the chemical will dissolve in water or bioaccumulate in lipids of plants and animals. The higher the octanol-water coefficient, the more likely a chemical is to bioaccumulate. All PBDE congeners have varying levels of environmental persistence [4, 9, 29, 30]. Gaseous PBDEs or airborne PBDE-contaminated dust are the main forms of transport in the environment [8, 31–33]. The primary fate of PBDEs is deposition in soil and sediment, which is a route of PBDE uptake into the food chain [8, 31, 34, 35].

Environmental exposure studies measuring PBDE concentration in various human biomarkers showed that PBDE exposure increased rapidly after commercialization [2, 36–43]. Common congeners found in human tissue include tetraBDE, hexaBDE, and decaBDE [28, 44]. Humans are exposed to PBDEs through their environment, primarily via air, food, and house dust and fetal exposure via maternal exposure that crosses the placenta [8, 26, 28, 43, 45•, 46–48].

The half-life of PBDE congeners varies by bromination level and by the environmental compartment or tissue [30]. The relatively consistent level of decaBDE measured in human blood sera by surveillance programs in several countries, combined with a relatively short half-life of decaBDE in human sera (11 to 18 days), suggests that humans are continuously exposed to this PBDE congener [26, 30, 49, 50•].

PBDE Exposure and Risk to Neurodevelopment

Prenatal exposure to neurotoxic agents, such as PBDEs, can interrupt neurodevelopment processes and have lasting adverse effects. Fetal neurodevelopment occurs in early gestation and is especially susceptible to environmental toxins [51]. Previous research indicates a positive association between

prenatal PBDE exposure and adverse neurodevelopment outcomes, but conflicting results in the research exist regarding the significance, magnitude and direction of association [2, 5, 8, 46, 47, 52–56]. Data from animal studies suggest exposure to certain PBDEs disrupts normal endocrine function associated with neurodevelopment, although the results are not consistent [5]. Toxicokinetic studies show reduced ability of young animals to excrete PBDEs, resulting in a higher body burden compared to adults [5].

With few epidemiological available studies available, the US Environmental Protection Agency (US EPA) established PBDE exposure thresholds for neurobehavioral effects based on animal studies [37–40]. The US EPA reference dose for oral exposure (RfD-oral) for neurobehavioral effects is 0.1 μg/kg/day for BDE-47 (tetraBDE) and BDE-99 (pentaBDE), 0.2 μg/kg/day for BDE-153 (hexaBDE), and 7 μg/kg/day for BDE-209 (decaBDE) [37–40]. PBDE concentrations in cord blood and colostrum from recent birth cohort studies are close to and, in some cases, exceed the US EPA RfD-oral threshold for neurobehavioral effects [52, 53, 55].

Study Objective

The aim of this research is to determine the summary effect of prenatal PBDE exposure on neurodevelopment outcomes (cognitive function, motor function, and behavior problems) in children. To accomplish this aim, we conducted a systematic review and meta-analysis of eligible birth cohort studies reporting a measure of association between prenatal PBDE exposure measured in cord blood, prenatal maternal blood or colostrum, and neurodevelopment test scores assessed in children.

Rationale

There are two motivations for conducting this research. First, while regulatory actions have removed PBDEs in *new* foam-containing furniture and electronics, there is a large stock of *existing* consumer products in use that contain PBDEs. Consumers using older furniture are likely to be of a lower socio-economic status (SES), such as college students and young families. Prenatal exposure to PBDEs might be modifying the effect of SES on neurodevelopment outcomes. Second, the rigor employed in conducting a systematic review and meta-analysis provides value in summarizing the effect of an exposure on a health outcome when controversy in existing research results exist, especially when the exposure occurs in utero.

Methods

The systematic review a priori protocol began with developing a literature search strategy and eligibility criteria for the selection of birth cohort studies. Case-control and cross-sectional studies were not eligible because temporality of prenatal PBDE exposure prior to or shortly after birth was a necessary condition. Search engines used were (1) PubMed®, (2) Google Scholar®, and (3) Web of Science®. Study selection followed the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) flow chart [57], shown in Fig. 1. Study eligibility criteria included type of study (birth cohort), study participants (consenting pregnant women and their infants/children), exposure (PBDEs detected prenatally or shortly after birth), outcome (neurodevelopment assess using a validated instrument by trained and competent personnel), measure of association, and effect size. Any study meeting eligibility criteria was screened for relevance without consideration to geography.

Study Search Strategy

Study inclusion criteria were limited to studies in English language conducted between January 1, 1996 and February 28, 2017. The search strategy was confined to peer-reviewed scientific articles, books, government documents, conference proceedings, technical reports, reviews, theses, and dissertations; the last source was reviewed for the citation list only. Exclusion criteria restricted patents, audio/visual sources, blogs, microfilm, newspaper articles, and studies on populations already covered under another study. Table S-1 in the *Supplemental Material* lists all search terms used. Study search terms included the use of a Boolean multi-character wildcard. Search terms were: "PBDE*" OR "polybrominated diphenyl ether" OR "brominated flame*" OR "BFR" AND/OR "neuro*" AND/OR "develop" AND/OR "*natal" AND/OR "infant" AND/OR "child*" AND/OR "in utero" AND/OR "review" AND/OR "meta-analysis."

