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Review

The association between prenatal exposure to phthalates and cognition and neurobehavior of children-evidence from birth cohorts

Qi Zhang[a,b], Xin-Zhen Chen[a,b], Xin Huang[a,b], Min Wang[a,b], Jing Wu[a,b,*]

[a] Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

[b] Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

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ABSTRACT

Background: Phthalate have been detected widely in the environment; while several studies have indicated that prenatal phthalate exposure has adverse effects on neurodevelopment, the results were inconsistent.

Objective: We aimed to determine the current research status of the relationship between prenatal exposure to different types of phthalate and cognition and behavioral development in children. We conducted a systematic review to evaluate the current state of knowledge.

Methods: We systematically searched PubMed, Web of Science, and EMBASE electronic databases up to May 2018 with manual searches of the references of retrieved publications and relevant reviews. Only birth cohort studies that reported on the association between phthalate exposure and cognitive or behavioral development were included in this review. We evaluated the risk of bias for each of the included studies using a modified instrument based on the Cochrane Collaboration's "Risk of Bias" tool.

Result: Twenty-six birth cohort studies met our inclusion criteria, nine of which investigated the impact of phthalate exposure during pregnancy on cognition, 13 on neurobehavior, and 4 on both cognition and neurobehavior. However, ten articles reported that the effect of prenatal exposure to phthalates on cognitive development was statistically significant, 15 articles reported that the effect of prenatal exposure to phthalates on neurobehavior was statistically significant. The effect of prenatal phthalate exposure on neurodevelopment differed according to sex, but the results are inconsistent, for instance, among the five studies investigating the association between mental development index (MDI) and Mono-*n*-butyl phthalate (MnBP), two of them showed a significantly decreasing MDI scores with increasing concentrations of MnBP among girls, but among boys one study showed the inverse association, another showed the positive association.

Conclusion: Di(2-ethylhexyl) phthalate, dibutyl phthalate, butyl-benzyl phthalate and di-ethyl phthalate exposure during pregnancy was associated with lower cognitive scores and worse behavior in offspring, and sex-specific effects on cognitive, psychomotor, and behavioral development were identified, especially the impact of phthalate exposure on neurobehavior in boys.

1. Introduction

As endocrine-disrupting chemicals (EDCs), phthalates are ubiquitous in daily life. They are used not only to increase the softness, flexibility, elongation, and durability of products as plasticizers for polyvinyl chloride (PVC) polymers in building and construction materials, floorings, toys, medical materials, food packing materials, cables and wires but also as additives in medical devices, enteric coating in medication, food supplements, cosmetics and personal care products, etc. Phthalates are classified into two distinct groups according to the length of their carbon chains: high molecular weight phthalates (HMWP) and low molecular weight phthalate (LMWP). HMWP include di(2-ethylhexyl) phthalate (DEHP), di-iso-decyl phthalate (DiDP), and di-iso-nonyl phthalate (DiNP), while LMWP include dibutyl phthalate (DBP), butyl-benzyl phthalate (BBzP), di-*n*-octyl phthalate (DnOP), and di-methyl phthalate (DMP) (Katsikantami et al., 2016; Koch and

* Corresponding author at: Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, No. 13, Hangkong Road, Wuhan, 430030, People's Republic of China.

E-mail address: wujingtj@hust.edu.cn (J. Wu).

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Table 1
Common phthalates and their urinary metabolites.

Phthalate	Abbreviation	Urinary metabolite		abbreviation
		Primary metabolite	Secondary metabolite	
Di(2-ethylhexyl) phthalate	DEHP	Mono-2-ethylhexyl phthalate		MEHP
			Mono-2-ethyl-5-hydroxyhexyl phthalate	MEHHP/5OH-MEHP
			Mono-2-ethyl-5-oxohexyl phthalate	MEOHP/5oxo-MEHP
			Mono-2-ethyl-5-carboxypentyl phthalate	MECPP/5cx-MEHP
			Mono-2-methylcarboxyhexyl phthalate	MMCHP
Di-iso-nonyl phthalate	DiNP	Mono-iso-nonyl phthalate	Mono-hydroxy-iso-nonyl phthalate	MHiNP/OH-MiNP
			Mono-oxo-iso-nonyl phthalate	MOiNP/oxo-MiNP/MHiOP
			Mono-carboxy-iso-octyl phthalate	MCiOP/cx-MiNP
Di-iso-decyl phthalate	DiDP		Mono-carboxy-iso-nonyl phthalate	MCNP
Dibutyl phthalate	DBP	Mono-n-butyl phthalate		MnBP
			3OH-mono-n-butyl phthalate	3OH-MnBP
			Mono-3-carboxypropyl phthalate	MCPP*
		Mono-iso-butyl phthalate		MiBP
Butyl-benzyl phthalate	BBzP	Mono-benzyl phthalate		MBzP
Di-ethyl phthalate	DEP	Mono-ethyl phthalate		MEP
Di-n-octyl phthalate	DOP/DnOP	Mono-3-carboxypropyl phthalate		MCPP
		Mono-n-octyl phthalate		MnOP
Di-methyl phthalate	DMP	Mono-methyl phthalate		MMP

Note : "*" : MCPP is a major di-*n*-octyl phthalate metabolite, or a minor dibutyl phthalate metabolite or a metabolite of several high molecular weight phthalates.

Calafat, 2009).

Given that phthalates are not chemically bound to products, they are easily resealed into the environment through abrasion, migration, release, and immersion and absorbed by the body via ingestion, inhalation, dermal contact, and intravenous injection (Gong et al., 2016; Teng et al., 2015; Verstraete et al., 2016; Wormuth et al., 2006). The biologic half-lives of phthalates are short, from hours to days, and their metabolites have been detected in human urine, blood, feces, amniotic fluid, breast milk, and sweat (Katsikantami et al., 2016; Meeker et al., 2009). At present, urinary concentrations of phthalate metabolites are usually used as internal dosimeters of exposure. The phthalate metabolites in urine from the birth cohort studies included are listed in Table 1. Although phthalates do not accumulate significantly in the body, their wide-scale use results in frequent exposure, and phthalate metabolites have been detected in an overwhelming majority of human populations. In general, children are exposed to higher phthalate doses than adults, and women have significantly higher levels of phthalate metabolites than men (Frederiksen et al., 2007; Katsikantami et al., 2016; Kelley et al., 2012; Wittassek et al., 2011). An emerging public health concern is that the widespread use of phthalates might affect neurodevelopment. Some studies have shown that phthalate exposure is a risk factor for attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) (Hu et al., 2017; Park et al., 2015; Testa et al., 2012), and also affects children's learning, behavior, and intelligence (Arbuckle et al., 2016; Cho et al., 2010; Chopra et al., 2014; Huang et al., 2017; Kim et al., 2009, 2016; Shiue, 2015; Won et al., 2016).

Phthalates can enter fetuses through placenta, during the brain growth spurt (BGS) in the prenatal period; exposure to EDCs has been suggested as a possible causal factor for neurodevelopmental disorders, and the BGS period usually begins during the third trimester of pregnancy and continues throughout the first two years of life (Jeddi et al., 2016). Animal model studies showed that prenatal exposure to phthalates had an impact on behavior and recognition memory (Barakat et al., 2018; Kougias et al., 2018). Human studies also indicated that prenatal phthalate exposure was associated with neurobehavior and cognition (Kim et al., 2011; Lien et al., 2015).

To date, although there have been a significantly increasing number of studies on the relationship between phthalate exposure during pregnancy and neurodevelopment in children, the results are inconsistent. Birth cohort studies are the best choice for investigating the relationship between prenatal phthalate exposure and neurodevelopment in offspring. Hence, to gain a better understanding of the impact of prenatal exposure to phthalates on cognitive and behavioral development in offspring, we conducted a systematic review based on birth cohort studies to assess the association between urinary phthalate metabolite concentration in pregnant women and child neurodevelopment.

2. Methods

2.1. Data sources

We first conducted a literature search in October 2017 of the PubMed, EMBASE, and Web of Science electronic databases for studies investigating the association between phthalate exposure and neurodevelopment in humans. To ensure that our study was based on the most recent results, we further updated the literature search on May 30, 2018. The search focused on two themes of Medical Subject Headings (MeSH) and related exploded versions: phthalate or phthalic acid esters, neurodevelopment, cognition, or behavior. The two themes were combined using the Boolean operator "and". No restrictions in the search strategy were inserted. The detailed search strategies are shown in the Supplemental Material. In addition, the bibliography lists of all included publications were searched.

2.2. Inclusion and exclusion criteria

Articles were considered for inclusion in the systematic review if: (1) the article studied the association between phthalate exposure and neurodevelopment, including cognition and behavior; (2) the authors reported data from an original human study; (3) the study was based on a prospective birth cohort; (4) phthalate metabolite concentrations were measured in urine; (5) the methods used to assess children's neurodevelopmental outcomes were generally accepted; and (6) the studies were published in English. Furthermore, reviews, meta-analyses, meetings, letters, abstracts, and comments were excluded. We first read the titles and abstracts of the retrieved articles to screen for eligible documents, and then reviewed the full text.

