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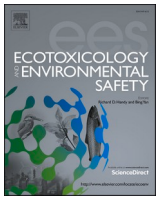

Review

The association between environmental endocrine disruptors and the risk of attention deficit and hyperactivity disorder in children: A systematic review and meta-analysis

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ABSTRACT

Objective: To provide a theoretical basis for investigating ADHD etiology in children, we aimed to investigate an association between environmental endocrine disruptors (EEDs) and attention deficit and hyperactivity disorder (ADHD) in children.
Methods: Relevant studies on the relationship between EEDs and ADHD in children from January 2008 to December 2023 were collected. The fixed-effects model was used for studies with $I^2 < 50$ %, whereas the random-effects model was used for studies with $I^2 > 50$ % per the results of the literature heterogeneity test. A sensitivity analysis was performed to evaluate the stability of the combined results. Furthermore, Egger's and Begg's tests were used in combination with funnel plots to evaluate publication bias.
Results: In total, 19 articles were included in the present meta-analysis. These results indicated that BPA and PAE exposure would increase the risk of ADHD. The results of the meta-analysis of sex subgroups showed that exposure to BPA, PAEs, PAHs increased the risk of ADHD in male children, whereas an inverse association was observed between exposure to PFAS and ADHD in female children.
Conclusion: EEDs included in this study, such as BPA and PAEs, were associated with the increased risk of ADHD in children.

1. Introduction

Attention deficit and hyperactivity disorder (ADHD) is one of the most prevailing neurodevelopmental disorders during childhood and is chiefly characterized by symptoms such as inattention and hyperactivity-impulsivity. ADHD prevalence in children worldwide is approximately 5 % (Thapar and Cooper, 2016). Notably, ADHD occurrence among adolescents and children in China is 6.3 % (Liu et al.,

Abbreviations: ADHD, Attention Deficit and Hyperactivity Disorder; ADHD - RS, Attention Deficit Hyperactivity Disorder - Rating Scale; ASD, Autism Spectrum Disorder; BASC - 2, The Behavior Assessment System for Children, Second Edition; BBOEP, Bis 2-butoxyethyl hydrogen phosphate; BDCIPP, Bis 1,3-dichloro-2-propyl phosphate; BPA, Bisphenol A; CABS, Clancy Autism Behavior Scale; C-ASQ, Conners' Abbreviated Symp-tom Questionnaire; CBCL/1½ - 5, The Child Behavior Checklist;1½ - 5; DBP, Dibutyl phthalate; DEHP, Diethylhexyl phthalate; DiNP, Diisononyl phthalate; DnBP, Dinitrobutylphenol; DPHP, Didecyl phthalate; DSM - IV, The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; EEDs, Environmental endocrine disruptors; GFAP, Glial fibrillary acidic protein; HTR3A, 5-hydroxytryptamine receptor 3 A; ICD-10, International Classification of Diseases - 10; K - ARS, Korean version of the ADHD Rating Scale; mPFC, medial prefrontal cortex; mEPS C, miniature excitatory postsynatic current; MBP, Monobutyl phthalate; MBzP, Monobenzyl phthalate; MCPP, MethylChloroPhenoxyPropionic acid; MEHHP, Mono 2-ethyl-5-hydroxyhexyl Phthalate Mixture of Diastereomers; MEHP, Mono-2-ethylhexyl phthalate; MEOHP, Monoethylhexyl phthalate; MEP, Methyl Ethylene Phosphate; MiBP, Monoisobutyl Phthalate; MnBP, Mono-n-Butyl phthalate; NP, Nonylphenol; OPE, Organophosphate Esters; OPFRs, Organophosphate flame retardants; PAEs, phthalic acid esters; PAHs, polycyclic aromatic hydrocarbons; PFAS, per-and polyfluoroalkyl substances; PFDA, Perfluorodecanoic acid; PFHxS, Perfluoroundecanesulfonic acid sodium salt; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFOS, Perfluorooctane sulfonic acid; SDQ, Strengths and Difficulties Questionnaire.

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2018), whereas that in children aged between 3 and 17 years in the United States is 9.8 %, and boys are at a higher risk of diagnosis than girls (Thapar and Cooper, 2016). Consequently, an array of investigations into the etiology and risk elements associated with ADHD in children has been undertaken to improve the management and mitigate the likelihood of ADHD in individuals. Existing studies show that ADHD is highly hereditary and multifactorial, with genetics playing a pivotal role in its onset. Additionally, prenatal and perinatal factors, such as smoking and drinking by the carrying mother, low weight at birth, premature delivery, and exposure to environmental toxins, such as organophosphorus pesticides, zinc, and lead, increase the risk of ADHD (Cortese and Coghill, 2018). In addition to these identified factors, ongoing research is focused on additional potential causes and risk factors.