Study Screening Strategy and Data Extraction

Titles of identified records were first screened for relevance and duplicates were removed. Studies were then screened for relevance using keyword searches, such as a "mouse," "rat," or "animal." Citation lists of non-relevant studies were reviewed and relevant studies from the citation list were then screened. Abstracts were screened by reading each abstract twice by one reviewer, yielding 17 eligible studies for full-text review, which were also read twice by one reviewer. The reference list of each eligible study was examined to identify additional studies meeting eligibility criteria. No new study was identified from this examination. Data extraction took place after full-text review for eligibility. Data from each eligible study was entered onto a systematic review coding sheet, yielding seven studies that met eligibility criteria for meta-analysis.

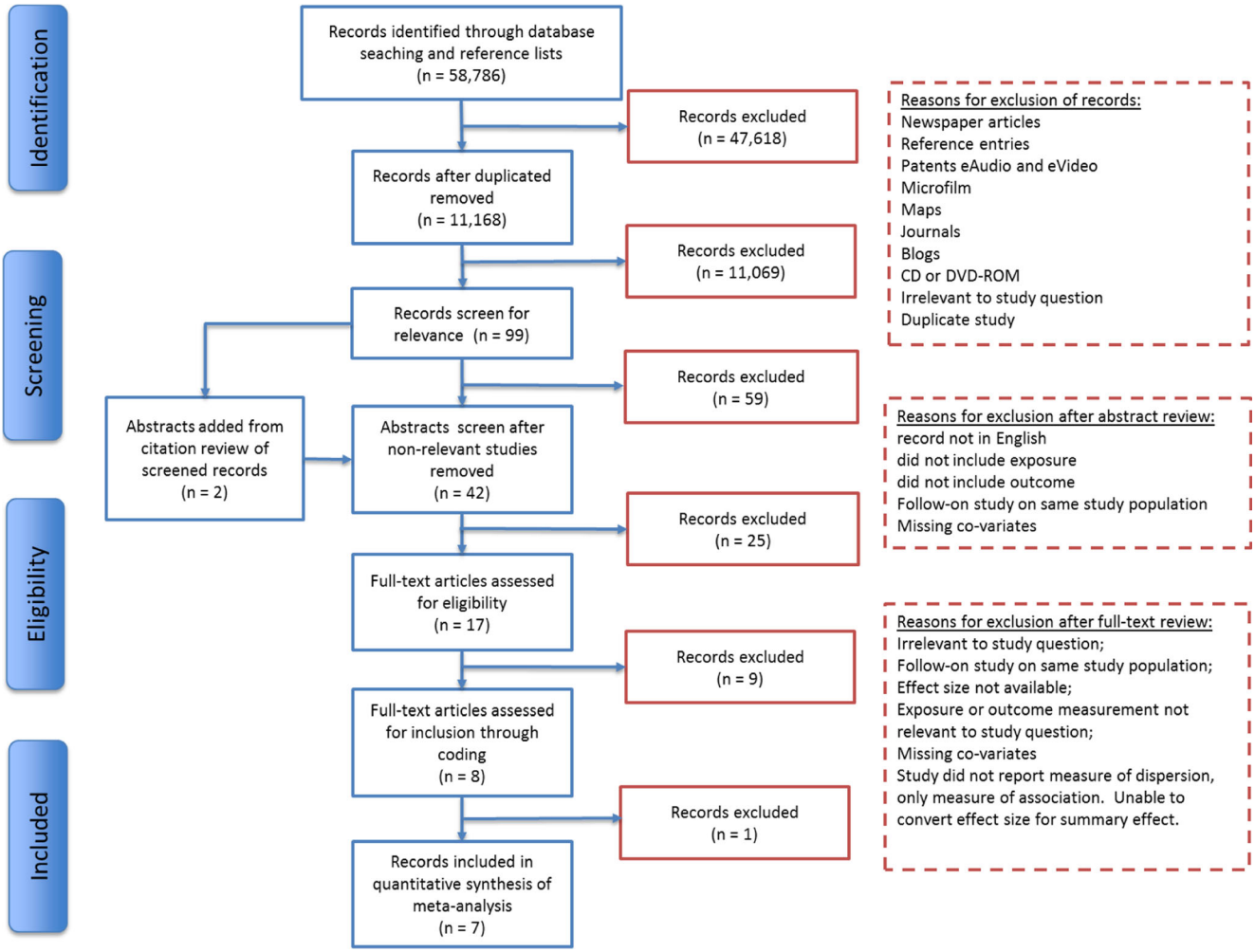


Fig. 1 PRISMA flow diagram on record selection and exclusion criteria [2]

Study Characteristics

The characteristics of participants in each study are listed in Table 1. The first birth cohort study to measure prenatal PBDE exposure and neurodevelopment outcomes was Roze [56], followed by Herbstman [55]; Shy [54]; Gascon, 2011 [53]; Gascon, 2012 [52]; Eskenazi [58]; and Chen [46]. Reporting choice of measures of association and dispersion were not consistent across studies. Shy et al. [54] met eligibility criteria for the systematic review but was not included in the meta-analysis because a measure of dispersion was not reported. Risk of bias at individual study level was assessed and estimated as low, given the narrow eligibility criteria of recent birth cohort studies published in peer-reviewed journals and that each study sample size was greater than 50 participants.