2.3. Study selection and data extraction

Two investigators independently assessed literature eligibility, and inconsistencies were resolved by consensus or consulting with the third investigator. Data were also extracted independently from papers by two reviewers. We extracted the following information from the studies: cohort characteristics (cohort name, study location, recruitment time, number of participants, exposure assessment time during pregnancy, and follow-up), authors, publication year, children's ages, tools used for neurodevelopmental assessment, phthalate metabolite types and concentrations measured in urine, results of the evaluation of cognitive and behavioral development, and the analysis methods used (statistical models, covariates adjusted in the models).

2.4. Quality assessment

We evaluated the risk of bias for each of the included studies using a modified instrument based on the Cochrane Collaboration's "Risk of Bias" tool (Higgins, 2011; Lam et al., 2017), including the selection bias, exposure assessment, outcome assessment, confounding, incomplete outcome data, selective outcome reporting outcome, and other source of bias for each article. The possible ratings for the risk of bias in each domain were "low", "probably low", "probably high", or "high". Two reviewers assessed the risk of bias, inconsistencies were resolved by consulting with the professor. The criteria for categorization for each point of possible bias was described (Table S1)

2.5. Analysis strategy

The included studies used different statistical analysis methods, including multiple linear regression, logistic regression, structural equations, and Bayesian models to investigate the association between phthalate exposure during pregnancy and neurodevelopment in offspring. Given that the same study might adjust for different confounding factors (age, gender, birth weight, maternal education, and so on) in the statistical models, this systematic review was based on the results of the model including the optimum adjustment factors from each cohort study. The results were summarized in the Tables 3–5, in addition, in order to clearly compare the results, we presented some results in the form of charts in Supplementary materials (Figs. S1–S6).

Based on the results of the studies, the relationships between prenatal exposure to different types of phthalates and children's cognitive development and behavioral development were elaborated. At the same time, the association was assessed separately at different developmental stages of children and in different genders. In addition, based on the existing studies, the possible biological mechanisms were illustrated.

3. Results

3.1. Literature search

We identified 9412 records, including 1492 articles from PubMed, 803 from EMBASE, and 7117 from Web of Science, and did not identify any other publications from the bibliography lists of the related articles. After screening based on the aforementioned criteria and detailed examination, duplicates and irrelevant articles were excluded, except the 30 cohort studies that were included in this systematic review; However, four of the 30 articles were excluded because of a non-birth cohort, or no measurement of urinary phthalate metabolite concentrations. Finally, 26 publications on the association between prenatal phthalate exposure and cognition and neurobehavior development were reviewed (Fig. 1), one of which was a prospective birth cohort, nested case-control study.

3.2. Cohort studies characteristic

The 26 studies that met the inclusion criteria came from 14 different birth cohorts and nine countries in Asia, Europe and the Americas. The cohorts established and recruited pregnant women between 1997 and 2012. The maternal age was greater than 16 years old and four birth cohorts studies were conducted in the United States, three in South Korea, and others in Mexico, Spain, Poland, France, Denmark, Norway, and Chinese. Nine articles only investigated the impact of phthalate exposure during pregnancy on cognition, 13 on neurobehavior, and the remaining four on both cognition and neurobehavior (Table 2).

The included birth cohorts collected urine samples during the second or third trimesters of pregnancy to evaluate the extent of phthalate exposure. Only the INMA-INfancia y Medio Ambiente Environment and Childhood (IIYMAEC) birth cohort and the Health Outcomes and Measures of the Environment (HOME) birth cohort measured urinary phthalate metabolite levels at two different time points during pregnancy; the other cohorts collected urine samples at only one time point. The majority of studies included in this review investigated the effects of DEHP, DBP, DEP, and BBzP exposure during pregnancy on the neurodevelopment of offspring, but few studies investigated the effect of other phthalate types. DBP is mainly excreted from the urine in the form of Mono-*n*-butyl phthalate/monobutyl phthalate (MnBP/MBP) and mono-iso-butyl phthalate (MiBP); for comparison, we replaced MBP with MnBP in some studies. The follow-up information of the birth cohorts is shown in Table S2 at length, except for the Polish Mother and Child Cohort (PEPRO_PL) birth cohort, because the cohort is a multicenter prospective cohort study, current analysis was restricted to 165 children from Lodz district, there is no description of the follow-up information in the article. Furthermore, in the included studies, cognitive development was mainly assessed in infants, whereas neurobehavioral development was primarily assessed in pre-school and school-age children. The results of the risk of bias assessment are shown in Table S3, the reliability of the two reviewers regarding the quality assessments was high, kappa value was 0.813, risk of bias of the included articles were low or "probably low", and few were "probably high". The concentrations of phthalate metabolites were listed for each birth cohort study (Table S4).

3.3. Prenatal exposure to phthalate and cognitive development

Table 3 shows the effects of phthalate exposure during pregnancy on cognition in children. Thirteen articles investigated the relationship between prenatal exposure to phthalate and cognition in children, only Nakiwala et al. (2018), Huang et al. (2015), and Kim et al. (2017) found no association between them. Overall, mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), MiBP, MnBP, mono-benzyl phthalate (MBzP), mono-ethyl phthalate (MEP) and mono-3-carboxypropyl phthalate (MCPP) affected children's cognitive and psychomotor development, but the results were not consistent.

Significant inverse associations between prenatal exposure to DBP and cognitive and psychomotor development were reported in several studies. Kim et al. (2011), Polanska et al. (2014) and Factor-Litvak et al. (2014) found that exposure to DBP during pregnancy had a negative impact on children's cognitive and psychomotor development. In addition, Kim et al. (2011) and Whyatt et al. (2012) reported that MnBP was inversely associated with the psychomotor development index (PDI) in boys and not in girls. Whyatt et al. (2012), Factor-Litvak et al. (2014) and Doherty et al. (2017) suggested that MnBP exposure only damaged cognitive development in girls. However, Doherty et al. (2017) reported increased PDI and mental development index (MDI) scores with increasing MnBP concentrations in boys.

Exposure to DEHP during pregnancy was inversely associated with children's cognitive and psychomotor development. Kim et al. (2011), Tellez-Rojo et al. (2013), and Polanska et al. (2014) demonstrated that

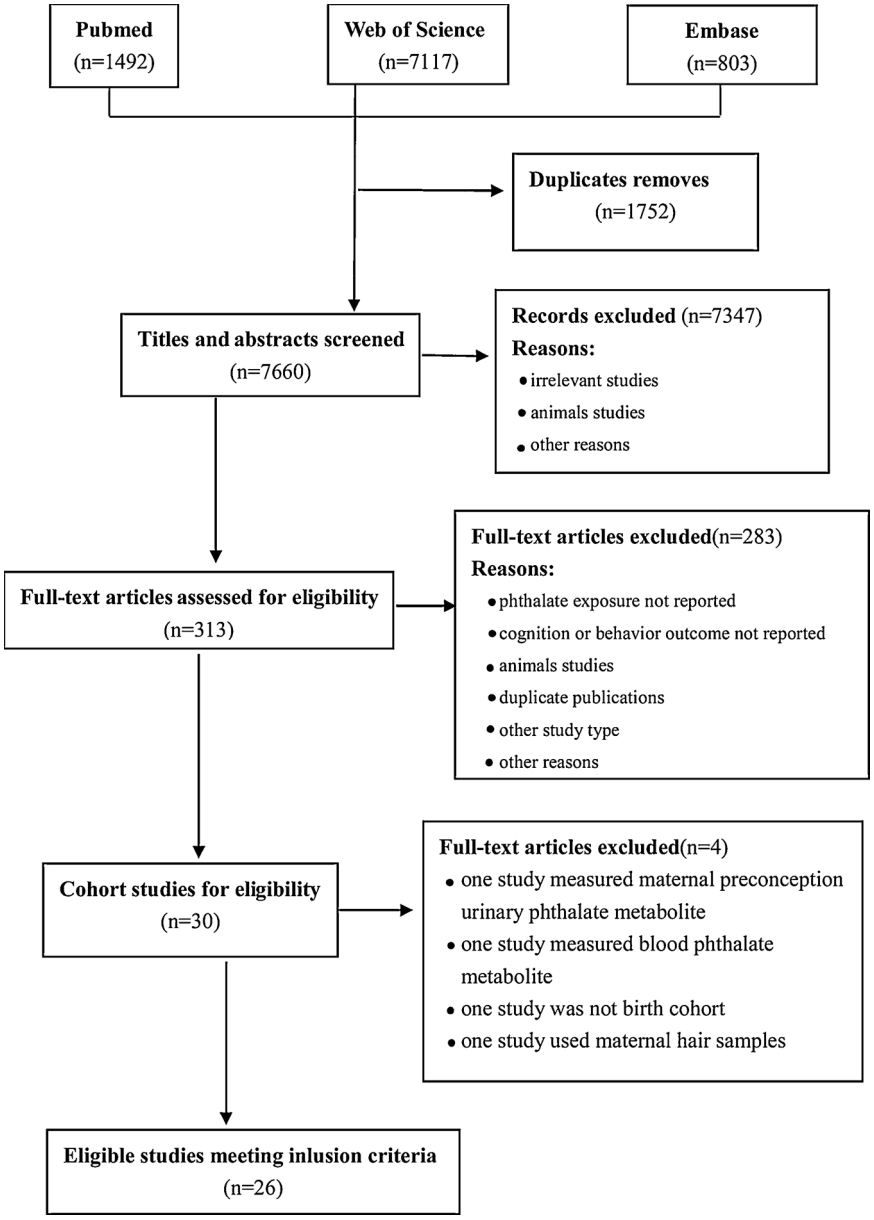

Fig. 1. Flowchart of the systematic review.

prenatal exposure to DEHP could be detrimental to children's cognitive or psychomotor development. Kim et al. (2011) found that DEHP exposure affected boys' cognitive and psychomotor development, while Tellez-Rojo et al. (2013) found that it had an effect on cognition only in girls. Moreover, Olesen et al (2018) reported that increasing prenatal DEHP exposure was associated with lower scores in language development for boys. Ipapo et al. (2017) demonstrated that maternal prenatal exposure to DEHP was negatively associated with visual recognition memory among girls. At the same time, visual recognition memory and language development were associated with intelligence quotients (IQ) scores (Liao et al., 2015; McCall and Carriger, 1993).

