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Prenatal exposure to phthalates and its effects upon cognitive and motor functions: A systematic review

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ABSTRACT

Phthalates are chemicals widely used in packaging and consumer products, which have been shown to interfere with normal hormonal function and development in some human and animal studies. In recent decades, pregnant women's exposure to phthalates has been shown to alter the cognitive outcomes of their babies, and some studies have found delays in motor development. Methods: electronic databases including PubMed/MEDLINE and Scopus were searched from their inception to March 2021, using the keywords "phthalate", "cognitive" and "motor". Results: most studies find statistically significant inverse relationships between maternal urinary phthalate concentration during pregnancy and subsequent outcomes in children's cognitive and motor scales, especially in boys rather than girls. However, many associations are not significant, and there were even positive associations, especially in the third trimester. Conclusion: the relationship between exposure to phthalates during pregnancy and low results on neurocognitive scales is sufficiently clear to adopt policies to reduce exposure. Further studies are needed to analyze sex differences, coordination and motor scales, and phthalate levels during breastfeeding.

Abbreviations: PA, phthalic acid; DBP, dibutyl phthalate; BPA, Bisphenol A; DEP, diethyl phthalate; DEHP, di-2-ethylhexyl phthalate; DiBP, diisobutyl phthalate; DnBP, di-n-butyl phthalate; BBzP, benzyl butyl phthalate; DiNP, di-iso-nonyl phthalate; DiDP, di-iso-decyl phthalate; DNOP, di-n-octyl phthalate; LMW, low-molecular-weight phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MCOP, mono(carboxyoctyl) phthalate; MCNP, mono(carboxynonyl) phthalate; MNP, monoisononyl phthalate; MMP, monomethyl phthalate; MnBP, mono-n-butyl phthalate; MEHP, mono-2-ethylhexyl phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MHXP, mono-hexyl phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEP, monoethyl phthalate; MHPP, mono-2-heptyl phthalate; OHMiNP, 7−OH-mono-methyloctyl phthalate; cx-MiNP, mono-4- methyl-7-carboxyheptyl phthalate; MHiNP, mono-hydroxy-iso-nonyl phthalate; MnOP, mono-n-octyl phthalate; MiBP, mono-isobutyl phthalate; MCMHP, mono-[(2-carboxymethyl) hexyl] phthalate; MMCHP, mono-2-methylcarboxyhexyl phthalate; MHiOP, mono-oxo-iso-nonyl phthalate; MCiOP, mono-carboxy-iso-octyl phthalate; TCEP, tris (2-chloroethyl) phosphate; ΣDEHP, sum of di-2-ethylhexyl phthalate metabolites; ΣHMW, sum of high-molecular-weight phthalate metabolites; ΣLMW, sum of low-molecular-weight phthalate metabolites; BRIEF, Behavior Rating Inventory of Executive Function; WCST, Wisconsin Card Sort Task-64; WISC-IV, Weschler Intelligence Scale for Children; ENI, "Evaluación neuropsicológica del niño" [Child neuropsychological evaluation]; SRS-2, Social responsiveness scale; BASC-2, Behavior Assessment System for Children; BASC-PRS, Behavior Assessment System for Children-Parent Rating Scales; SRP, Self-Report of Personality; CADS, Conners Attention Deficit Hyperactivity Disorder DSM-IV Scales; CPT-II, Conners Continuous Performance Test; BSID-CR, Bayley Scales of Infant Development of China Revision; MDI, Mental Development Index; PDI, Psychomotor Development Index; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency 2nd edition; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence-Third Edition; BSID, Bayley Scales of Infant Development; MSCA, McCarthy Scales of Children's Abilities; CPSCS, California Preschool Social Competence Scale; SDQ, Strengths and Difficulties Questionnaire; CSRS, Conners' Parent Rating Scales; MS, Motor scale; GCI, General Cognitive Index; MeS, Memory scale; WPPSI-IV CN, Wechsler Preschool and Primary Scale of Intelligence: Fourth edition; SON-R, Snijders-Oomen Nonverbal Intelligence Test–Revised; DS, Intelligence and Development Scales; K-CBCL, Korea Child Behavior Checklist; EC-Home, Early Childhood Home Observation for Measurement of Environment; CAT, Comprehensive attention test; SDQ-Kr, Strengths and Difficulties Questionnaire; K-ARS, Attention-deficit/hyperactivity disorder Rating Scales; CDI, MacArthur-Bates Communicative Development Inventories "Words and Sentences"; KEDI-WISC, Korean Educational Development Institute's Wechsler Intelligence Scales for Children; NEPSY, Developmental NEuroPSYchological Assessment; SB5, Stanford-Binet intelligence test V (SB5); CDT, Cookie Delay Task.

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1. Introduction

Phthalates are a group of substances that most frequently contaminate homes, and are found in virtually all bodies (Ait Bamai et al., 2014; Kashyap and Agarwal, 2018). They warrant particular attention because exposure to them has been linked to several harmful effects on various organs and systems (Benjamin et al., 2017; Chiang et al., 2017; Weng et al., 2020). These substances include diethylhexyl phthalate (DEHP), diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), dimethyl phthalate (DMP), diethyl phthalate (DEP) and dibutyl phthalate (DPB). Because of the adverse effects of these phthalates, the authorities in North America and Europe have enacted strict restrictions on the use of DEHP, DPB and BzBP in consumer products. These regulations have led to the replacement of some of the phthalate congeners considered more toxic, such as DEHP, DPB and BzBP, with other less toxic substances, especially diisononyl phthalate (DINP) (Babich et al., 2020; Kashyap and Agarwal, 2018). In the United States, the Consumer Product Safety Improvement Act (title 16 Code of Federal Regulations Title 21 Part 1307) limits to 0.1 % by weight the concentrations of eight phthalates (DEHP, DBP, BBP, DINP, DIBP, DPENP, DHEXP, DCHP) in objects used by children under 12 years of age. It does not only limit children's products: since 2018, the Code of Federal Regulations (Title 21 Part 178.3740) limits the concentrations of BBP, DCHP, DINP, DEP in containers intended for contact with food. In Europe, the REACH regulation (Registration, Evaluation, Authorization and Restriction of Chemicals) prohibits concentrations of BBP, DBP, DEHP and DIBP from being greater than 0.1 % of the product's weight. Until 2020, these restrictions only applied to toys and children's products, but they have become more general since July 2020. In children's products there is an additional limitation for DINP, DIDP and DNOP. Further regulations have been published, including the RoHS Directive for electronic products such as cables and USB ports (PBB, PBDE, DEHP, BBP, DBP, DIBP), Regulation (EC) 1223/2009 for cosmetic products (BBP, DBP, DEHP), EN 71−3: Specification for migration of certain elements, Regulation (EC) 10/2011 on plastic materials and articles intended to come into contact with food (DEHP, DBP, BBP, DAP, DIDP, DINP), EN 71−4 on Experimental sets for chemistry and related activities, and EN 71−5 on Chemical toys (sets) other than experimental sets. Table 1 classifies some of the phthalates according to Annex XVII to the Regulation on the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) of the European Chemicals Agency (ECHA).