Covariates

Common study characteristics reported across all studies were location, type of biomarker collected as a substitute for prenatal PBDE exposure, timing of biomarker collection, and age of the infant/child when neurodevelopment was assessed. Highest age of neurodevelopment testing in eligible studies was 7 years old. Maternal age was reported across studies, but as a categorical variable in some studies and a continuous variable in others. An estimate of mean maternal age is 27–30 years old. An infant/child age category variable was created, with categories delineating development phases of infant/toddler (0–2 years) preschool (3–5 years) and early school years (6–7 years) [59]. Other covariates included region (the USA, EU, or Asia), latitude (absolute), time period of study, and neurodevelopment category.

The neurodevelopment assessment instruments utilized in individual studies included in this meta-analysis ($k = 6$) are described in detail in Table 2. Several neurodevelopment assessment instruments have overlapping primary measures. Based on a review and categorization of each assessment instrument's scales and subscales, we created a neurodevelopment outcome category with three variables, cognitive function, motor function, and behavior problems, for use in this meta-analysis. Not

Table 1 Characteristics of participants in studies included in the systematic review and meta-analysis

	Roze et al. [56]	Herbstman et al. [55]	Gascon et al. [53]	Shy et al. [54]	Gascon et al. [52]	Eskenazi et al. [58]	Chen et al. [46]
Sample size	62	152	88	36	290	360	309
Study/cohort Name	COMPARE	WTC	INMA	N/A	INMA	CHAMACOS	HOME
Location	Groningen, the Netherlands	NYC, USA	Menorca, Spain	Southern Taiwan	Basque Region and Catalonia, Spain	Salinas, CA, USA	Cincinnati, OH, USA
Exposure biomarker	Maternal blood (35th week)	Cord blood	Cord blood or sera at 4 years	Cord blood	Colostrum collected ≤ 4 days of delivery	Maternal blood (~ 24–29 weeks) and/or at delivery; sera at 7 years	Maternal blood (16th week)
Maternal age at delivery	*32*[a]	*31.2*	*29.7*	*29.8*	Study reported maternal age at delivery as < 29 years, (22.8%); 29–31 years, (29.6%); 32–33 years, (26.2%); > 34 years (21.4%)	*25*[c]	Study reported maternal age at delivery as "< 25" (20%); "25–34" (63%); "≥ 35" (17%).
Mean (SD or range)	(24–42, range)	(4.9, SD)	(4.3, SD)	(4.88, SD)		(5, SD)	
Maternal BMI, prepregnancy	*23*[a]	Reported as "prepregnancy weight (lb.)," 135.7 (7.16, SD)[b]	*22.5*	*22.6*	Study reported maternal prepregnancy BMI as ≤ 21.7, (33.4%); 21.7–24, (33.4%); > 24, (33.2)	Reported as "underweight, < 18.5%" (37.6%); "normal, 18.5–24.9" (41.5%); "overweight, 25–29.9" (0.4%); "obese, > 30" (20.5%)[c]	*Not reported*
Mean Kg/m2 (SD or range)	(17–37, range)		(3.4) SD	(4.52) SD			
Maternal education (%)				*Not reported*			
< High school	Maternal education reported as "primary" $n = 4$; "secondary" $n = 30$; and "tertiary" $n = 28$	13.8	Study reported as "completed secondary school or higher" (55.7%).		Study reported maternal education as: "primary or without education," 21.3%; "secondary," 45.9%; "university," 32.8%	Reported as "< 6th grade" (42.0%); "7th–12th grade" (36.9%); "completed high school" (2.1%)[c]	Study reported "high school or less" (23%);
		16.4					23
		22.4					33
		22.4					21
High school		25.0					
Some college or 2-year degree							
College degree							

Table 1 (continued)