Exposure to BBzP during pregnancy affects cognition, psychomotor, and language development in children, but the studies are controversial. Gascon et al. (2015) showed a negative association between MBzP and psychomotor development; Doherty et al. (2017) found that MBzP was positively associated with cognitive development in boys and negatively associated with psychomotor development in girls; while Ipapo et al. (2017) and Olesen et al. (2018) respectively found that prenatal exposure to BBzP was not advantageous to girls' visual recognition memory or boys' language development. However, Tellez-Rojo et al. (2013) reported that MBzP was positively related to psychomotor development among boys. The other birth cohort studies found no association between BBzP and children's neurodevelopment.

With regard to the effect of MCPP, MEP, and mono-methyl phthalate (MMP) on cognitive outcomes of offspring, Doherty et al. (2017) reported that MCPP was not helpful for psychomotor development or cognitive development in girls; however, Tellez-Rojo et al. (2013) indicated that MCPP improved psychomotor development in boys. Kim et al. (2018) and Ipapo et al. (2017) showed that MEP interfered with psychomotor or cognitive development but the correlation was demonstrated only in girls. Furthermore, Olesen et al. (2018) showed that MEP was inversely related to language development in boys. At present, there is no evidence that DMP exposure during pregnancy affects psychomotor and cognitive development in children.

With respect to the near and long-term effects of exposure to phthalate during pregnancy on children's cognition, we can't make an inference yet. Ten studies assessed the short-term effect of phthalate exposure, eight of which showed an effect on children's cognitive or

Table 2
Summary of the cohort studies' characteristics and exposure-outcome assessment of children's neurodevelopment.

Cohort	Location	Pregnant woman age (year)	Enrollm-ent years	Exposure timing during pregnancy	reference	Analysis population	Phthalate metabolite analyzed	Outcome measurement Time for children	Neurodevelopment measurement tool
IIYMAEC	Sabadell (Catalonia, Spain)	≥ 16	2004-2006	at 12 and 32 weeks of gestation	(Gascon et al., 2015)	367	Σ_4DEHP; MBzP; MEP; MiBP; MnBP	At the age of 1, 4 and 7 years	At 1 years old: BSID II; At 4 years old: MSCA; CPSCS; ADHD-DSM-IV; At 7 years old: SDQ; CSRS
MSCEHC	New York	—	1998-2002	between 25 and 40 weeks	(Engel et al., 2009)	295	Σ_6HMWP; Σ_4LMWP	within 5 days of delivery	BNBAS
					(Engel et al., 2010)	188	Σ_6HMWP; Σ_4LMWP	at 4–9 years of age	BRIEF; BASC
					(Miodovnik et al., 2011)	137	Σ_6HMWP; Σ_4LMWP; MEP; MMP; MnBP.	between the ages of 7 to 9	SRS
					(Singer et al., 2017)	IBQ :204; TBAQ 279	MiBP; MnBP; MEP; MCPP; MBzP; Σ_4DEHP	At 1 and 2 years old	At 1 years old : IBQ At 2 years old : TBAQ
					(Doherty et al., 2017)	258	MEP; MnBP; MiBP; MCPP; MBzP; Σ_4DEHP	At 2 years old	BSID-II
NTMIC	Taiwanese	25-35	2000-2001	Range:28-36 weeks;	(Huang et al., 2015)	110	MMP; MEP; MnBP; MBzP; MEHP; MEHHP; MEOHP; Σ_3DEHP	At ages 2,5,8 and 11 years	At 2 years old: BSID-II; At 5 years old: WPPSI-R; At 8 years old: WISC-III; At 11 years old: WISC-IV.
					(Lien et al., 2015)	122	MMP; MEP; MnBP; MBzP; MEHP; MEHHP; MEOHP	At 8 years of age	CBCL
EDOCC	Korea	–	2008-2011	Range:14 -27 weeks	(Kim et al., 2017)	175	MnBP; MEHHP; MEOHP.	At age 6 years	KEDI-WISC; CPT
OCC	Denmark	—	2010-2014	At gestational week 28	(Olesen et al., 2018)	M-CDI Vocabulary: 518 M-CDI Complexity: 384	MEP; MiBP; MnBP; MBzP; MEHP; MEHHP; MEOHP; MECPP; MHiNP; MOiNP; MCiOP; Σ_4DEHP; Σ_2DBP;	Among 1.7-3 years old	MB-CDI
SFF	California; Minnesota; Missouri; Iowa	18-42	1999-2005	Mean: 28.3 weeks	(Swan et al., 2010)	150	MEHP; MEHHP; MEOHP; Σ_3DEHP; MnBP; MiBP; Σ_2DBP	Among 3.6- 6.4 years old	PSAI
				Range: 10–39 weeks	(Kobrosly et al., 2014)	153	Σ_3DEHP MnBP; MiBP; MBzP; MEP	At 6–10 years of age	CBCL
HOME	Cincinnati	≥ 18	2003-2006	around 16 and 26 weeks	(Yolton et al., 2011)	350	Σ_4DEHP; Σ_2DBP	at 5 weeks	NNNS
					(Braun et al., 2014)	175	MnBP; MiBP; MEP; MBzP; MCPP; MEHP; MEHHP; MECPP	At 4 and 5 years old	SRS
					(Braun et al., 2017)	198	MBzP; MnBP; MiBP; MEP; MCPP; Σ_4DEHP	at 8 years of age	VMWM
					(Percy et al., 2016)	227	MEP; MnBP; MiBP; MCPP; MECPP; MEHHP; MEOHP; MEHP	at 8 years of age	GIQ; PPPSI
EDEN	France	18-44	2006-2003	Between 22 and 29 weeks	(Philippat et al., 2017)	546(only boys)	MEP; MnBP; MiBP; MCPP; MBzP; MCOP; MCNP; Σ_4DEHP	At 3 years and 5 years	SDQ
					(Nakiwala et al., 2018)	452(only boys)	MEP; MnBP; MiBP; MCPP; MBzP; MCOP; MCNP; Σ_4DEHP	At 5 years old	WPPSI-III
MOCEH	Seoul; Cheonan; Ulsan;	≥ 18	2006-2009	Rang:35.7–41.7 weeks	(Kim et al., 2011)	460	MEHHP;MEOHP;MnBP;	At 6 months of age	BSID II
CCCEH	New York	18-35	1999-2006	during the third trimester	(Whyatt et al., 2012)	Total: 319 BSID-II : 297 CBCL : 277	MnBP; MBzP; MiBP; Σ_4DEHP	At 3 years old	BSID II; CBCL
					(Factor-Litvak et al., 2014)	328	MnBP; MiBP; MBzP; MEP; MEHP; MEHHP	At age 7 years	WISC-IV
					(Ipapo et al., 2017)	168	Σ_4DEHP, MEHHP; MEOHP; MECPP;MEHP; MiBP; MBzP; MnBP; MCPP; MEP	At 27 weeks	FTII

(*continued on next page*)

Table 2 (*continued*)

Cohort	Location	Pregnant woman age (year)	Enrollm-ent years	Exposure timing during pregnancy	reference	Analysis population	Phthalate metabolite analyzed	Outcome measurement Time for children	Neurodevelopment measurement tool
ELEMENT	Mexico City	—	1997-2003	during the third trimester	(Tellez-Rojo et al., 2013)	135	MEP; MnBP; MiBP; MBzP; MCPP; MEHP; MEHHP; MEOHP; MECPP; Σ_4DEHP	Between 2 and 3 years old	BSID II
REPRO_PL	Lodz district	—	2007-2011	Range:30-34weeks	(Polanska et al., 2014)	165	MEP; MiBP; MnBP; 30H-MnBP; MBzP; MEHP; MEHHP; MEOHP; OH-MiNP; oxo-MiNP; MnOP; Σ_3DEHP; Σ_2DiNP ; ΣLow-MWP; ΣHigh-MWP; ΣDnBP;	At 2 years old	Bayley-III
CHECK	Seoul; Anyang; Ansan; Jeju	23-46	2011-2012	During pregnancy(no specified time)	(Kim et al., 2018)	140	MiBP; MnBP; MEHP; MEHHP; MEOHP; MEP	At 1 to 2 years of age	BSID II; SMS; CBCL
MoBa	Norway	—	1999-2008	At approximately 17 week gestation	(Engel et al., 2018)	Controls: 553 Cases: 297	MEP; MiBP; MnBP; MBzP; Σ_5DEHP; Σ_3DiNP	—	ICD-10 criteria