Hundreds of thousands of tons of phthalates are used every year in a wide variety of products, and many of those products are widely used in households. Phthalates account for a significant part of the weight of plastics such as polyvinyl chloride products, in which they are used as softeners or plasticizers (they can represent up to 30 % of the total weight) (Babich et al., 2020; Kashyap and Agarwal, 2018), and they are therefore released from surfaces covered with these plastics. Phthalates are also present in several other products such as glues and adhesives, electronic and medical devices, construction materials, cleaning products, personal care products (gels, shampoos, soaps, lotions, cosmetics), perfumes, packaging (such as water bottles), paints, varnishes, toys, modeling clay, waxes, printing inks, clothes and fabrics, air fresheners, and pesticides (Babich et al., 2004; Koniecki et al., 2011; Smith et al., 2021; Wittassek et al., 2007; Xu et al., 2020). They are also found in large quantities in household dust (Ait Bamai et al., 2014; Bornehag et al., 2005; Hammel et al., 2019) from where they pass into the bloodstream either by inhalation, or through oral or dermal routes. Occupational exposure occurs primarily through inhalation and dermal contact, while consumer exposure is primarily via oral and dermal routes.

Several scientific investigations have associated exposure to phthalates with various health problems, primarily due to their effects as hormone disruptors (Brehm and Flaws, 2019; Mariana et al., 2016; Stojanoska et al., 2017; Zlatnik, 2016). The European Union has banned their use in items including pacifiers, teats and teething rings, but no restrictive measures have been adopted for many other uses, and it is precisely in household areas such as children's bedrooms where these substances are most likely to be present (as well as outside the home, in places such as nurseries, on floors, vinyl wallpapered walls, in toys, mats, plastic tablecloths, etc.) (Lioy et al., 2015; Sharma et al., 2014; Sharpe, 2000). Several studies have associated exposure to some phthalates with a wide range of effects. The association has often been found at quite low concentration levels, is present in large sectors of the population, and several timings of exposures have been investigated e.g. prenatal exposure, in childhood, in adults (Fréry et al., 2020; Heudorf et al., 2007; Johns et al., 2015; Porras et al., 2020; Wittassek et al., 2007). The most extensively investigated effects associated with phthalate exposure are asthma and childhood allergy (Mattila et al., 2021; North et al., 2014; Robinson and Miller, 2015), sperm alterations (Wang et al., 2016), abnormalities in male genital development (such as cryptorchidism), altered testosterone levels, gynecomastia in adolescent boys, shortening of the anogenital distance in new-born boys (symptom of feminization) (Sweeney et al., 2015), early thelarche (premature breast development in girls), endometriosis, breast cancer, altered ovarian follicle formation (Crain et al., 2008), obesity and insulin resistance (linked to diabetes development) (Stojanoska et al., 2017; Zettergren et al., 2021). Mature neurons in the human nervous system cannot proliferate for self-repair, making this system particularly vulnerable to environmental pollutants (Li et al., 2019; Shah et al., 2020). The major windows of developmental vulnerability occur *in utero*, during infancy, and in early childhood. As a result of the widespread use of phthalate esters and our subsequent exposure to them, their adverse effects on children's neurocognitive development have become a significant public health concern (Birnbaum and Bornehag,

Table 1
Classification of phthalates by molecular weight.

Low molecular weight phthalates (ester side-chain lengths of 1−4 carbons)	High molecular weight phthalates (ester side-chain lengths >4 carbons)
DBP: dibutyl phthalate*	BBzP: benzyl butyl phthalate*
DEP: diethyl phthalate	cx-MiNP: mono-4- methyl-7-carboxyheptyl phthalate
DiBP: diisobutyl phthalate*	DEHP: di-2-ethylhexyl phthalate*
MBP: mono-n-butyl phthalate	DiDP: di-iso-decyl phthalate**
MBzP: monobenzyl phthalate	DiNP: di-iso-nonyl phthalate**
MCPP: mono(3-carboxypropyl) phthalate	DNOP: di-n-octyl phthalate**
MEHP: mono-2-ethylhexyl phthalate	MCiOP: mono-carboxy-iso-octyl phthalate
MEP: monoethyl phthalate	MCMHP: mono-[(2-carboxymethyl) hexyl] phthalate
MHPP: mono-2-heptyl phthalate	MCNP: mono(carboxynonyl) phthalate
MHXP: mono-hexyl phthalate	MCOP: mono(carboxyoctyl) phthalate
MiBP: mono-isobutyl phthalate	MECPP: mono(2-ethyl-5-carboxypentyl) phthalate
MMP: monomethyl phthalate	MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate
MnBP: mono-n-butyl phthalate	MEHP: mono-2-ethylhexyl phthalate
MnOP: mono-n-octyl phthalate	MEOHP: mono(2-ethyl-5-oxohexyl) phthalate
MNP: monoisononyl phthalate	MHiNP: mono-hydroxy-iso-nonyl phthalate
	MHiOP: mono-oxo-iso-nonyl phthalate
	MMCHP: mono-2-methylcarboxyhexyl phthalate
	OHMiNP: 7-OH-mono-methyloctyl phthalate

* Substance under Entry 51 of Annex XVII, with a sunset date in 2015.
** Substance under Entry 52 of Annex XVII.
Source: adapted from Phthalates and Cumulative Risk Assessment: The Tasks Ahead ("Phthalates and Cumulative Risk Assessment: The Tasks Ahead," 2008). The asterisked substances are subject to restrictions on their manufacture, marketing and use because they are included in Annex XVII of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) of the European Chemicals Agency (ECHA).

2021; Engel et al., 2010). Determining how gestational exposure to these chemicals may affect the development of cognitive and motor functions in childhood and beyond is of significant interest.

The aims of this review were:

- To summarize data reporting the association between prenatal exposure to phthalates and cognitive and motor functions in animal models and humans.
- To summarize the effects based on phthalate congeners.
- To evaluate sex differences.

2. Methods

This study was designed and developed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses PRIMA guidelines (Moher et al., 2009), which represent an evidence-based minimum set of items aimed at assessing the benefits and harms of a given health issue.

2.1. Literature search

We searched the literature in the most widely used electronic bibliographic databases, Medline and Scopus, for all entries up until March 30, 2021. The bibliographic searches were performed with no time limitation in each database. The reference lists of all the relevant articles were manually cross-referenced in order to identify additional articles. The primary search terms used were "phthalate", AND "cognit*" or" motor" with no filters.

2.2. Inclusion and exclusion criteria

In order to answer our research questions, we applied the following inclusion criteria to the manuscripts we considered: 1) it was acknowledged as an original article, including reports such as experimental studies (animal studies) and observational studies such as cohort and cross-sectional studies, and case-control studies for human studies; 2) it was a full-text published either in English or Spanish; 3) cognitive and/or motor function was specifically assessed; 4) a description of how cognitive and motor function were evaluated in the methods section; 5) the time of exposure to phthalates and the outcomes measurement time were included.