	Roze et al. [56]	Herbstman et al. [55]	Gascon et al. [53]	Shy et al. [54]	Gascon et al. [52]	Eskenazi et al. [58]	Chen et al. [46]
Graduate school							
Socio-economic status				*Not reported*			
Below US poverty level for publication year (%)	Study reported Home Observation for Measurement of the Environment (HOME) questionnaire mean score (range) completed by mother during the first year after birth as 33 [24–37]	10.5	Not reported *17.9* *54.8* *9.5* *17.9*		Study reported social class as "professionals and technicians" (44.5%); "other non-manual" (30.0%); "manual" (25.5%)	Reported as "worked during pregnancy" (64.1%). Family income reported as "≤ poverty level" (61.3%); "within 200% of poverty level" (35.0%); "> 200% of poverty level" (3.7%)[c]	Study reported "household income" as "< $20,000" (20%); "$20,000–79,999" (51%); "> $80,000" (29%)
Occupation			Not reported				
Professional, mngr., tech. (%)							
Skilled manual (%)							
Partial skilled or unskilled (%)							
Unemployed (%)							
Material hardship							
Race/ethnicity (%)							
May be > 100% due to more than one race/ethnicity per study participant.							
American Indian/ Alaska Native	100[e]	Not reported	100[e]	100[e]	100[e]	100[e]	Study reported race/ ethnicity as "non-Hispanic white" (67%); non-Hispanic black and others" (33%)
Asian		32.9					
Black		15.1					
Caucasian		40.8					
Hispanic		Not reported					
Other		11.2					
Marital status (%)	*Not reported*		*Not reported*	*Not reported*	*Not reported*		
Married/living as married		82.9				80.1[c]	81
Smoking status (%)	*Not reported*			*Not reported*			*Not reported*
Non-smoker		Not reported	Not reported		Not reported	Not reported	
Smoked during pregnancy		Not reported	17.1		12.9	6.1[c]	
Exposed to 2nd hand smoke		17.1	Not reported		Not reported	Not reported	
Infant gestation age (weeks) Mean (SD or range)	*40*[a] (37–42, range)	*39.4* (1.2, SD)	Study reported percent of preterm births (<37 gestation weeks) at 4.6%.	*38.5* (1.29, SD)	Study reported Gestation Age as "< 39.8 weeks (median)" (50.0%)	*38.9*[c] (1.7, SD)	*Not reported*
	3653[a]	*3412.0*	*3186*	*3350*		*3449*[c]	*Not reported*

Table 1 (continued)

	Roze et al. [56]	Herbstman et al. [55]	Gascon et al. [53]	Shy et al. [54]	Gascon et al. [52]	Eskenazi et al. [58]	Chen et al. [46]
Infant birth weight (g) Mean (SD or range)	(2335–5790, range)	(487.4, SD)	(from primary study; no range or SD reported)	(433, SD)	Study reported as "Low birth-weight (< 2500 g)" "yes" (2.4%); "no" (97.6%)	(516, SD)	
Infant sex Male (%)	*Not reported*	50.7	48.9	*Not reported*	48.3	*48.6*[d]	46

[a] Primary study, Meijer, et al., (2008). *Environmental Science & Technology*; 42 [9]:3428–3433

[b] Primary study, Lederman, et al., (2004). *Environmental Health Perspectives*, 112 [17]: 1773–1778

[c] Primary study, Eskenazi, et al., [58]. *Environmental Health Perspectives*, 112 [10]: 1116–1124

[d] Eskenazi, et al., [58]. *Pediatrics*, 118 [1]: 233–241

[e] Study did not report race/ethnicity but did report location where recruitment took place and/or maternal birthplace and/or language preference of participants. The percentage is assumed to be the race/ethnicity of the sample population for general purposes only

all instruments in each study were included in the meta-analysis. Only Gascon et al. [53] utilized a social competence instrument (California Preschool Social Competence Scale, CP-SCS) so it was not included in the meta-analysis. The Development Coordination Disorder Questionnaire (DCD-Q), utilized by Roze et al. [56], was included in the meta-analysis using inverse value as the effect size direction of the DCD-Q is opposite of other motor function assessments.

Data Analysis

Comprehensive Meta-Analysis (CMA, v. 3.3.070, November 20, 2014) was used for descriptive statistics and to calculate summary effect and meta-regression [60]. A random effects model was used as the comparison model for meta-analysis since there was a high level of heterogeneity in both the exposure and the outcome between studies. Due to non-normal distributions of effect sizes across studies, Fisher's Z transformation with 95% confidence interval (95% CI) was chosen as the meta-analysis effect size. Fisher's Z was calculated directly from Pearson's correlation coefficient or from odds ratio or risk ratio using CMA software. Effect size was estimated from beta coefficients using a multi-step process. First, CMA software converted beta coefficients and 95% CI to point estimates and standard errors. Next, Peterson's imputation formula was used to convert point estimates to correlation coefficient, r, and converted to the effect size used in the meta-analysis with Fisher's Z transformation equation [60–63].

Power analysis for a random effects meta-analysis followed the recommended approach from Borenstein et al. and is described in detail in the Supplemental Material [60]. Power analysis for each neurodevelopment category, as well as estimates for the number of studies needed to achieve a power of 0.80, is shown in Table 3.

The potential influence of publication bias was examined using techniques also recommended by Borenstein et al., including Rosenthal's fail-safe N, Orwin's fail-safe N, Duval and Tweedie's trim and fill with funnel plot, and restricting analysis to larger studies [60]. Detailed descriptions of the publication bias tests are in the Supplemental Material.

This systematic review protocol was registered with PROSPERO® on January 20, 2017 as CRD42017055622 and followed the guidance provided PRISMA statement checklist [57], provided in Table S-2 of the Supplemental Material. IRB review determined this study did not meet the definition of research using human subject as set forth by the Department of Health and Human Services, 45 CFR 46.