Note: **Abbreviations: Cohor name abbreviations : IIYMAEC :** The INMA-INfancia y Medio Ambiente (Environment and Childhood) ; **MSCEHC:** The Mount Sinai Children's Environmental Health Center ; **NTMIC:** The nationwide Taiwan Maternal and Infant Cohort ; **EDOCC:** The Environment and Development of Children cohort; **OCC** : The Odense Child Cohort; **SFF:** The Study for Future Families ; **HOME:** The Health Outcomes and Measures of the Environment; **MOCEH:** The Mothers and Children's Environmental Health Study; **CCCEH:** The Columbia Center for Children's Environmental Health; **ELEMENT:** The Early Life Exposure in Mexico to Environmental Toxicants; **REPRO_PL:** The Polish Mother and Child Cohort; **MoBa:** The Norwegian Mother and Child Cohort. **Scale abbreviations** : **BSID-II** : Byley Scales of Infant Development- II; **MSCA:** McCarthy Scales of Children's Abilities; **WPPSI-R:** Wechsler Preschool and Primary Scale of Intelligence-Revised; **WPPSI-III:** Wechsler Preschool and Primary Scale of Intelligence Third Edition; **WISC-III:** Wechsler Intelligence Scale 8for Children-Version III; **WISC-IV:** Wechsler Intelligence Scale for Children-Fourth Edition; **KEDI-WISC:** Korean Educational Developmental Institute's Wechsler Intelligence Scale for Children; **FTII:** The Fagan Test of Infant Intelligence; **MB-CDI:** The MacArthurBates Communicative Development Inventories; **BRIEF:** Behavior Rating Inventory of Executive Function; **ADHD-DSM-IV:** Attention-Deficit Hyperactivity Disorder (ADHD) Criteria of the Diagnostic and Statistical Manual of Mental Disorders – 4th edition; **CPT:** the Comprehensive Attention Test; **CSRS:** The Conners' Parent Rating Scales; **PSAI:** Pre-School Activities Inventory; **VMWM:** the Virtual Morris Water Maze; **CPSCS:** the California Preschool Social Competence Scale; **SRS:** the Social Responsiveness Scale; **IBQ:** the Infant Behavior Questionnaire; **TBAQ:** Toddler Behavior Assessment Questionnaire; **CBCL:** the Child Behavior Checklist; **BASC:** the Behavior Assessment System for Children; **SDQ:** the Strengths and Difficulties Questionnaire; **BNBAS:** the Brazelton Neonatal Behavior Assessment Scale; **NNNS:** the NICU Network Neurobehavioral Scale; **SMS**: Social Maturity Scale**; GIQ**: Gender Identity Questionnaire; **PPPSI**: Playmate and play style preferences structured Interview; **ICD-10:** Clinical Descriptions and Diagnostic Guidelines. **Sum of phthalate metabolites abbreviations** : **Σ_5DEHP:** sum of the five di-(2-ethylhexyl) phthalate metabolites: MEHP, MEHHP, MEOHP, MECPP, MMCHP **Σ_4DEHP:** sum of the four di-(2-ethylhexyl) phthalate metabolites: MEHP, MEHHP, MEOHP and MECPP; **Σ_3DEHP:** sum of the three di-(2-ethylhexyl) phthalate metabolites: MEHP, MEHHP and MEOHP; **Σ_2DiNP:** sum of OH-MiNP and oxo-MiNP; **Σ_3DiNP:** sum of MHiNP; MOiNP and MCiOP; **ΣLMWP:** sum of MEP, MiBP, MnBP, 30H-MnBP and MBzP(in the Polish Mother and Child Cohort, ΣLMWP = MEP + MiBP + MnBP + 3OH-MnBP + MBzP; in the Mount Sinai Children's Environmental Health Center birth cohort, ΣLMWP = MMP + MEP + MnBP + MiBP); **ΣHMWP:** sum of MEHP, MEHHP, MEOHP, OH-MiNP, oxo-MiNP and MnOP **(**in the Polish Mother and Child Cohort, ΣHMWP = MEHP + MEHHP + MEOHP + OH-MiNP + oxo-MiNP + MnOP, in the Mount Sinai Children's Environmental Health Center birth cohort, ΣHMWP = MBzP + MEHP + MECPP + MEHHP + MEOHP + MCPP**); ΣDnBP:** sum of MnBP and 3OH-MnBP; **Σ_2DBP:** sum of MiBP and MnBP.

Table 3
Research findings included in the review on neurocognitive development in children.

Reference	Type of phthalates metabolite	Neurocognitive problems outcome (point estimation, confidence interval or *p* value)	Age (year)	Measurement tool
(Kim et al., 2011)	MEHHP	In all children: ↓MDI (β: -0.97, -1.85 -0.08), ↓PDI (β: -1.20, -2.33 -0.08). In boys: ↓MDI (β: -1.46, -2.70 -0.22); ↓PDI (β: -2.36, -3.97 -0.79). In girls: MDI (β: -0.56, -1.87 -0.75); PDI (β: -0.29, -1.94 1.37).	0.5	BSID-II
	MEOHP	In all children: ↓MDI (β: -0.95, -1.87 -0.03); PDI (β: -0.92, -2.10 0.26). In boys: ↓MDI (β: -1.57, -2.87 -0.28); ↓PDI (β: -2.05, -3.71 -0.39); In girls: MDI (β: -0.43, -1.79 0.94); PDI (β: -0.08, -1.79 1.64).		
	MnBP	In all children: MDI (β: -0.54, -1.18 0.10); PDI (β: -0.79, -1.60 0.03). In boys: ↓MDI (β: -0.93, -1.82 -0.05); ↓PDI (β: -1.25, -2.40 -0.11). In girls: MDI (β: -0.21, -1.17 0.75); PDI (β: -0.42, -1.63 0.78).		
(Whyatt et al., 2012)*	MiBP	In all children: ↓PDI (β: -2.28, -3.90 -0.67). In boys: PDI (β: -2.21, -4.61 0.19). In girls: ↓PDI (β: -2.33, -4.59 -0.08).	3	BSID-II
	MnBP	In all children: MDI (β: -1.12, -2.62 0.39); ↓PDI (β: -2.81, -4.63 -1.0). In boys: MDI (β: 0.30, -1.99 2.59); ↓PDI (β: -3.08, -5.82 -0.33); In girls: ↓MDI (β: -2.67, -4.70 -0.65); PDI (β: -2.41, -4.91 0.08).		
	MBzP; Σ_4DEHP.	In all children: PDI (β: -0.92, -2.23 0.40); (β: 1.31, -0.26 2.89). In boys: PDI (β: -0.57, -2.74 1.60); (β: 2.33, -0.21 4.87). In girls: PDI (β: -1.05, -2.77 0.67); (β: 0.69, -1.35 2.73).		
(Tellez-Rojo et al., 2013) *	MBzP; MCPP.	In all children: PDI (β: 0.10, -1.16 1.37); (β: 0.86, -0.41 2.15). In boys: ↑PDI (β: 1.79, 0.14 3.45); (β: 1.64, 0.15 3.12). In girls: PDI (β: -1.21, -3.31 0.88); (β: -0.26, -2.83 2.30).	2-3	BSID II
	MEHP; MEHHP; MEOHP; MECPP; Σ_4DEHP.	In all children: MDI (β: -0.16, -1.89 1.55); (β: -0.61, -2.02 0.79); (β: -0.54, -1.91 0.82); (β: -0.80, -2.38 0.77); (β: -0.48, -2.30 1.34). In boys: MDI (β: 1.72, -0.89 4.34); (β: 0.66, -1.39 2.72); (β: 0.85, -1.11 2.81); (β: 0.91, -1.18 3.01); (β: 1.45, -0.75 3.66). In girls: ↓MDI (β: -2.11, -3.73 -0.49); (β: -1.89, -3.64 -0.15); (β: -1.80, -3.58 -0.03); (β: -2.52, -4.44 -0.61); (β: -3.41, -5.26 -1.55)		
(Gascon et al., 2015) *	MBzP; Σ_4DEHP; MEP; MiBP; MnBP.	In all children: ↓Motor (β: -1.49, -2.78 -0.21); Motor (β: 0.25, -1.42 1.93); (β: 0.41, -0.67 1.48); (β: -1.39, -2.82 0.04); (β: -0.28, -1.67 1.11).	4	MSCA
(Polanska et al., 2014)*	3OH-MnBP; MEHHP; MEOHP; Σ_3DEHP; ΣDnBP; ΣHMWP; MEP; MiBP; MnBP; MBzP; MEHP; Σ_2DiNP; ΣLMWP	In all children: ↓Motor (β: -2.3, -4.0 -0.6); (β: -1.2, -2.2 -0.3); (β: -1.8, -3.3 -0.2); (β: -2.2, -3.6 -0.8); (β: -1.9, -3.4 -0.4); (β: -2.5, -4.1 -0.9); Motor (β: 0.1, -1.5 1.8); (β: -0.6, -1.3 0.2); (β: -1.2, -2.5 0.1); (β: -0.4, -2.1 1.3); (β: 0.2, -1.3 1.7); (β: -1.0, -2.5 0.5); (β: -0.5, -2.2 1.3);	2	Bayley-III
(Doherty et al., 2017)	MnBP	In all children: MDI (β: 0.67, -0.67 2.01); PDI (β: 0.55, -0.76 1.87). In boys: ↑MDI (β: 1.71, 0.08 3.34); ↑PDI (β: 1.92, 0.31 3.54). In girls: ↓MDI (β: -2.78, -5.03 -0.54); PDI (β: -2.29, -4.63 0.05).	2	BSID-II
	MiBP	In all children: MDI (β: 0.11, -1.35 1.57). In boys: MDI (β: 1.55, -0.39 3.48). In girls: ↓MDI (β: -2.28, -4.33 -0.22).		
	MBzP	In all children: MDI (β: 0.73, -0.51 1.97); PDI (β: 0.55, -1.21 2.31). In boys: ↑MDI (β: 1.83, 0.07 3.58). In girls: ↓PDI (β: -2.08, -3.77 -0.38)		
	MCPP	In all children: MDI (β: 0.36, -1.24 1.96); PDI (β: -0.12, -1.68 1.44). In boys: MDI (β: 2.03, -0.02 4.08); PDI (β: 1.61, -0.42 3.64). In girls: ↓MDI (β: -2.39, -4.72 -0.05); ↓PDI (β: -2.93, -5.35 -0.51)		
(Kim et al., 2018)	MEP	In all children: ↓MDI (β: -2.40, -4.39 -0.40); ↓PDI (β: -2.25, -4.03 -0.47). In boys: MDI (β: -1.03, -4.55 2.50); PDI (β: -0.25, -3.48 2.98). In girls: ↓MDI (β: -2.98, -5.48 -0.48); ↓PDI (β: -3.21, -5.51 -0.90).	1-2	BSID-II
(Olesen et al., 2018)*	MEP; MEHHP; MEOHP; MECPP; Σ_4DEHP	In boys: ↓ vocabulary scores (OR: 1.24, 1.05 1.46); (OR: 1.32, 1.03 1.70); (OR: 1.35, 1.04 1.73); (OR: 1.37, 1.02 1.85); (OR: 1.33, 1.01 1.75). In girls: vocabulary scores (OR: 1.08, 0.92 1.27); (OR: 0.87, 0.67 1.13); (OR: 0.81, 0.63 1.05); (OR: 0.83, 0.62 1.11); (OR: 0.82, 0.61 1.11).	1.7-3	MB-CDI
	MBzP; MEHHP; MEOHP; MECPP; Σ_4DEHP	In boys: ↓complexity scores (OR: 1.28, 1.02 1.59); (OR: 1.38, 1.04 1.83); (OR: 1.41, 1.06 1.87); (OR: 1.48, 1.04 2.09); (OR: 1.43, 1.03 1.97). In girls: complexity scores (OR: 0.96, 0.76 1.21); (OR: 0.86, 0.66 1.11); (OR: 0.89, 0.68 1.16); (OR: 0.90, 0.67 1.21); (OR: 0.88, 0.65 1.18).		
(Ipapo et al., 2017)*	MEP	In all children: ↓visual recognition memory (β: -3.38, -5.93 -0.84). In boys: visual recognition memory (β: -0.69, -3.94 2.56). In girls: ↓visual recognition memory (β: -4.39, -8.29 -0.49).	At 27 weeks	FTII
	Σ_4DEHP; MBzP	In all children: visual recognition memory (β: -2.54, -5.07 0.00); (β: -0.87, -3.43 1.68). In boys: visual recognition memory (β: -1.61, -5.05 1.82); (β: 2.39, -1.26 6.04). In girls: ↓visual recognition memory (β: -4.23, -8.13 -0.32); (β: -3.98, -7.71 -0.25).		
	MEHHP	In all children: visual recognition memory (β: -1.05, -3.60 1.50). In boys: ↓visual recognition memory (β: -4.25, -7.67 -0.82). In girls: visual recognition memory (β: -2.92, -6.81 0.10).		