2.3. Data collection and analysis

The database search results were uploaded into a web-based system which was used to manage the screening process, and duplicate citations were removed. In order to determine which studies would be included, the three members of the review team independently screened the title and abstracts of the articles extracted from the literature search. Based on the inclusion/exclusion criteria, the electronic full text was retrieved for the studies on which the reviewers agreed. For each of these articles, two reviewers independently extracted the following data: the country where the study was conducted, the number of participants, the age of participants at the time of inclusion, their sex, the type of phthalates analysed, how cognitive and motor functions were evaluated, and the main outcomes. Any disagreement between the two reviewers regarding the papers and data extracted from them was resolved by the third author. The methods used to decide which results to collect were: evaluation of cognitive and motor function by well-defined psychometric scale or behavioural tests and any statistical analysis (e.g. risk ratio, mean differences, ect) between the selected outcomes (cognitive and motor function) and phthalates concentration in any biological sample. The information mentioned before were tabulated in excel file and than revised by two authors.

2.4. Analysis of the quality of epidemiological studies

The quality of the studies was assessed using the Newcastle–Ottawa scale, a tool valid for assessing the quality of epidemiological studies (Deeks et al., 2003). Using the tool, each study is judged based on eight items classified in three groups: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively.

3. Results

For human studies, our search strategy identified 265 studies in PubMed/Medline and Scopus databases. After duplicates had been eliminated, 134 papers required further full-text screening, and 29 met the inclusion criteria and were analysed in detail. Finally, 25 articles fulfilled all the criteria and aims of this review (Fig. 1). Most articles were excluded because they investigated other brain functions such as social aspects, language development, autism or ADHD (attention-deficit and hyperactivity disorder) traits, they were animal studies or narrative reviews, or did not analyze the relationship between phthalate exposure and the selected outcomes. A parallel selection of studies was performed for animal studies (they were all studies performed on mice or rats) regarding phthalate exposure and cognitive and motor functions. The most important variables and outcomes from the selected human studies are summarised in Tables 2 and 3, and details of their results are presented and discussed in the following sections under the headings outlined above. A visual graphic approximation by color code can be seen in Fig. 2. The analysis of the quality of epidemiological studies (cohort or case-control design study) (Table 4). With the Newcastle–Ottawa scale (Deeks et al., 2003) was applicable to 23 all cohort design studies. Two articles (Hutter et al., 2013; Hong et al., 2015) were based on cross-sectional studies and the Newcastle–Ottawa scale fo case-control studies was adapted (and this these criteria could not be applied. The analysis of the 23 cohort studies shows quality scores ranging between 5–8 points (moderate-high quality). Scores of 0–3, 4–6 and 7–9 were considered as low, moderate and high quality, respectively (Lo et al., 2014) Two studies had high bias risk e.g. score 5 (Huang et al., 2015; Weng et al., 2020)) and 7 studies had a moderate bias risk (score 6 (Balalian et al., 2019; Choi et al., 2021; Doherty et al., 2017; Li et al., 2019; Nakiwala et al., 2018; Oulhote et al., 2020; Whyatt et al., 2012). The other studies (11) had high quality scores, meaning a low bias risk. The two cross-sectional studies had moderate risk of bias.

3.1. Effects of in utero exposure to phthalates on cognitive and motor function in experimental animals

Many mammalian species experience a period of accelerated brain growth known as the "brain growth spurt", in which numerous biochemical changes occur, as well as fundamental developmental stages such as axon maturation, dendrite growth, the establishment of growth of dendrites, the establishment of neuronal synaptogenesis, accompanied by the glial cell multiplication with myelination (Dencker and Eriksson, 1998) which transform the immature brain of the feto-neonate into the mature brain. The establishment of connections and organization of neural circuits are very sensitive to neurotoxicants (Kponee-Shovein et al., 2020); and specifically in the microenvironment in which these transformations are taking place. In laboratory animals such as mice and rats, this period is entirely neonatal, and comprises the third and fourth week of postnatal life. For this reason, experiments to evaluate the effects of exposure to neurotoxicants during gestation are evaluated in the perinatal period (including gestation and post-natal day 7 in most cases).

Perinatal exposure to phthalates has been shown to alter cognitive and motor functions in animal models in rats and mice (Kougias et al., 2018; Lin et al., 2015; Mao et al., 2016; Peng, 2015; Sun et al., 2014).

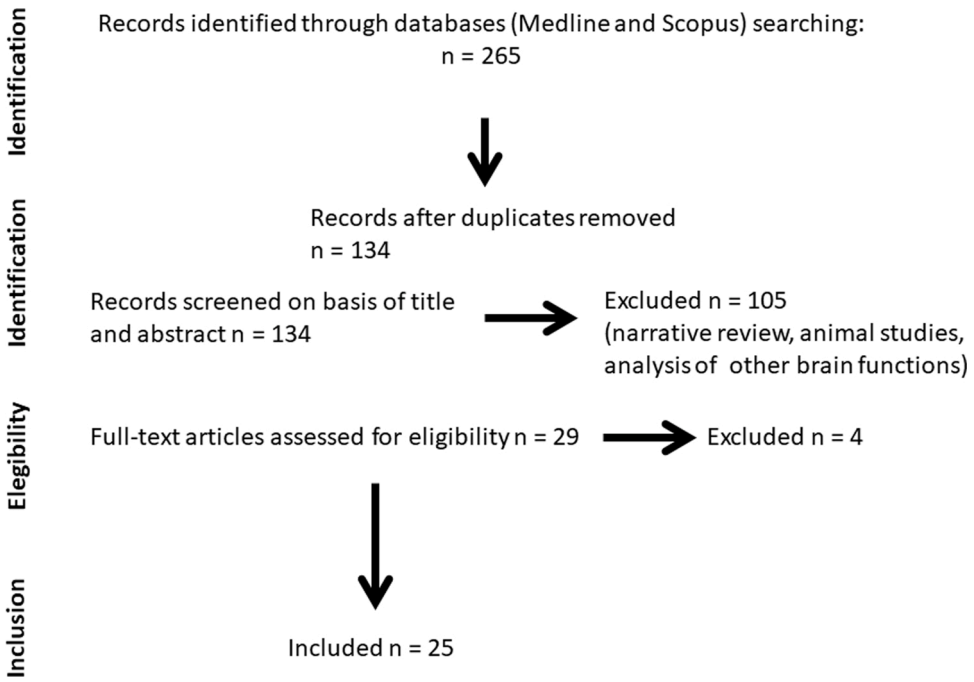

Fig. 1. PRISMA guidelines flowchart for literature searches.