Results

The pooled sample size of each neurodevelopment category for the six studies included in the meta-analysis (n_{pooled}), and a

Table 2 Neurodevelopment assessment instruments utilized in each eligible study

Study (year)	Number	Exposure matrix	Motor function	Age tested	Cognitive function	Age tested	Behavior problems	Age tested
Roze et al. [56]	90	Maternal blood	Movement ABC Touwen's test DCD-Q	5, 6 years	WPPSI-R NEPSY-II AVLT TEACh	5, 6 years	CBCL ADHD (Scholte)	5, 6 years
Herbstman et al. [55]	152	Cord blood	BSID-II	1, 2, 3 years	BSID-II WPPSI-R	1, 2, 3 years 4, 6 years		
Gascon et al. [53]	88	Cord blood	BSID-I	12, 18 months				
Shy et al. [54]	36	Cord blood	BSID-III	8, 12 months	BSID-III	8, 12 months		
Gascon et al. [52]	290	Colostrum	MSCA	4 years	MCSA PPVT	4 years	CADS ADHD-DSM-IV	4 years
Eskenazi et al. [58]	283	Maternal blood	MSCA WRAVMA Finger-tapping	5, 7 years 5, 7 years 5, 7 years	WISC-III PPVT WISC-IV	7 years 5 years 7 years	CBCL ADHD Conf. Index CADS-ADHD K-CPT BASC-2	5 years 5 years 7 years 5 years 7 years
Chen et al. [46]	309	Maternal blood	BSID-II	1, 2, 3 years	BSID-II WPPSI-III	1, 2, 3 years 5 years	BASC-2	2, 3, 4, 5 years

DCD-Q Developmental Coordination Disorder Questionnaire, *BSID-I, II, III* Bayley Scales for Bayley Scales of Infant Development (BSID) I, II or III, respectively, *MSCA* McCarthy Scales of Children's Abilities, *WRAVMA* Wide Range Assessment of Visual Motor Ability, *WPPSI-III, -R* Wechsler Preschool and Primary Scale of Intelligence III, Revised, respectively, *NEPSY-II* Neuropsychological Assessment, Second Ed., *AVLT* Rey's Auditory Verbal Learning Test, *TEACh* Test of Everyday Attention for Children, *PPVT* Peabody Picture Vocabulary Test, *WISC-IV* Wechsler Intelligence Scale for Children, Fourth Ed., *CBCL* Child Behavior Checklist, *CADS* Conners ADHD/DSM-IV Scales

number of studies in each neurodevelopment category (k) are as follows: $n = 804$, $k = 6$ for cognitive function, $n = 794$, $k = 5$ for motor function, and $n = 307$, $k = 3$ for behavior problems. Results indicate that prenatal PBDE exposure is significantly correlated with decreased cognitive function ($\beta = -0.237$; 95% CI −0.441, −0.010; $p = 0.041$), decreased motor function ($\beta = -0.350$; 95% CI −0.610, −0.022; $p = 0.037$), and increased behavior problems ($\beta = 0.393$; 95% CI 0.133, 0.602; $p = 0.004$). Figure 2a–c provides the forest plots for each neurodevelopment category.

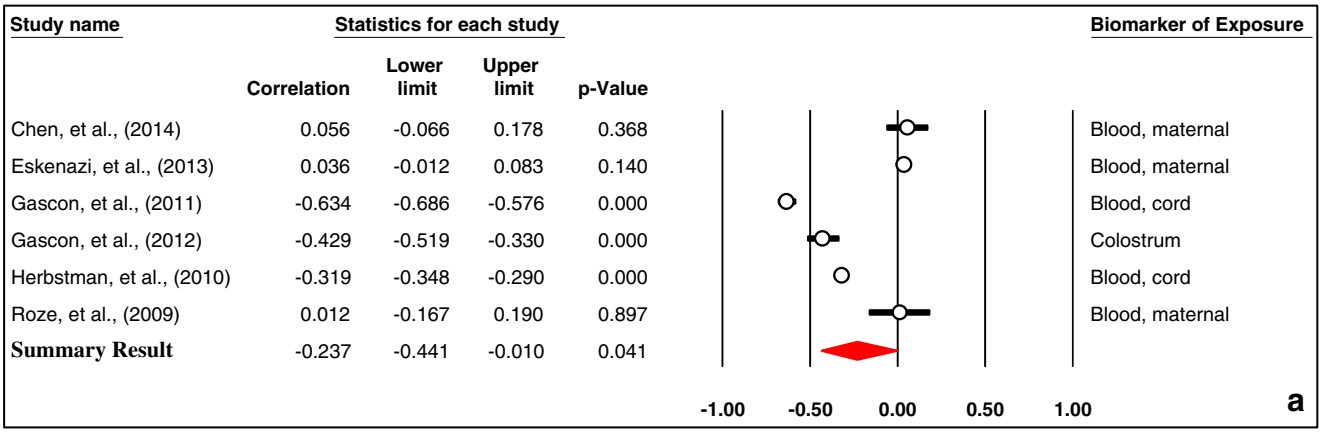
Multivariate analysis from meta-regression indicates biomarker type and infant/child age category are significant moderator variables. Meta-regression analysis on other covariates was not significant. Colostrum had a similar effect size to cord blood as a biomarker estimate for prenatal PBDE exposure, but the effect size was smaller when prenatal PBDE exposure was estimated with maternal blood. Studies that assessed cognitive function and motor function used cord blood, colostrum, and prenatal maternal blood to estimate prenatal PBDE exposure. Studies that measured behavior problems only used maternal blood as the biomarker.