(*continued on next page*)

Table 3 (*continued*)

Reference	Type of phthalates metabolite	Neurocognitive problems outcome (point estimation, confidence interval or *p* value)	Age (year)	Measurement tool
(Factor-Litvak et al., 2014)	MiBP	In all children: ↓IQ (β: -2.69, -4.22 -1.16). In boys: ↓IQ (β: -2.92, -5.17 -0.67). In girls: ↓IQ (β: -2.38, -4.50 -0.26).	7	WISC-IV
	MnBP	In all children: ↓IQ (β: -2.69, -4.33 -1.05). In boys: IQ (β: -1.89, -4.34 0.56). In girls: ↓IQ (β: -3.15, -5.44 -0.87).		

Note: "↓"represents risk factor; "↑" represents protective factors; "*": the effect size was listed based on the order of phthalate metabolites preceding.

psychomotor development. Five studies investigated the long-term effects of phthalate exposure, three of which demonstrated an effect of children's IQ or psychomotor development.

3.4. Prenatal exposure to phthalate and behavioral syndromes

Seventeen articles reported that the associations between prenatal urinary concentrations of phthalate metabolites and neurobehavior among children were examined using behavioral assessments including various behavioral questionnaire. The behavior syndromes could be divided into externalizing behavior (hyperactivity/impulsivity, conduct problems, aggression problems, delinquent behavior, rule-breaking behavior), internalizing behavior (emotion, peer relationships, anxiety/depression, somatization, withdrawal), and other types of neurobehavior (attention, gender-typical play behaviors, social behavior, visual-spatial ability, etc).

3.4.1. Prenatal phthalate exposure and internalizing and externalizing behaviors

Engel et al. (2010), Whyatt et al. (2012), Kobrosly et al. (2014), Lien et al. (2015), Philippat et al. (2017), Kim et al. (2018), and Gascon et al. (2015) assessed the association between prenatal urinary concentrations of phthalate metabolites and internalizing and externalizing behaviors, of which only Gascon et al. (2015) found no associations between prenatal phthalates exposure and behavior problems. Overall, exposure to DBP, DEP, DEHP, and BBzP during pregnancy interfered not only with internalizing behavior, but also with externalizing behavior (Table 4).

Higher concentration of prenatal exposure to DBP led to more serious internalizing and externalizing behavior problems. Whyatt et al. (2012) and Philippat et al. (2017) reported that higher prenatal urinary concentrations of DBP metabolites were associated with greater internalizing behavior problems; Kobrosly et al. (2014), Engel et al. (2010), and Lien et al. (2015) reported that increasing severe externalizing behavior problems were associated with higher maternal urinary MnBP or MiBP concentrations. Finally, Philippat et al. (2017), Whyatt et al. (2012) and Kobrosly et al. (2014) reported that DBP exposure contributed to internalizing or externalizing behavior problems in boys but not in girls.

Our review supported positive associations between maternal DEHP exposure and children's externalizing and internalizing behavior syndromes. Kobrosly et al. (2014) and Philippat et al. (2017) reported that DEHP exposure during pregnancy was positively associated with internalizing behavior scores only in boys, indicating more internalizing behavior problems. Lien et al. (2015) also reported that maternal urine DEHP metabolites were related to externalizing behavior problems.

The studies indicated that prenatal exposure to BBzP might play a role in the behavioral development of children. Prenatal urinary concentrations of MBzP were associated with internalizing behavior problems, only in girls according to Whyatt et al. (2012) and only in boys by Philippat et al. (2017); however, Kobrosly et al. (2014) reported that higher MBzP concentrations were associated with increasing externalizing behavior problems in boys and decreasing internalizing behavior problems scores in girls.

In addition to DBP, DEHP, and BBzP, Engel et al. (2010) and Kim et al. (2018) reported that MEP exposure was associated with increased internalizing or externalizing behavior problems. Engel et al. (2010) divided phthalates into HMWP and LMWP, finding that only LMWP affected internalizing or externalizing behavior problems; MiBP, MnBP, MMP and MEP were the chief components of LMWP, although no other studies observed a relationship between DEP exposure and internalizing or externalizing behavior problems in children. We found that phthalate exposure during pregnancy was more likely to interfere with boys' behavioral development than with that of girls

Table 4
Research results included in the review on internalizing and externalizing behavior problems in children.