Interestingly, some of the effects of perinatal exposure reported in experimental animals change from non-significant to decreasing or increasing cognitive and motor functions in the offspring, depending not only on the phthalate congener investigated but also on the dose of exposure. Exposure to 1% DPB in the diet enhanced spatial learning and reference memory (postnatal day 35) in male pups, but exposure to 0.037 % DPB inhibited spatial learning and reference memory in male pups (Li et al., 2019). Sex differences were found in spatial learning and reference memory, and the male pups appeared to be more susceptible than the females (Li et al., 2009). However, all levels of DPB exposure did not significantly alter motor function measured in the open field test in either sex (Li et al., 2009). Prenatal DEHP exposure (from gestational day 12–21) in rats altered spatial learning in the offspring (Lin et al., 2015; Sun et al., 2014). Perinatal exposure to phthalates can alter protein expression in the brain (Lin et al., 2015). Genome-wide microarray analysis has showed that perinatal DEHP exposure down-regulates the expression of Ccnd1 and Cdc2 genes, which are critical for neuron proliferation (Lin et al., 2015). Exposure to DHEP alters the gene expression of insulin and insulin-like growth factor in the hippocampus, an area of the brain crucial for spatial learning and memory processes. In addition, the fact that phthalate exposure alters insulin and insulin-dependent growth factor in the brain (Sun et al., 2014; Xu et al., 2020) may represent a risk factor for Alzheimer's disease (Bosco et al., 2011; Gasparini and Xu, 2003).

3.2. *Effects of in utero exposure to phthalates on cognitive and motor function in children*

During fetal development, the developing central nervous system is able to adapt to and compensate for early mild perturbations or damage. However, the central nervous system is most vulnerable to chemically induced damage during this period (Lein et al., 2007; Tilson et al., 1998). This is because in the transition from the neuroblasts to mature neurons, the cells transiently maintain a certain degree of phenotypic plasticity, and for this to occur, a microenvironment in optimal conditions is necessary to define their functions very precisely. Neurogenesis in different brain regions is differential during development (Rodier, 1980); the maximum rate of neurogenesis takes place almost exclusively during brain ontogeny, during which processes such as migration, the development of receptors, transmission systems and myelination continue after birth, albeit but to a lesser extent. Neuroblasts damaged during ontogeny by exposure to neurotoxic substances may lose their very limited capacity for regeneration or neuronal plasticity, permanently altering the functioning of the central nervous system and causing severe neuronal damage and/or behavioral changes, without compromising the individual's growth and viability. Since the effects of prenatal exposure differ in each trimester of gestation for many environmental neurotoxicants (Andersen et al., 2000; Eriksson, 1997; Pelé et al., 2013), we have summarized the outcomes based on the exposure data in each gestational trimester.

3.2.1. *First trimester*

The only study that only collects urine samples in the first trimester is by Oulhote et al. (Oulhote et al., 2020), which found an association between increased MBP and MCPP in urine during pregnancy, and higher social impairment in the social responsiveness scale scores: higher levels of social cognition, social communication, social motivation, restricted interests, and repetitive behaviours. These behaviours were not associated with the levels of MBzP, MEP or DEHP. Some studies analyze various trimesters, including the first. When analyzing the first and third trimesters, Shah et al. (Shah et al., 2020) reported a deficiency in cognitive development after exposure to MEHHP mono (2-ethyl-5-hydroxyhexyl) phthalate and MEOHP mono (2-ethyl-5-oxohexyl) phthalate. Exposure to the congener MEHHP inversely affected the MDI (Mental Developmental Index) and PDI (Psychomotor Developmental Index) values at six months in boys. Qian et al. (Qian et al., 2019) used average concentrations during the entire pregnancy (three samples) instead of trimester by trimester. They found negative associations between PDI (Psychomotor Developmental Index) scores and concentrations of MnBP mono-n-butyl phthalate, and of ΣDPB (dibutyl phthalate sum), and positive associations between PDI scores and concentrations of HMWP (high-molecular-weight phthalate) metabolites such as MECPP (mono(2-ethyl-5-carboxypentyl phthalate)) ($\beta = 2.15$; 95 % CI: 0.01, 4.29). This positive association is particularly emphatic in boys and at levels with several congeners (MEHP (mono (2-ethylhexyl) phthalate), MEOHP, MECPP, ΣDEHP and ΣHMWP. No significant association between exposure to any individual phthalate and the MDI scale was found.

Table 2
General description of the papers, variable comparisons and main outcomes.