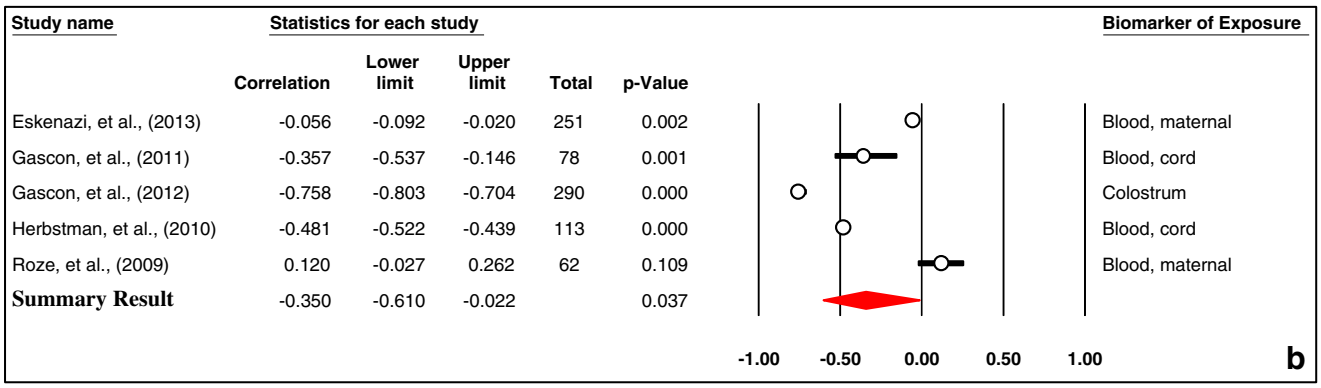
Meta-regression analysis results on cognitive and motor function for biomarker type are summarized in Table 4. Meta-regression was not conducted on behavior problems for biomarker type since all studies in this neurodevelopment category only used maternal blood as the prenatal PBDE exposure biomarker, and hence, there were no other biomarkers available for comparison. The summary in Table 4 indicates that using maternal blood as an estimate of prenatal PBDE exposure may reduce the effect size on cognitive function and motor function.

Power calculations indicate that this meta-analysis is underpowered. The power for each neurodevelopment category is 0.304, 0.313, and 0.354 for cognitive function, motor function, and behavior problems, respectively. The summary of power calculations in Table 3 lists the number of studies

Table 3 Power analysis for each neurodevelopment category and estimate of studies needed to achieve 0.5 and 0.8 powers in future meta-analysis

Neurodevelopment category	Power actual	K actual	Power estimate 50%	K estimate	Power estimate 80%	K estimate
Cognitive function	0.304	6	0.500	12	0.800	23
Motor function	0.313	5	0.500	9	0.800	19
Behavior problems	0.354	3	0.500	5	0.800	10





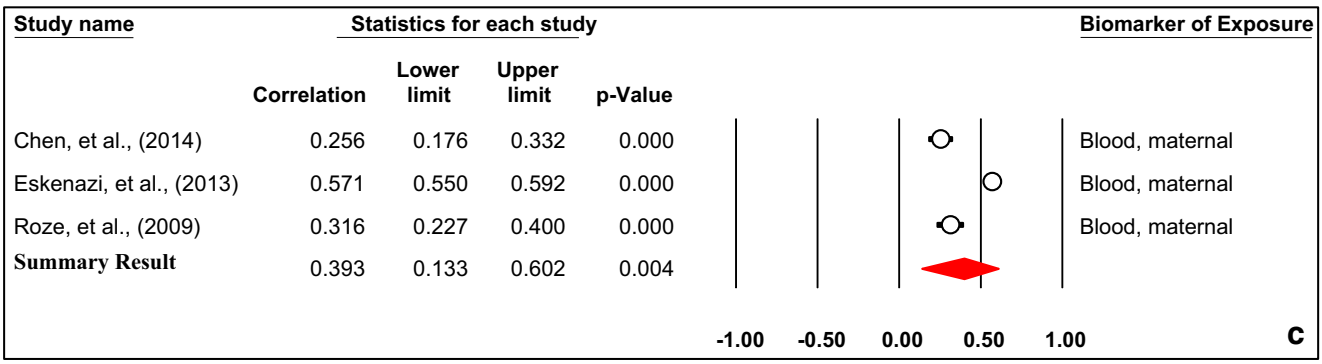


Fig. 2 **a** Summary effect (random model) of prenatal PBDE exposure on *cognitive function*, $n_{pooled} = 804$, $k = 6$. **b** Summary effect (random model) of prenatal PBDE exposure on *motor function*, $n_{pooled} = 794$, $k = 5$. **c** Summary effect (random model) of prenatal PBDE exposure on *behavior problems*, $n_{pooled} = 307$, $0 = 3$

needed to achieve 0.50 and 0.80 power for each neurodevelopment category. For cognitive function, motor function, and behavior problems, respectively, 12, 9, and 5 studies are needed to achieve a power of 0.50; 23, 19, and 10 studies are needed to achieve a power of 0.80, respectively.