Reference	Type of phthalates metabolite	Internalizing behavior problems (point estimation, confidence interval or *p* value)	Externalizing behavior problems (point estimation, confidence interval or *p* value)	Age (year)
(Whyatt et al., 2012)	MiBP	In all children: ↑Emotional (β: 0.32, 0.01 0.62); Internalization (β: 0.97, -0.002 1.94).		3
	MnBP	In all children: ↑Somatization (β: 0.54, 0.19 0.90); ↑Withdrawal (β: 0.40, 0.05 0.74); ↑Internalization (β: 1.45, 0.40 2.50). In boys: ↑Emotional (β: 0.71, 0.22 1.19); ↑Somatization (β: 0.77, 0.21 1.33); ↑Withdrawal (β: 0.56, 0.09 1.03); ↑ Internalization (β: 2.21, 0.66 3.76). In girls: Internalization (β: 1.29, -0.15 2.72).		
	MBzP	In all children: ↑withdrawal (β: 0.31, 0.07 0.55); ↑Internalization (β: 0.83, 0.11 1.56); Anxiety (β: 0.22, -0.04 0.48). In boys: Anxiety (β: -0.05, -0.046 0.35); Internalization (β: 0.29, -0.83 1.42). In girls: ↑Anxiety (β: 0.51, 0.17 0.85);↑ Withdrawal (β: 0.61, 0.29 0.93); ↑Internalization (β: 1.79, 0.88 2.69).		
(Lien et al., 2015)[#]	MEOHP; MnBP ; MEHP; MEHHP	In all children: Internalization (β: 1.02, -1.21 3.25); (β: 2.17, -1.20 5.54); (β: 1.67, -1.96 5.30); (β: 0.42, -1.42 2.26)	In all children:↑Delinquent (β: 3.95, 1.81 6.09); (β: 3.57, 0.20 6.94); (β: 3.77, 0.16 7.38); (β: 1.87, 0.05 3.69); ↑Externalization (β: 3.74, 1.33 6.15); (β: 4.29, 0.59 7.99); (β: 4.28, 0.03 8.26); (β: 1.49, -0.55 3.53).	8
	MEP; MBzP; MMP	In all children: Internalization (β: -1.75, -5.45 1.95); (β: -2.87, -7.36 1.62); (β: -1.70, -4.86 1.46).	In all children: Externalization (β: -0.49, -4.63 3.65); (β: -1.13, -6.17, 3.91); (β: -0.68, -4.23 2.87).	
(Kobrosly et al., 2014)	Σ_3DEHP	In all children: ↑Somatization (β: 0.10, 0.01 0.2); Anxiety (β: -0.09, -0.22 0.03). In boys: ↑Somatization (β: 0.15, 0.03 0.28); Anxiety (β: 0.02, -0.15 0.18). In girls: ↓Anxiety (β: -0.21, -0.38 -0.04); Somatization (β: 0.06, -0.07 0.18).	In all children: Externalization (β: -0.04, -0.18 0.11).	6-10
	MnBP	In all children: Internalization (β: -0.08, -0.33 0.16).	In all children: ↑Conduct (β: 0.19, 0.02 0.37). In boys: ↑Conduct (β:0.36, 0.15 0.56). In girls: Conduct (β: 0.02, -0.19 0.23).	
	MiBP	In all children: Internalization (β: 0.02, -0.21 0.25).	In all children: ↑Aggression (β: 0.24, 0.03 0.45); ↑Conduct (β: 0.22, 0.05 0.38); Externalization (β: 0.20, -0.02 0.42). In boys: ↑Aggression (β: 0.34, 0.09 0.59); ↑Conduct problems (β: 0.39, 0.20 0.58);↑Externalization (β: 0.32, 0.06 0.58). In girls: Aggression (β: 0.12, -0.14 0.39); Conduct (β: -0.004, -0.21 0.20); Externalization (β: 0.06, -0.22 0.34).	
	MBzP	In all children: Internalization (β: -0.13, -0.30 0.05); Anxiety (β: -0.13, -0.28 0.03). In boys: Internalization (β: -0.04, -0.25 0.18), Anxiety (β: -0.06, -0.25 0.13). In girls: ↓Internalization (-0.22, -0.44 0); ↓Anxiety (-0.20, -0.39 -0.01).	In all children: Conduct (β: 0.07, -0.06 0.2). In boys: ↑Conduct (β: 0.21, 0.06 0.37). In girls: Conduct (β: -0.07, -0.23 0.09).	
	MEP	In all children: Internalization (β: -0.05, -0.18 0.07).	In all children: Externalization (β: -0.03, -0.15 0.09).	
(Engel et al., 2010)[*]	Σ_4LMWP	In all children: ↑Depression (β: 1.18, 0.11 2.24). In boys: Depression (β: 1.20, -0.06 2.46). In girls: Depression (β: 1.14, -0.47 2.76).	In all children: ↑Conduct (β: 2.40, 1.34 3.46); ↑Aggression (β: 1.24, 0.15 2.34); ↑ Externalization (β: 1.75, 0.61 2.88). In boys: ↑Conduct (β: 2.79, 1.55 4.03); ↑Aggression (β: 1.46, 0.17 2.76); ↑Externalization (β: 2.08, 0.74 3.42). In girls: ↑Conduct (β: 1.70, 0.09 3.31); Externalization (β: 1.17, -0.55 2.89).	4-9
	MnBP		In all children: ↑Aggression; ↑Externalization.	
	MEP	In all children: ↑Depression.	In all children: ↑Externalization;↑Conduct.	
	MMP	In all children: ↑Depression ; ↑Internalization.		
(Philippat et al., 2017)[#]	Σ_4DEHP; MEP; MiBP; MCPP; MCOP; MCNP	In boys: Internalization (IRR: 1.04, 0.99 1.10); (IRR: 1.00, 0.96 1.04); (IRR:1.01, 0.95 1.07); (IRR:1.04, 0.98 1.10); (IRR: 1.01, 0.95 1.06); (IRR: 1.00, 0.95 1.05)	In boys: Externalization (IRR: 0.98, 0.94 1.02); (IRR: 1.00, 0.97 1.03); (IRR: 0.97, 0.94 1.01); (IRR: 0.97, 0.93 1.01); (IRR: 1.00, 0.96 1.04); (IRR: 0.98, 0.95 1.01).	3
	MnBP; MBzP	In boys: ↑Peer relationship (IRR: 1.06, 1.00 1.12); (IRR: 1.07, 1.01 1.13); ↑ Internalization (IRR: 1.06, 1.01 1.11); (IRR: 1.04, 1.00 1.09).	In boys: Externalization (IRR: 1.00, 0.97 1.03); (IRR: 0.99, 0.96 1.02).	
(Kim et al., 2018)	MEP	In all children: ↑Internalization (*P*: 0.0074).		1-2

Note: "↓" represents a decline in specific behavior problems; "↑" represent a rise in specific behavior problems. "*": in the study, phthalate metabolites were grouped into two categories defined by the molecular weight of the monoesters [high (> 250 Da) and low (< 250 Da)], MiBP, MnBP, MEP and MMP only show the point estimation, not confidence interval. "#": the effect size was listed based on the order of phthalate metabolites preceding.

Table 5
Research results included in the review on others behavior problems in children.