First author, year	Pregnancy trimester and/or age of children % sex	Phthalates measured in the study	Measurements instruments for cognitive /motor functions	Main effects of phthalates
	Prenatal, and 0.5, 1, 2, 3.5, 7, 9, 10.5, 12, 14 and 16 years old. 49.9 % boys; 50.1 % girls	MBP, MBzP, MCPP, MCOP, MCNP, MECPP, MEHP, MEHHP, MEOHP, MEP, MiBP, ΣDEHP, ΣHMW, ΣLMW	BRIEF, WCST, WISC-IV, ENI, SRS-2, BASC-2, SRP, CADS, CPT II	MEP concentrations were associated with decreased WMIQ scores. MiBP concentrations were associated with increased PSIQ scores.
	3 prenatal tests, 2 years old. 53.36 % boys, 46.64 % girls	MEP, MiBP, MnBP, MBzP, MEHP, MEOHP, MEHHP, MECPP, MEP, MiBP, DEP, DiBP, DnBP, BBzP, DEHP	BSID-CR, MDI, PDI	MnBP and ΣDBP were negatively associated with PDI scores in all children. MECPP was positively associated with PDI scores in all children.1st-trimester concentration of MnBP was negatively associated with PDI scores in all children The 3rd-trimester concentrations of HMW phthalates were inversely associated with MDI scores for MEHHP, MECPP, ΣDEHP and ΣHMW.
	3rd trimester of pregnancy and 3, 5, 7, 11 years old. 46.35% boys, 53.65% girls	DnBP, BBzP, DiBP, DEHP and DEP	BOT-2, MDI, PDI	Maternal exposure to phthalates has effects on motor function.
	Prenatal and 5 years old. Only boys, no girls	MEP, MBP, MiBP, MECPP, MEHHP, MEOHP, MEHP, MBzP, MCOP, MCPP, MCNP	WPPSI-III	Positive association between MCPP and verbal IQ.
	Prenatal and 1, 4 and 7 years old. 52% boy, 49% girls	MEHHP, MEHP, MEOHP, MECPP, MBzP, MEP, MiBP, MnBP	BSID, MSCA, CPSCS, SDQ, CSRS	The only association was between prenatal MBzP and psychomotor development at the age of 4 years. Increasing concentrations of Σ 4DEHP in the 1st trimester were associated with better cognitive scores at the age of 4 years.
	Prenatal and 4 years old. 46.8% boys; 53.2% girls	MEHP, MEHHP, MEOHP, MECPP, MBzP, MCPP	MSCA, MS, GCI, MeS	Negative associations between all metabolites and their sums and the MS and GCI scores. However, only those of HMWP, MEHHP, MEOHP, MECPP and DEHP were statistically significant in relation to the MS. The effect estimate was stronger for the first trimester exposure, followed by the second trimester and null for the third trimester. The strongest effect estimate was mainly seen in association with MS.
	3 prenatal, 42 days, 3 months, 6 months, 9 months, 12 months, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 and 6 years old	MMP, MEP, MBP, MBzP, DEHP, MEHP, MEHHP, MEOHP	WPPSI-IV CN	Significant inverse relationship between phthalate metabolites and preschooler IQ in the total sample, with a 1 point increase in MBP associated with 0.30-point, 0.32-point and 0.31-point declines in the VCI, VSI and FSIQ, respectively. MEP concentration was positively associated with both the FRI and PSI.
	Prenatal, 2, 5, 8, 11 years old 52.7 % boys, 42.3 % girls	MMP, MEP, MBP, MBzP, MEHP, MEHHP, MEOHP, ΣMEHP	Bayley and Wechsler tests	Inverse associations between the children's levels of urinary mono(2- ethyl-5-oxohexyl) phthalate and the sum of the three metabolites of di(2-ethylhexyl) phthalate and their IQ scores
	Prenatal and 6 years old 50.5 % boys, 49.5 % girls	LMWP, HMWP, DEHP, DNOP, PA, MMP, MEP, MBP, MIBP, MHWP, MECPP, MEHHP, MEOHP, MCMHP, MCMHP, MCPP, MBzP, MHXP, MHPP, DEHP	SON-R	Association of phthalates with child's lower nonverbal IQ scores. Inverse association between (DNOP) exposure and nonverbal IQ.
	3rd trimester, 2 and 7 years old 45 % boys, 55 % girls	MEP, MiBP, MnBP, OH-MnBP, MBzP, MEHP, OHMEHP, oxo-MEHP, OHMiNP, MnOP	SDQ, IDS	Association between MEP and peer relationship problems. Not conclusive for IDS child's cognitive and psychomotor development. Negative associations between MEP and MnBP in early childhood and fluid intelligence and cognition. Positive associations of prenatal oxo-MEHP for fluid intelligence. affected the neurodevelopment of boys at six months.
	3rd trimester and 7 years old 46 % boys, 54 % girls	LMW, DMP, DEP, BBzP, DiBP, DnBP, HMW, DEHP, DiNP, DiDP, MCPP	SDQ, IDS	Association between DMP and DnBP with total difficulties scores. Negative association between DnBP and DMP with fluid IQ and crystallized I Negative association between DMP, DEP and DnBP and mathematical skill
	Prenatal, 6 months and 1,2,3,4,5 years old 52 % male, 48 % female	Not specified - merely "phthalate metabolites."	BSID, WPPSI-R, K-CBCL, SRS, EC-Home, CAT, SDQ-Kr, K-ARS	MEHHP, MEOHP, and MBP, negatively
	3rd trimester, 11 years old	MEOHP, MECPP, MEHP, MBP, MEP, MiBP, MBzP	BOT-2	Significantly lower fine motor scores for children exposed to phthalates during pregnancy.
	Prenatal and every 3 months from 16 to 36 months	MEP, DEP, MnBP, MiBP, DiBP, DnBP, MBzP, BBzP, MEHP, MEHHP, MEOHP, MECPP, DEHP, MiNP, MHiNP, MHiOP, MCiOP, DiNP	CDI	Complexity scores were significantly lower in children with high levels of exposure to MEP, MBzP, ΣDEHPm, MEHHP, MEOHP and MECPP.
	Prenatal, 5 and 8 years old		WPPSI-III	The sum of ΣDEHP, MCPP, and MEP at age 3 years, and MBzP at 16 weeks

(*continued on next page*)

Table 2 (*continued*)

First author, year	Pregnancy trimester and/or age of children % sex	Phthalates measured in the study	Measurements instruments for cognitive /motor functions	Main effects of phthalates
				gestation and children aged 3, 5, and 8 years were inversely associated with children's full-scale IQ
	43 % boys, 57 % girls	MEP, MnBP, MiBP, MCPP, MBzP, MCOP, MCNP, DEHP, MEHP, MEHHP, MEOHP, MECPP		Each 1-standard deviation increase in ΣDEHP at age 3 was associated with a 1.9-point decrease in full-scale IQ.
				MBP and MiBP at age 4 years were positively associated with children's full-scale IQ.
	Prenatal, 3 and 4-6 years old	MiBP, MEP, MMP, MnBP, MBzP, MCNP, MCOP, MCPP, MEHP, MEHHP, MEOHP, MECPP, MCMHP	BSID at age 3 and Stanford Binet-5 at age 4 to 6	Only MBzP was negatively associated with the Bayley language score
	49.5 % boys, 50.5 % girls			A phthalate mixture (MMP+MCOP) was associated with higher language scores.
	Mean 7.17 years old	Phthalates (not specified)	Standard Progressive Matrices test	Significant correlations of TCEP in classroom dust and filter samples with cognitive performance. Cognitive performance decreased with increasing concentrations of TCEP.
	50% boys, 50% girls			
	Prenatal, every 3 months between 18 and 36 months. 52.9 % boys, 47.1 % girls	BPA	CDI at 21 months	High BPA concentration is significantly associated with poorer language in boys.
	9-year-old students 52.6 % boys, 47.4 % girls	MnBP, MEOHP, MEHP	KEDI-WISC	Association between lead in blood and lower IQ Full Scale.
	Prenatal and 3 years old	MnBP, MBzP, MiBP	MDI, PDI, BSID	Child PDI scores decreased with increasing log MnBP and log MiBP.
	47.3 % boys; 52.7 % girls			Chances of motor delay increased significantly per each increase of log MnBP..
				The ORs for clinically withdrawn behavior were 2.23 and 1.57 per log unit increase in MnBP and MBzP respectively.
	Prenatal and 7 years old	DnBP, BBzP, DiBP, DEHP, DEP	WISC-IV	Inverse association between child's full-scale IQ and DnBP and DiBP.
	47.3 % boys, 52.7 % girls			Among children of mothers with the highest versus lowest quartile DnBP and DiBP metabolite concentrations, IQ was 6.7 and 7.6 points lower, respectively.
				Negative association between DnBP and DiBP and child's processing speed, perceptual reasoning and working memory.
	Prenatal and 2 years old 54 % boy, 46 % girl	MEHP, MEHHP, MEOHP, MECPP, MnBP, MiBP, MEP, MBzP, MCPP	BSID-II, MDI, PDI	Positive associations among boys (1-2 point increase in score per ln-unit increase in metabolite concentration)
	Prenatal and 3.5 years old	MEP, MiBP, MnBP, MBzP, BBzP, MEHP, MEHHP, MEOHP, MECPP, MMCHP, DEHP, OH-MiNP, OHMiNP, cx-MiNP, DiNP	BRIEF-P, NEPSY, SB5, CDT	Association between MBzP and poor executive functions in both sexes.
	56.9 % boys, 43.1 % girls			An interquartile range increase in MBzP was associated with poorer working memory rated by parents and teachers.