The influence of publication bias on the summary effect is summarized in Table 5. Based on the analysis of the four tests recommended by Borenstein et al. [60], the likelihood there are unpublished studies that could influence the significance or change the substantive importance of the meta-analysis summary effect is low.

Discussion

The results of this study indicate that prenatal PBDE exposure is associated with a significant decrease in cognitive and motor function and a significant increase in behavior problems among children 7 years of age or younger.

There is a difference between the types of PBDE congener manufactured and types of congeners detected in human biomarkers, suggesting that PBDE metabolism includes debromination. Smaller PBDE congeners are more persistent, bioaccumulative and toxic, and have structural similarities to

Table 4 Summary of meta-regression analysis on cognitive function and motor function for biomarker type

Neurodevelopment category	Covariate	Coefficient	SE	95% lower	95% upper	*p* value (two-sided)
Cognitive function	Intercept maternal blood as reference	0.036	0.079	− 0.118	0.191	0.645
	Cord blood	− 0.564	0.119	− 0.797	− 0.330	0.000*
	Colostrum	− 0.495	0.157	− 0.802	− 0.188	0.002*
Motor function	Intercept maternal blood as reference	− 0.046	0.018	− 0.081	− 0.011	0.010*
	Cord blood	− 0.470	0.032	− 0.533	− 0.407	0.000*
	Colostrum	− 0.944	0.062	− 1.065	− 0.824	0.000*

Studies reporting behavior problems only used maternal blood as biomarker and, therefore, not included in this summary

*p value $< \alpha = 0.05$

thyroid hormones [64•, 65••, 66]. From conception through the 10th week of gestation—a critical window of human neurodevelopment—maternal thyroid hormones signal differentiation and relocation to neuronal cells in the embryo, forming main structures in the brain, such as the limbic system, as well as the spinal cord and major peripheral nerves [67–69]. The nervous system continues to develop in the second trimester when the fetal thyroid gland is able to synthesize thyroid hormones [67]. The last trimester is a time of rapid brain growth and the ramping up of synaptogenesis and myelination processes, which extend into early childhood [67]. The limbic system, formed during the first trimester of fetal development, directs sensory stimuli to the cerebral cortex, where cognition, motor coordination, and executive function take place [67]. Thus, damage to the developing limbic system can impact cognition, motor function, and behavior. Prenatal PBDE exposure may contribute to limbic system damage and subsequent adverse neurodevelopment assessment test scores [64, 65••, 70•, 71].

Although, regulation restricts PBDEs in new consumer products, upholstered furniture, mattresses, vehicles, and car seats manufactured before 2014 are still likely to contain PBDEs. Consumers using older durable goods are likely to be in a lower socio-economic strata [72•]. Infants born to families living in a lower SES are more vulnerable to factors associated with cognitive and behavior problems [72•, 73]. In 2008, Zota et al. discovered people living in a lower SES are more likely to have a higher body burden of PBDEs [74•]. Thus, it is important to consider prenatal PBDE exposure as a potential effect modifier when investigating the effect of SES attributes on neurodevelopment outcomes. Some factors to consider in prenatal PBDE exposure include the age of the

Table 5 Summary of analysis of potential effects of publication bias on summary effect of meta-analysis for each neurodevelopment category

		Test parameters			
Test	Neurodevelopment Category	Effect	Metric	Measurement	Likelihood of effect[a]
Rosenthal's fail-safe N	Cognitive function	Missing studies nullify significance of summary effect	No. of missing studies to bring p-value > alpha	436	L
	Motor function			422	L
	Behavior problems			764	L
Orwin's fail-safe N	Cognitive function	Missing studies nullify substantive importance of summary effect	No. of missing studies to bring summary effect to ± 0.05	24	L
	Motor function			19	L
	Behavior problems			32	L
Duval and Tweedie's trim and fill	Cognitive function	Estimate unbiased summary effect	Estimated unbiased effect (calculated effect)	− 0.256 (− 0.237)	L
	Motor function			− 0.233 (− 0.350)	L
	Behavior problems			0.523 (0.393)	L
Restricting to larger studies	Cognitive function	Removal of small studies decreases bias	Magnitude of summary effect change (calculated effect)	− 0.292 (− 0.237)	L
	Motor function			− 0.451 (− 0.350)	L
	Behavior problems			0.456 (0.393)	L

Source: [51]

[a] Likelihood of effect: low = L, medium = M, high = H [60].

home, bed mattress, upholstered furniture, and car, as well as the amount of time spent inside the home, cleaning frequency and method, and time spent in the car.