Reference	Type of phthalates metabolite	Others behaviors problems (point estimation, confidence interval or *p* value)	Age (year)
(Lien et al., 2015)	MEOHP	In all children: ↑Social problems (β:2.98, 0.37 5.59).	8
(Kobrosly et al., 2014)#	Σ_3DEHP; MnBP; MBzP; MEP	In all children: Attention (β: -0.08, -0.04 0.21); (β: -0.06, -0.14 0.26); (β: -0.05, -0.20 0.10); (β: -0.04, -0.14 0.07).	6-10
	MiBP.	In all children: ↑Attention (β: 0.20, 0.01 0.39). In boys: ↑Attention (β: 0.27, 0.04 0.5). In girls: Attention (β: 0.12, -0.12 0.36).	
(Engel et al., 2010)*	Σ_4LMWP	In all children: ↑Attention (β: 1.29, 0.16 2.41); ↓emotional control (β: 1.33, 0.18 2.49); ↓Global Executive Composite (β: 1.23, 0.09 2.36). In boys: ↑Attention (β: 1.55, 0.22 2.88). In girls: Attention s (β: 0.83, -0.87 2.54).	4-9
	MnBP	In all children: ↓Working memory.	
	MiBP	In all children: ↓adaptability.	
	MEP	In all children: ↑Attention; ↓emotional control.	
	MMP	In all children: ↑Attention; ↓emotional control; ↓Behavioral Regulation Index; ↓Working memory; ↓Global Executive Composite.	
(Philippat et al., 2017)#	Σ_4DEHP; MEP; MnBP; MBzP; MCOP; MCNP; MiBP; MCPP.	In boys: Hyperactivity-inattention (IRR: 0.97, 0.93 1.01); (IRR: 1.00, 0.97 1.03); (IRR: 0.99, 0.95 1.02); (IRR: 0.98, 0.94 1.01); (IRR: 0.98, 0.94 1.03); (IRR: 0.97, 0.93 1.01). In boys: ↓Hyperactivity-inattention (IRR: 0.95, 0.91 1.00); (IRR: 0.96, 0.92 1.00).	3
(Kim et al., 2018)	MEP	In all children:↓Social adaptive(β: -2.54, -4.44 -0.65). In boys: Social adaptive (β: -1.07, -4.69 2.55). In girls: ↓Social adaptive (β: -3.34, -5.51 -1.17);	1-2
(Gascon et al., 2015) #	Σ_4DEHP	At 4 years in all children: ↑Social competence (β: 2.00, 0.22 3.79); ↓Inattention (IRR: 0.84, 0.72 0.98). At 7 years in all children: ↓ADHD index (IRR: 0.88, 0.77 1.00); ↓Cognitive/Inattention (IRR: 0.83, 0.71 0.95).	4 or 7
	MEP; MiBP; MnBP; MBzP.	At 4 years in all children: ↓Inattention (IRR: 0.88, 0.80 0.97); Inattention (IRR: 0.95, 0.84 1.07); (IRR: 0.98, 0.87 1.11); (IRR: 0.96, 0.86 1.07). At 7 years in all children: Cognitive/Inattention (IRR: 0.95, 0.87 1.04); (IRR: 0.96, 0.86 1.08); (IRR: 0.94, 0.84 1.06); (IRR: 1.03, 0.93 1.15).	
(Yolton et al., 2011)	Σ_2DBP	In all children: ↓arousal (β: -0.072, *P*: 0.04); ↓handling (β: -0.038, *P*: 0.02); self-regulation (β: 0.08, *P*: 0.05), movement (β: 0.054, *P*: 0.067)	5 weeks
(Engel et al., 2009)	Σ_4LMWP	In boys: ↑Motor performance (β: 0.09, *p*: 0.01).	5 days
	Σ_6HMWP	In girls: ↓Orientation (β: -0.37, *p*: 0.02); ↓quality of altertness (β: -0.48, -0.83 -0.12).	
(Swan et al., 2010)#	MiBP; MEHHP; MEOHP; Σ_2DBP; Σ_3DEHP.	In boys: ↓male typical play behavior (β: -4.53, 8.12 -0.94); (β: -3.29, -6.14 -0.43); (β: -2.94, -5.78 -0.10); (β: -4.20, -8.18 -0.23); (β: -3.18, -6.26 -0.10). In girls: feminine play behavior (β: 0.69, -2.24 3.62); (β: 0.42, -2.38 3.23); (β: 0.45, -2.45 3.34); (β: 1.01, -2.13 4.14); (β: 0.32, -2.53 3.17).	3-6
(Percy et al., 2016)	MiBP; MEP	In boys: ↓masculine play behavior (OR: 1.69, 1.00 2.86); male typical play behavior (OR: 0.72, 0.51 1.02). In girls: feminine play behavior (OR: 0.68, 0.41 1.14); ↑feminine play behavior (OR: 0.7, 0.51 0.97).	8
(Braun et al., 2017)	MnBP	In all children: ↓distance to find a hidden platform (β: -0.9, -1.8 -0.0). In boys: ↓time to find a hidden platform (β: -3.0, -5.6 -0.4). In girls: ↓distance to find a hidden platform (β: -1.7, -2.8 -0.5).	8
(Miodovnik et al., 2011)#	Σ_4LMWP; MEP.	In all children: ↓Social Communication (β: 1.86, 0.48 3.24) (β: 1.67, 0.44 2.90); ↓Social Cognition (β: 1.40, 0.07 2.74) (β: 1.28, 0.10 2.47); ↓Social Awareness (β: 1.25, 0.09 2.42) (β: 1.10, 0.06 2.14); ↑social deficits (β: 1.53, 0.25 2.82) (β: 1.38, 0.23 2.53).	7-9
(Singer et al., 2017)#	MiBP; MnBP.	In all children:↓gross motor activity (-0.2, -0.4 0.0) (-0.2, -0.5 0.0).	1
	MBzP	In all children:↓gross motor activity (β: -0.2, -0.4 0.0); ↓smiling (β: -0.1, -0.2 0.0); ↑duration of orienting (β: 0.3, 0.0 0.5).	
	MEP	In all children:↓gross motor activity (β: -0.1, -0.3 0.0); ↓soothability (β: -0.1, -0.3 0.0).	
	MCPP	In all children:↓smiling (β: -0.1, -0.3 0.0).	
	MCPP; MBzP.	In all children:↑social fear (β: 0.3, -0.1 0.6); (β: 0.3, 0.0 0.5); ↓pleasure (β: -0.2, -0.4 -0.1); (β: -0.1, -0.2 0.0).	2
	Σ_4DEHP	In all children:↑anger levels (β: 0.2, 0.0 0.4).	
	MEP	In all children:↑activity (β: 0.1, 0.0 0.3).	
(Engel et al., 2018)	Σ_5DEHP	In all children: ↑Attention deficit hyperactivity disorder(ADHD) (OR: 1.47, 1.09 1.94). In boys: ↑ ADHD (OR: 1.41, 1.00 1.95). In girls: ADHD (OR: 1.62, 0.95 2.58).	

Note: "↓" represents a decline in specific behavior problems; "↑" represent a rise in specific behavior problems. "*": in the study, phthalate metabolites were grouped into two categories defined by the molecular weight of the monoesters [high (> 250 Da) and low (< 250 Da)], MiBP, MnBP, MEP and MMP only show the point estimation, not confidence interval. "#": the effect size was listed based on the order of phthalate metabolites preceding.

3.4.2. Prenatal exposure to phthalate and other behavior

Phthalate exposure during pregnancy could interfere with children's social development, attention, hyperactivity (ADHD-related symptoms), temperament, visual-spatial abilities, and gender-related play behaviors, which have been demonstrated during the neonatal period. Engel et al. (2009) and Yolton et al. (2011) reported that phthalate exposure in gestation affected the neurobehavior of infants on the fifth day and fifth week after birth, and observed significant sex-phthalate interactions (Table 5).

Phthalate exposure during pregnancy affected children's attention, but the results were inconsistent. Kobrosly et al. (2014), Engel et al. (2010), Kim et al. (2017) and Gascon et al. (2015) discussed the relationship between phthalate exposure and children's attention using different scales and tests. Kobrosly et al. (2014) and Engel et al. (2010) respectively used the Child Behavior Checklist (CBCL) and the Behavior Assessment System for Children (BASC) scales to find that increasing MiBP, MEP, and Σ_4LMWP levels were associated with an increased risk of attention problems. Kim et al. (2017) observed no associations between prenatal phthalate exposure and attention using the Comprehensive Attention Test (CPT), however Gascon et al. (2015) reported that increasing prenatal MEP and Σ_4DEHP concentrations were associated with a reduced risk of inattention symptoms and ADHD index; furthermore, in a recent prospective, nested case-control study, Engel et al. (2018) found evidence that maternal urinary concentrations of DEHP were monotonically associated with an increased risk of ADHD.

Prenatal phthalate exposure impaired children's social behavior development. Lien et al. (2015), Kim et al. (2018) and Miodovnik et al. (2011) reported that elevated concentrations of Σ_4LMWP, MEP and MEOHP increased social behavior problems. Gascon et al. (2015) reported that increasing prenatal Σ_4DEHP concentrations were associated with better social competence using the California Preschool Social Competence Scale (CPSCS), and Braun et al. (2014) simultaneously

analyzed a variety of EDCs and found no associations between phthalates and social behavior in two-stage hierarchical analysis.

In addition to the behavioral problems described above, phthalate exposure during pregnancy impaired children's executive function, decreased boys' masculine play behavior, and affected Virtual Morris Water Maze (VMWM) performance, especially among boys (Table 5). Engel et al. (2010) reported that MMP had a greater impact on children's executive function, although its concentration was much lower than that of MEP, MBzP, MBP, and MEHHP. In addition, Braun et al. (2017) reported that MCPP interfered with VMWM performance, and Singer et al. (2017) reported that MCPP was associated with reduced smiling and increased social fear.

3.4.3. The near and long-term effects on behavioral development

In terms of children's growth and development, six and 12 articles studied the effect of phthalate exposure during pregnancy on the neurobehavior of children aged 0–3 and 4–10 years, respectively. Although there were been few studies on short-term behavioral development of children, the association between phthalate exposure and behavior was found. In conclusion, prenatal exposure to phthalates could interfere with the neurobehavior of children aged 0–12 years.

4. Discussion

To our knowledge, this study was the first systematic review to assess the associations between prenatal phthalate exposure and children's cognitive and behavioral development using data from birth cohorts. We assessed various aspects of neurodevelopment including cognitive development, psychomotor development, internalizing behavior, externalizing behavior, social related behavior, temperament, visual-spatial ability, attention, and sexually dimorphic behavior, and separately analyzed the effects of phthalate exposure during pregnancy on children's short-term and long-term neurodevelopment. This review also evaluated the effects of exposure to multiple types of phthalates during pregnancy, including DEHP, BBzP, DEP, DBP, DMP, DiNP, DiDP, and DnOP.

4.1. Main findings

In general, the results showed that prenatal exposure to DEHP, BBzP, DEP, and DBP influenced cognition and behavior development. Exposure to phthalates had adverse effects on cognitive development in boys and girls, with gender differences. In addition, phthalate exposure was more likely to cause behavioral problems in boys. Phthalate exposure interfered with testosterone concentrations (Sathyanarayana et al., 2014) and aromatase activity (Mankidy et al., 2013), which play major roles in the conversion of testosterone to estradiol. Testosterone levels in humans are associated with male-typical behaviors (Saenz and Alexander, 2013) and androgen levels were important predictors of sexually dimorphic behaviors (Collaer and Hines, 1995), which may explain why boys are more sensitive than girls to the effects of phthalate exposure on neurobehavior. Other cohort studies have also reported associations between prenatal phthalate exposure and cognitive development or attention deficit by measurement of phthalate metabolite in hair or blood (Jones et al., 2018; Minatoya et al., 2016; Verstraete et al., 2016).