Torres-Olascoaga et al. (Torres-Olascoaga et al., 2020) found that the effect on cognitive development was stronger for exposure in the first trimester than in the second one, and not significant for exposure in the third trimester. In the first trimester, there was a negative relationship between the General Cognitive Index and all the phthalate metabolites studied: MEHP, MEHHP, MEOHP, MECPP and MCPP (mono-3--carboxypropyl phthalate), and was only statistically significant for MBzP (monobenzylphthalate). For the Motor Scale, the inverse link was statistically significant for HMWP, MEHP, MEHHP, MEOHP, MECPP, MBzP and DEHP, but it was not detected for MCPP. There were no statistically significant associations between phthalate exposure and the memory scale. By sex, the negative association between first trimester phthalates and GCI and motor scale scores was stronger in boys than in girls, while this difference was absent in the second and third trimesters.

According to the research by Zhu et al. (Zhu et al., 2020), each increase in MBP (monobutyl phthalate) in the first trimester was associated with reductions of 0.56-points on the verbal comprehension index (VCI) scale; 0.60-points on the visual space index (VSI) scale, and 0.49 points on the full-scale intelligence quotient (FSIQ) scale. They also found gender differences: among boys there was a negative association with the score in processing speed index (PSI) and exposure in the first trimester to MMP (Mono-methyl phthalate), MEHHP, and ΣPhthalates.

In the study by Van den Dries et al. (van den Dries et al., 2020), during early pregnancy (<18 weeks) the levels of some metabolites were significantly associated with the child's nonverbal IQ (Intelligence Quotient) score. A 10-fold increase in LMWP (low-molecular-weight phthalate) reduced the nonverbal IQ score by 1.7 points; for DNOP (di-n-octyl phthalate) it was by 2.0 points, and for phthalic acid by 1.9 points. Other associations that were negative but not statistically significant were found for HMWP and DEHP.

3.2.2. *Second trimester*

In the second trimester there are negative associations between exposures to HMWP, MEHHP, MEOHP, MECPP and MBzP, but not for MEHP and MCPP congeners and the motor scale (Torres-Olascoaga et al., 2020). No statistically significant associations were found for IQ, cognitive function (Torres-Olascoaga et al., 2020;van den Dries et al., 2020;Zhu et al., 2020) or the memory scale (Torres-Olascoaga et al., 2020).

Mothers' urine and blood samples were analyzed in the second trimester of pregnancy, and an association was found between elevated MBzP and poorer executive function and IQ during preschool age for the children measured with the Behavior Rating Inventory of Executive Function-Preschool (BRIEF-P) and the Full-Scale Intelligence Quotient (FSIQ) (Choi et al., 2021; Li et al., 2019), respectively. No associations between ΣLMWP, ΣHMWP, and ΣDEHP and executive functions were

Table 3
Main differences in outcomes between sexes.

First author, year	Effects on boys	Effects on girls
(Hyland et al., 2019)	High prenatal ΣHMW concentrations were associated with lower FSIQ and WMIQ scores among boys. Higher ΣDEHP concentrations were associated with lower WMIQ scores in boys.	High prenatal ΣHMW concentrations were associated with higher FSIQ, WMIQ and PSIQ scores among girls. Higher ΣDEHP concentrations were associated with increased FSIQ, WMIQ and PSIQ scores among girls.
(Qian et al., 2019)	3rd-trimester concentrations of MEOHP, MECPP and ΣDEHP were positively associated with PDI scores in boys.	–
(Balalian et al., 2019)	Boys: the BOT-2 fine motor composite score was inversely associated with prenatal concentrations of MBzP. No association with gross motor score. In boys: no association between any prenatal phthalate metabolite concentration and the BOT-2 gross motor score.	Girls: the BOT-2 total composite score was lower with higher prenatal concentrations of MnBP, MBzP, MiBP and MEP. The BOT-2 fine motor composite score was lower with higher prenatal MnBP. The gross motor composite score was also inversely associated with the prenatal concentrations of MiBP and MEP.
(Torres-Olascoaga et al., 2020)	Boys showed stronger negative associations than girls between first trimester phthalates and MS and GCI scores.	
(Oulhote et al., 2020)	Associations between phthalate concentration levels and SRS scores seemed stronger in boys than in girls, with several associations for MBP and MEP showing significant effect change by sex.	
(Zhu et al., 2020)	Boys: 0.56-point and 0.38-point decreases in VCI and FSIQ.	No effect
(Shah et al., 2020)	MEHHP, MEOHP, and MBP negatively affected the neurodevelopment of boys at six months.	
(Daniel et al., 2020)	No statistically significant association for DEHP phthalates and weighted quartile sum scores was found in males.	A significant reduction in fine motor functions was observed among females (especially MBP, MBZP, and MIBP), but not among males. No significant associations in gross motor functions among females for DEHP.
(Olesen et al., 2018)	Boys: with high phthalate exposure had lower vocabulary and complexity scores for elevated MEP and ΣDEHPm levels (no dose-response relationships).	Girls: no association between maternal phthalate exposure and language scores.
(Weng et al., 2020)		Correlation between MBzP and activity in the anterior cingulum gyrus and insula in girls.
(Jensen et al., 2019)	Boys: BPA exposure in the highest tertile had an odds ratio of 3.70 of being in the lowest 15th percentile of vocabulary score, compared to boys with mothers in the lowest tertile for BPA exposure after adjustment.	No association was found in girls.
(Morgenstern et al., 2017)	No association between free thyroxine and metabolites in boys	In girls, reduced free thyroxine at high levels of MnBP, MEP, MEHHP, MEOHP.
(Messerlian et al., 2017)	Significant association between maternal MnBP and MiBP concentrations with internalizing behavior by sex (more in boys than girls). Increased internalizing behavior among boys.	Reduced internalizing behavior among girls.
(Whyatt et al., 2012)	In boys, significant differences between MnBP concentrations and risk of somatic complaints, mental delay, withdrawn behavior, emotionally reactive behavior, and internalizing behaviours.	In girls, MDI scores declined with rising log MnBP.
(Doherty et al., 2017)	One unit increase in maternal urine concentrations of MnBP, MCPP, and MBzP was associated with a 1.5–2 point increase in MDI score in boys. In addition, among boys, one unit increase in MnBP concentration was significantly associated with a 1.92 point increase in PDI scores.	In girls: negative associations between metabolite concentrations and both MDI and PDI scores (a 2−3 point decline in the score per ln-unit increase in creatinine-standardized metabolite concentration).
(Choi et al., 2021)	Executive function domains reported by parents using BRIEF-P were the most apparently implicated, with stronger associations among boys.	

found, except for a higher prenatal ΣLMWP and better scores for perseverative errors among boys (but not girls) (Hyland et al., 2019). No associations were found between ΣLMWP, ΣHMWP, and ΣDEHP and IQ scores (Hyland et al., 2019). An interquartile range increase in MBzP was associated with poorer working memory (rated by both teachers and parents), and poorer performance-based nonverbal inhibition control, performance-based emotional control, and reporter-based emotional control. MiBP (Monoisobutyl phthalate) and MnBP levels in urine were associated with poorer executive functions in boys, but these functions were based on parents' reports. Poorer inhibition was reported by both teachers and parents in boys; but no significant associations were found in girls. No associations between DEHP or DiNP (Diisononyl phthalate) and executive functions were found.