A goal of conducting epidemiological research is to quantify the magnitude and direction of association between exposure and outcome, but this can be especially difficult for prenatal exposures. Prenatal exposure to lipophilic environmental contaminants, like PBDEs, partition into lipids of blood, adipose tissue and breast milk. Breast milk is a common biomarker surrogate for prenatal exposure because it is considered non-invasive relative to using maternal blood during pregnancy. Umbilical cord blood is also considered non-invasive and, as our results indicate, may be more representative of fetal exposure. The use of colostrum as a biomarker for prenatal PBDE exposure in Gascon et al. [52] was novel and was more likely to approximate third trimester prenatal exposure than samples of breast milk collected after 1-week postnatal. The results of our study indicate PBDE concentrations measured in colostrum had a similar summary effect to that of cord blood for cognitive and motor function assessment scores.

Behavior problem was the neurodevelopment category requiring the *least number* of additional studies [10] to achieve a study power of 0.80, indicating a larger effect size associated with prenatal PBDE exposure and behavior problems, even with a small number of studies ($k = 3$). Studies that assessed behavior problems in this meta-analysis only used maternal blood as a biomarker, which attenuated the effect size of cognitive and motor function in the results of our study. This suggests that the summary effect of behavior problems might have been higher if cord blood or colostrum was the biomarker. Hence, the summary effect size of prenatal PBDE exposure on behavior problems may be *underestimated* in this study.

Infant/child age category relative to the type of neurodevelopment assessment was a significant moderator variable on test scores, suggesting assessing cognitive function and motor function in age category 0–2 years. A larger summary effect was observed for behavior problems in the 6–7 years age category, suggesting that assessing specific neurodevelopment categories in these respective age categories may reveal a more pronounced effect size.

Strengths and Limitations

This research had several strengths. The narrow eligibility criteria of birth cohort studies and exposure biomarkers provide evidence of strength of association, temporality, plausibility and biological gradient. Development of a neurodevelopment assessment category for use in the meta-analysis streamlined the coding and statistical analysis process and helped visualize trends in meta-regression. Studies that reported beta coefficients were not discarded. Instead, they were converted to a point estimate that could be used with the CMA® software to calculate summary effect, which increased the number of eligible studies, pooled sample sizes and overall power of the meta-analysis results.

There are also limitations. First, only one reviewer conducted the eligibility screening and assessment coding for the systematic review. Various guides on systematic reviews recommend screening and coding activities be conducted in parallel by at least two reviewers and results compared and measured with a kappa statistic [75]. Utilizing one reviewer creates potential susceptibility to selection and information bias. To control for this, the reviewer read each abstract twice and each full-text study included in meta-analysis at least twice. Second, the creation and use of a neurodevelopment category (i.e., cognitive function, motor function, and behavior problems) from the primary measures of neurodevelopment assessment instruments somewhat diluted the effect size of subscales that overlapped two or more neurodevelopment categories. This was viewed as an acceptable tradeoff because it made for a more conservative summary effect estimate, reduced processing time and complexity, and increased pooled sample sizes for different ages and neurodevelopment categories. Finally, the project was underpowered due to the low number of studies included in the meta-analysis. Power = 1—type II error (false negative). For meta-analysis, a false negative is failing to detect an effect when the effect is present. Thus, a low-powered study suggests an underestimation of effect size.

Conclusions

The epidemiologic utility of a systematic review and meta-analysis is the rigor employed in study selection and review and the value to translational science in summarizing evidence from existing studies to communicate a clearer picture of overall public health effect to clinicians, policy-makers, and the public. There is increasing evidence that PBDE exposure affects endocrine disruption, especially with regard to thyroid function, which in turn affects neurodevelopment. The effect of prenatal PBDE exposure on behavior needs further investigation, and we recommend exploring this effect using cord blood or colostrum to estimate fetal exposure.

We also recommend conducting additional systematic reviews and meta-analyses using broader eligibility criteria to include birth cohort studies that use breast milk or meconium along with colostrum and maternal/cord blood as biomarkers for prenatal PBDE exposure and conducting a systematic review and meta-analysis on the efficacy of various human biomarkers in approximating postnatal exposures to PBDEs and other halogenated organics that are suspected of endocrine disruption.

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Author Contributions Hudson-Hanley wrote the manuscript, which is based on an independent project final report in fulfillment of a Ph.D. program requirements. Kile, Irvin, and Flay reviewed the final report and manuscript and provided recommendations for improvement. MacDonald provided guidance neurodevelopment assessment instruments that aided in the creation of the neurodevelopment category covariate as an outcome measure in the meta-analysis. MacDonald also reviewed the draft final report and provided guidance. Bellinger provided guidance on neurotoxicity and neurodevelopment assessments that informed the creation of the neurodevelopment category used in the meta-analysis. Su provided guidance on toxicology. Smit provided guidance on manuscript format.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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