The current results suggested that phthalate exposure during pregnancy affected neurobehavior in children aged 0–12 years. Phthalates tended to have an impact on short-term cognitive development, which may be due to the fact that the assessment of the intelligence scale required special training and that follow-up is more difficult with longer duration, resulting in a lack of literature on the long-term effects. More researches is required to verify these findings.

At present, there are few studies on the effects of DnOP and DMP on neurodevelopment. Doherty et al. (2017) reported that MCPP interfered with children's cognitive development, Singer et al. (2017) and Braun et al. (2017) reported that MCPP had an impact on behavior development. Moreover, Engel et al. (2010) reported that prenatal DMP exposure disturbed children's execution function, however, no association between DMP exposure and cognition was found.

The results evaluating the association between prenatal phthalate exposure and neurodevelopment were inconsistent, which could be due to the different methods of correcting for urinary dilution (specific gravity or creatinine), different transformation methods of phthalate concentrations (nature log-transformated, log10-transformed or log2-transformed), different collection time of urine samples, different instruments of outcome measurement, different ethnic population, different sample sizes and different adjustment factors in the models (Table S5). We believed that it was most appropriate to adjust the confounding factors of children's age, sex, maternal age, maternal education, breastfeeding, maternal alcohol use during pregnancy, smoking during pregnancy, race, HOME score in the model by consulting literatures (Doherty et al., 2017; Singer et al., 2017). Moreover, Philippat et al. (2017) and Nakiwala et al. (2018) analyzed pregnant women whose children were boys.

Kim et al., 2011 conducted a categorical analysis to estimate associations of MDI and PDI with quartiles of creatinine-corrected phthalate biomarkers according to infant sex, and demonstrated that among male infants, MDI and PDI scores decreased with increasing MEHHP quartiles, MEOHP quartiles, and MnBP quartiles, but there were no significant differences among female infants. Doherty et al. (2017) estimated associations between MDI and PDI scores and tertile of creatinine-standardized metabolite concentrations in additional sensitivity analyses, and supported the assumption of linearrity, demonstrated threshold-type and non-monotonic. Factor-Litvak et al. (2014) reported that IQ scores were lower among children born to mothers with urinary DBP concentrations in the highest compared the lowest quartiles. Ipapo et al. (2017) reported that the magnitude of effect on novelty preference score was similar and lower in tertiles 2 and 3 compared to tertile 1 for each of the phthalate metabolites excepting MnBP and MCPP among girls. Olesen et al. (2018) showed that lower vocabulary and complexity percentile scores were found among boys in the highest quartile of prenatal phthalate exposure compared to the three other quartile, but no dose-response relationships were apparent. Nakiwala et al. (2018) reported that no significant association was observed after categorizing exposure in tertiles. The results were inconsistent probably due to the different population sizes, maternal ethnicity, and assessment scales, for example, Factor-Litvak et al. (2014) included Hispanics and African Americans women of New-York which could limit comparability with Nakiwala et al. (2018) which relied on a polulation that mostly included highly educated Caucasian European women. In addition, Engel et al. (2010, 2009), Swan et al. (2010) reported that behavior problems increased with higher quartiles of phthalate metbolites. In brief, we speculated that there was a relationship between the extent of phthalate exposure and the effects on neurological outcomes.

4.2. Biological mechanisms

Although a specific mechanism linking maternal phthalate exposure to neurodevelopment has not yet been established, extensive evidence suggests that phthalates can interfere with systems and processes essential to the development of the fetal brain and nervous system (Johns et al., 2015; Liu et al., 2009; Miodovnik et al., 2014; Sun et al., 2018). Based on the current findings, the following possible biological mechanisms can be elucidated. Maternal phthalates levels were significantly and negatively associated with serum thyroid-stimulating hormone (TSH) in cord blood (Kuo et al., 2015) and maternal serum thyroid (Johns et al., 2015, 2016; Yao et al., 2016), phthalates exposure in early life were inversely associated with children cognitive outcomes (Morgenstern et al., 2017), while thyroid function was related to cognition, behavior, and ADHD symptoms (Ghassabian et al., 2011;

Modesto et al., 2015; Perez-Lobato et al., 2015; Thompson et al., 2018). Both animal and epidemiological studies have found that phthalate exposure could interfere with the homeostasis of sex hormones (progesterone, androstenedione, and testosterone) in vivo (Hannon et al., 2015; Sathyanarayana et al., 2014). Steroid hormones, including sex hormones, may affect children's neurodevelopment and relevant behaviors (Gore et al., 2014); testosterone levels in humans were associated with male-typical behaviors (Auyeung et al., 2009; Saenz and Alexander, 2013); in addition, phthalates may interfere with aromatase activity, which plays a major role in the conversion of testosterone to estradiol (Mankidy et al., 2013) and may be important in brain masculinization (Weiss, 2012). Phthalates could interfere with lipid metabolism in the body (Jia et al., 2015, 2016; Xu et al., 2008), which may be detrimental to neurodevelopment (Helland et al., 2003; Xu et al., 2007). Furthermore, phthalates have been shown to activate peroxisome proliferator-activated receptors (PPARs) in vitro and induce PPARγ overexpression, resulting in apoptosis of undifferentiated neurons (Cocci et al., 2015; Ernst et al., 2014; Lampen et al., 2003; Lin et al., 2011). PPARs are a diverse class of nuclear receptors expressed in the fetal rat and human brain tissue with wide-ranging epigenetic and developmental effects(Abbott., 2009) and play an important role in neural tube development and cell proliferation (Kota et al., 2005).

Above all, there are some plausible biological mechanisms. Phthalate metabolites interfered with calcium signaling coupled with nicotinic acetylcholine receptors (nAchRs) in human cell lines (Liu et al., 2009), nAchRs-mediated calcium channel in the brain and the peripheral nervous system play essential roles in a variety of neurodevelopment processes (Resende and Adhikari., 2009). Besides, animals studies showed that phthalate exposure resulted in hippocampal neuron loss and structural and functional alternations (Holahan and Smith, 2015; Li et al., 2013); the hippocampus has long been studied for its prominent role in learning and memory (Nadel and Moscovitch., 2001). Moreover, phthalate altered the expression of neuropeptide Y (NPY) in human cells (Rendel et al., 2017); NPY coordinates energy homeostasis regulation, anxiety, aggression, and other feeding-related behavioral aspects (Loh et al., 2015), and haplotype-driven NPY expression was related to trait anxiety (Zhou et al., 2008). Finally, DEHP and DBP are epigenetically toxic, and maternal exposure to DEHP was shown to increase DNA methylation and expression levels of DNA methyltransferases in mouse testis (Singh and Li., 2012). Epigenetic alterations may also affect behavior (Champagne and Rissman, 2011; Tops et al., 2019).

4.3. Limitations of the current research

This review has some limitations. First, only five cohort studies collected urine samples at two different trimesters of pregnancy; the others only obtained one prenatal urinary sample, which might result in an imprecise assessment of phthalate exposure during pregnancy. Secondly, of the 14 birth cohorts, 10 and five measured urinary phthalate metabolites during the third and second trimester, respectively; thus it was unclear how phthalate exposure during early pregnancy affected child neurodevelopment. Furthermore, few articles investigated the effect of DnOP and DMP exposure on neurodevelopment; in addition to DnOP being metabolized to MCPP in vivo, DBP, DiNP and several high molecular weight phthalates can also be metabolized to MCPP, and we could not determine which affected children's cognitive and behavioral development. Besides, the studies reported the outcomes on different assessments, most of which measured slightly different constructs of behavior or neurodevelopment. In addition, most studies assessed the association between exposure and outcomes at different ages. Moreover, some studies did not address the issue of postnatal exposure, as brain development did not stop at birth, however, Polanska et al. (2014) reported that postnatal children exposure to phthalates was not associated with cognition. In addition to the limitations mentioned above, based on a variety of behavioral rating scales, we classified behavioral issues as internalizing and externalizing behavioral problems for analysis, which might affect the results. Finally, there might be some publication bias, which led to some meaningless results being missed.

4.4. Areas for future research

Given that female reproductive development might be more vulnerable to the effects of phthalate exposure during special critical periods of in utero development (Watkins et al., 2017), we hypothesized that there is a critical in utero window of susceptibility for neurodevelopment in children. Future studies are warranted to investigate the effect of phthalate exposure during different periods of pregnancy. Multiple urine samples should be collected to better evaluate phthalate exposure levels during pregnancy. In addition, when investigating the effects of DMP and DnOP exposure on neurodevelopment, the main source of MCPP in vivo should also be identified. Furthermore, the differences in the effects of phthalate exposure during pregnancy on children's short-term intelligence and long-term intelligence require further clarification. Finally, it is necessary to further identify the biological mechanisms to prevent the adverse effects of phthalate exposure.

5. Conclusions

Prenatal exposure to DEHP, DBP, DEP, and BBzP had an adverse impact on cognitive development, psychomotor development, internalizing behavior, externalizing behavior, attention, gender-typical play behaviors, social behavior and visual spatial ability in children, but results are not always consistent. Some effects were gender-specific, especially the impact of phthalate exposure on neurobehavior in boys. No association had been reported between prenatal DMP exposure and cognitive and psychomotor development. The findings served as confirmatory evidence of the diverse neurodevelopment hazards of phthalates in children.

Conflict of interests

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

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neuro.2019.04.007.

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