No statistical significance was found for associations between ΣDEHP, MnBP, MiBP, MCPP, MEP (Monoethyl phthalate), MCNP (mono-carboxynonyl phthalate) or MCOP (mono-carboxyoctyl phthalate) concentrations in pregnancy and FSIQ scores. There were no differences by sex with the associations between phthalate metabolite concentrations and FSIQ scores (Li et al., 2009). However, when stratifying by sex, an association was found (for boys between higher ΣHMW and lower FSIQ and WMIQ (Working Memory IQ), and higher scores among girls on the scales FSIQ, WMIQ and PSIQ (Processing Speed IQ). A similar effect happened with ΣDEHP, which was associated with lower WMIQ scores in boys, and with higher scores among girls on the FSIQ, WMIQ and PSIQ scales. No associations were found for the VCIQ (Verbal Comprehension IQ) scale in either sex (Hyland et al., 2019). Social cognition has been rarely measured, and the only significant association was reported for higher ΣDEHP and improved NEPSY-II (Developmental NEuroPSYchological Assessment) scores among all children, and particularly among girls (Hyland et al., 2019). In contrast, associations between prenatal ΣLMW and more errors in the CPT-II (Continuous Performance Test, version 5) and poorer behaviors on the BASC-2/SRP scale (Behavior Assessment System for Children-Parent Rating Scales) were reported, particularly for hyperactivity, attention problems, anxiety, internalizing problems (Hyland et al., 2019). There was also a statistically significant association between urinary concentrations of MEP, MBzP, MCPP, and MCOP during pregnancy and high scores for internalizing problems and/or commission errors. Another association was noticed between prenatal urinary concentrations of MEP and MCPP and increased self-reported internalizing problems at age 16 (Hyland et al., 2019).

3.2.3. *Third trimester*

Exposure to oxo-MEHP in the third trimester of pregnancy was

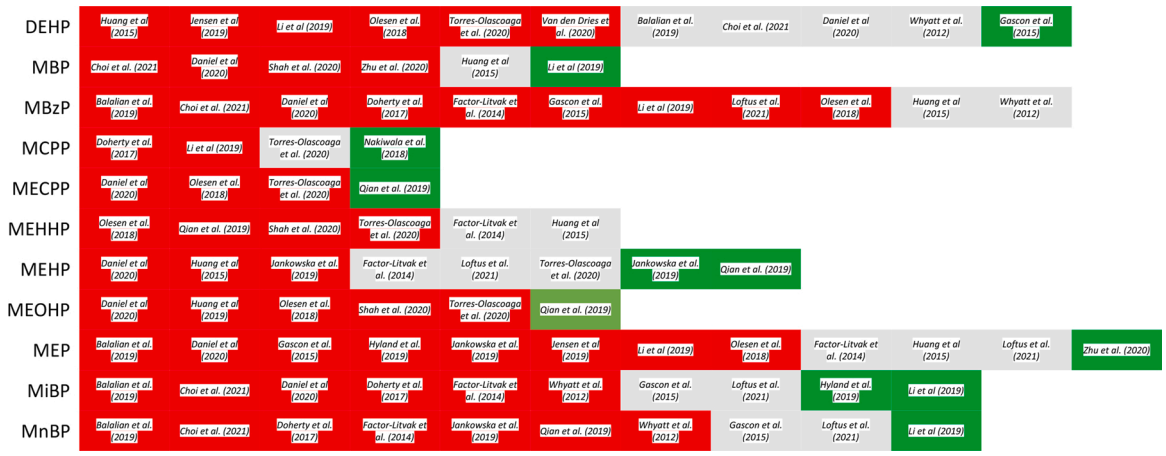

Fig. 2. Graphic display of the findings of the main studies. The red field means negative associations, the grey field means no statistically significant associations, and the green field means positive associations or protective effect between phthalate exposure and the outcomes. In order to simplify the content of these informations, the phthalate metabolites studied in less than four studies were not included (e.g. BPA (negative association in Jensen et al., 2019), DEP, DnBP and DMP (negative association in Jankowska et al., 2019a, 2019b), DiBP and DnBP (negative associations).

positively associated with child fluid intelligence and cognition (Jankowska et al., 2019a). There was no other statistically significant association between other phthalate congeners (MEP, MiBP, MnBP, OH–MnBP, MBzP, OH-MEHP, oxo-MEHP, OHMiNP 7−OH-mono-methyloctyl phthalate) and the various aspects of the Intelligence and Development Scales, such as fluid intelligence, crystalized

Table 4
Analysis of the quality of epidemiological studies with the Newcastle–Ottawa scale.

First author, year	Design of the study	Selection	Comparability	Exposure (case-control studies) or Outcome (Cohort studies)
(Hyland et al., 2019)	Cohort	★★★	★	★★★
(Qian et al., 2019)	Cohort	★★★	★	★★★
(Balalian et al., 2019)	Cohort	★★	★	★★★
(Nakiwala et al., 2018)	Cohort	★★	★	★★★
(Gascon et al., 2015)	Cohort	★★★	★	★★★
(Torres-Olascoaga et al., 2020)	Cohort	★★★	★	★★★
(Zhu et al., 2020)	Cohort	★★★	★	★★★★
(Huang et al., 2015)	Cohort	★★	★	★★
(van den Dries et al., 2020)	Cohort	★★★	★	★★★★
(Jankowska et al., 2019a)	Cohort	★★★	★	★★★
(Jankowska et al., 2019b)	Cohort	★★★	★	★★★
(Shah et al., 2020)	Cohort	★★★	★	★★★★
(Daniel et al., 2020)	Cohort	★★★	★	★★★
(Olesen et al., 2018)	Cohort	★★★	★	★★★
(Li et al., 2019)	Cohort	★★	★	★★★
(Loftus et al., 2021)	Cohort	★★★	★	★★★★
(Hutter et al., 2013)	Cross-sectional	Not applicable		
(Jensen et al., 2019)	Cohort	★★★	★	★★★
(Hong et al., 2015)	Cross-sectional	Not applicable		
(Whyatt et al., 2012)	Cohort	★★★	★	★★
(Factor-Litvak et al., 2014)	Cohort	★★★	★	★★★
(Doherty et al., 2017)	Cohort	★★★	★	★★
(Choi et al., 2021)	Cohort	★★★	★	★★
(Oulhote et al., 2020)	Cohort	★★	★	★★★
(Weng et al., 2020)	Cohort	★★	★	★★

intelligence, cognition mathematical skills, psychomotor skills, and language skills. Unlike exposure during the first and the second trimester of pregnancy, in the third trimester Torres-Olascoaga (Torres-Olascoaga et al., 2020) found no statistically significant associations for the six metabolites studied on either the motor development, memory or cognitive index scale.

In the third trimester, Zhu (Zhu et al., 2020) only found a statistically significant association between MBzP exposure and an increased verbal comprehension index (VCI) score. They also found a gender difference: there was a positive association in boys between the fluid reasoning index (FRI) and exposure to MEP, MEHP, and HMWP in the third trimester. In girls, the fluid reasoning index (FRI) had a positive association with third trimester exposure to MMP and MBzP, but a negative association with MEHP levels.

One of the studies did not find statistical associations between individual or grouped phthalate metabolites concentrations in the third trimester of pregnancy and performance on the Mental Development Index (MDI) and Psychomotor Development Index (PDI) scales of the Bayley Scales of Infant Development II (BSID-II) (Doherty et al., 2017). However, when classified by sex, some associations emerge: a negative association between prenatal concentrations of MnBP, MiBP and MCPP and MDI scores in girls, and a positive association between prenatal concentrations of MnBP, MCPP and MBzP and MDI scores in boys. For the PDI scale, there was a negative association in girls for MnBP, MCPP and MBzP, and there was a positive association in boys for MnBP. Factor-Litvak et al. (Factor-Litvak et al., 2014) also measured metabolites in urine in the third trimester, and assessed the intelligence of the children at 7 years old using the Wechsler Intelligence Scale for Children. They found an inverse association with MnBP and MiBP levels, but not for the other metabolites. Analysis of the associations in the different sub-scales showed an inverse association between perceptual reasoning and MnBP, MiBP and MBzP levels; processing speed and MnBP and MiBP; verbal comprehension and MiBP levels; and working memory with MnBP and MiBP levels. However, there was no significant association for MEHP, MEHHP or MEP (Factor-Litvak et al., 2014). Whyatt (Whyatt et al., 2012) also studied the third trimester concentration of metabolites, assessing the children at 3 years with the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). There was no association between prenatal MBzP and ΣDEHP concentrations and the results on both scales. An inverse significant association was found between MnBP and MiBP with PDI scores. The MnBP concentration had an inverse association with MDI in girls.

The analysis of 12 phthalate metabolites in third-trimester urine samples were found to be associated with scores for the MacArthur-Bates Communicative Development Inventories (MBCDI) when the children were 20–35 months old (Olesen et al., 2018). They found a significant association between MEP and ΣDEHP concentrations and lower vocabulary scores in boys. On the complexity scales, the scores were significantly lower in boys exposed to MEP, MBzP, ΣDEHP, MEHHP, MEOHP, MECPP. Importantly, no associations were found among girls.

The mental development index (MDI) and the psychomotor development index (PDI) were investigated using the Bruininks-Oseretsky Test of Motor Proficiency to assess the impact of prenatal phthalate exposure (Balalian et al., 2019; Daniel et al., 2020) in children (3 years old). Those with higher levels of prenatal exposure to phthalates (DnBP di-n-butyl phthalate, BBzP benzyl butyl phthalate, DiBP diisobutyl phthalate, DEHP and DEP) performed significantly better in the PDI and the MDI, and at age 7 performed better on the full-scale composite, and the verbal comprehension composite (Balalian et al., 2019). Girls with higher MBP, MBZP and MIBP exposure showed reduced fine motor skills (Daniel et al., 2020). MCPP, MEOHP and ΣMEHP levels had a significant inverse association with IQ scores (Huang et al., 2015). There were no statistically significant associations between maternal levels of MMP, MEP, MBP, MBzP, MEHP and MEHHP and the children's IQ scores.

4. Conclusion and Future Directions

The analysis of the published literature reveals a negative association between prenatal exposure to some phthalate congeners and cognitive functions in children. Future research is needed to confirm whether low and high molecular weight phthalates have different or sex-specific effects when investigating the association between phthalates and neurocognitive development. The effects on motor function and coordination have been less well studied, and more research is needed. A limitation of the studies analysed in the review concerns the fact that in some of the studies the phthalate metabolite concentrations were measured by a single urine sample or these data are not specified, meaning that these measurements may not represent long-term exposure (Balalian et al., 2019; Choi et al., 2021; Daniel et al., 2020; Doherty et al., 2017; Factor-Litvak et al., 2014; Gascon et al., 2015; Huang et al., 2015; Jankowska et al., 2019a, 2019b; Nakiwala et al., 2018; Olesen et al., 2018; Whyatt et al., 2012). The measurements of phthalates in children are also affected by rapid changes in physiology, diet, and use of personal care products (Adibi et al., 2008; Braun et al., 2012; Watkins et al., 2014). Some studies are aware of this issue, and measure urine concentrations in different quarters to limit the variability of a single measurement, since exposures can be episodic and the half-life short (Chin et al., 2019). In fact, other studies analised in this review quantified urinary phthalate metabolite concentrations several times during in each trimester of gestation or in the children/teens (Hyland et al., 2019; Li et al., 2019; Loftus et al., 2021; Qian et al., 2019; Shah et al., 2020; Torres-Olascoaga et al., 2020;van den Dries et al., 2020;Zhu et al., 2020) and as such represent measurements more likely to be related to a more continuous exposure. As a recommendation, future studies should consider collecting several urine samples in each time period to obtain a more accurate estimation of urinary phthalate metabolite concentrations. The analysis of the effects of persistent exposure due to product use should clarify whether the snapshots reflect phthalate exposure in the given trimester.

However, recent studies have found significant correlations between the use of personal care products and concentrations of phthalate metabolites in urine (Berger et al., 2018; Romero-Franco et al., 2011). A monotonic dose-response relationship between the total number of products used and urinary phthalate metabolite concentrations has been demonstrated (Braun et al., 2012). In overall terms, women have higher exposure to phthalates found in personal care products than men, and Black and Latina women have higher exposure to certain phthalates compared to White women, regardless of socioeconomic status (Zota and Shamasunder, 2017). Exposure to specific phthalates has changed in the last decade (Zota et al., 2014), e.g. exposure to di-n-butyl phthalate (DnBP), BBzP, and DEHP has declined in the United States, while exposures to replacement phthalates such as DiNP and diisobutyl phthalate (DiBP) have increased, and such future studies could focus on the phthalates found in the products currently used.

This review underscores the urgency of policies aimed at reducing phthalate exposure among pregnant women. The influence of phthalate exposure during breastfeeding on cognitive development is also needed because no data are as yet available.

CRediT authorship contribution statement

María Isabel Martínez-Martínez: Methodology, Formal analysis, Data curation. **Antoni Alegre-Martínez:** Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft. **Omar Cauli:** Conceptualization, Methodology, Formal analysis, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

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