Environmental endocrine disruptors (EEDs) are exogenous substances originating naturally or from human-made sources and detrimentally affect the human endocrine system. EEDs are ubiquitously present in human habitats and exert a broad spectrum of effects on various species (Encarnação et al., 2019). Moreover, they alter cell metabolism and interfere with the synthesis, secretion, transport, metabolism, binding, or elimination of natural blood-derived hormones. Additionally, EEDs may exert adverse effects on the human nervous system (Fu et al., 2023), immune system (Fu et al., 2022), and cardiovascular system (Yang et al., 2024) and can increase the risk of disease occurrence in various body systems. These EEDs include bisphenol A (BPA), organic chlorine (Encarnação et al., 2019), per- and polyfluoroalkyl substances (PFAS) (Evich et al., 2022), polybrominated flame retardants, alkylphenols, and phthalic acid esters (PAEs) (Ahn and Jeung, 2023). The pivotal functions of the neuroendocrine system include appropriately responding to environmental cues and maintaining homeostasis in the body by regulating sleep, growth, circadian rhythms, and behavior. Neuroendocrine system disruption may result in maladaptation or the onset of chronic illnesses, such as mental health disorders including depression (Patisaul, 2021).

The neuroendocrine system is regulated by steroids, peptides, and hormones, which is why it may be susceptible to EEDs. Most EEDs including BPA and other phenols, phthalates, heavy metals, pesticides, and PFAS cross the placenta by passive diffusion or active transport and affect fetal neural development (Patisaul, 2021). Moreover, some metals, brominated flame retardants, and polycyclic aromatic hydrocarbons (PAHs) accumulate in placental tissues and affect the function of the fetal neuroendocrine system (Patisaul, 2021). Additionally, exposure to high doses of nonylphenol (NP) may decrease the levels of the neurotrophic factor growth-associated protein 43, thereby inhibiting neuronal development and differentiation (Jie et al., 2016). Further, NP exposure in first-filial-generation rats is associated with increased numbers of *c-jun*- and *c-fos*-positive cells and decreased activities of choline acetyltransferase and acetylcholinesterase in the hippocampus, which lead to adverse effects on their learning and memory capabilities (Jie et al., 2017). Furthermore, exposure to NP can induce depression-like behavioral changes in rats probably by decreasing brain-derived neurotrophic factor levels and increasing corticosterone levels. Long-term exposure to NP can alter the morphology of cells, dendrites, and synapses, which may aggravate with increasing exposure time (Yu et al., 2019). Wangle et al. found that exposure to BPA decreased *c-fos* expression in the medial prefrontal cortex (mPFC) of mice, impaired glutamatergic (pyramidal) neuron morphology and functions, interfered with calcium signaling, and decreased mEPSC frequency, thereby resulting in anxiety and depression-like behaviors in mice (Wang et al., 2023). Microglia activation in the mPFC may play a role in BPA-induced depression and anxiety-like behaviors (Wang et al., 2023). Perinatal exposure to BPA is associated with anxiety-like behaviors, which are potentially related to reduced dopamine metabolites in the brain (Matsuda et al., 2012). Epidemiological research indicates a correlation between exposure to BPA at the prenatal stage and symptoms of anxiety and depression in young boys (Perera et al., 2016). A study in China revealed a linear association between exposure to BPAF and symptoms of depression in the general population, especially among males (Zhang et al., 2022a). Studies on the effects of PAHs on neurodevelopment in children have shown an increased risk of depression in adults (Zhen et al., 2023). Furthermore, population-based studies and animal experiments have highlighted the neurotoxic effects of EEDs on neuropsychiatric disorders such as anxiety and depression. The relationship between EEDs and ADHD risk in children is unclear. Existing studies suggest a connection between exposure to BPA and ADHD in children as well as the detrimental effects of exposure to phthalates on neurodevelopment (Minatoya and Kishi, 2021). A meta-analysis revealed correlations between ADHD occurrence and various chemicals, with moderate-to-high evidence supporting its relationship with exposure to lead, phthalates, and BPA (Moore et al., 2022). Nevertheless, these associations remain inconclusive and warrant further robust investigation. Hence, herein, we performed a meta-analysis of existing observational studies to determine the relationship between exposure to EEDs and ADHD in children and aimed to provide information on the association between EEDs and ADHD risk.

2. Materials and methods

2.1. Search strategy

Relevant literature published from January 2008 to December 2023 was retrieved from PubMed and Web of Science. The search terms included “environmental endocrine disruptors” or “EEDs,” “bisphenol A” or “BPA,” “per and polyfluoroalkyl substances” or “PFAS,” “phthalate or PAEs,” “polycyclic aromatic hydrocarbons” or “PAHs,” and “attention deficit and hyperactivity disorder” or “ADHD.”

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) Studies that investigated the association between EEDs and ADHD, with a specific sample size, 2) original English journal articles, and 3) diagnostic criteria for ADHD were specified while meeting the conditions for the combination of effect values in the meta-analysis, thereby providing the corresponding effect values and 95 % confidence intervals (CIs) for the association between EEDs and ADHD.

The exclusion criteria were as follows: 1) Non-English literature and unpublished literature, dissertations, conference abstracts, reviews, literature reviews, treatises, and case reports, 2) studies without the specific information of the research design, and 3) studies with research topic irrelevant to ADHD and EEDs.

2.3. Literature selection

Two researchers retrieved the literature from the two databases (PubMed and Web of science), and manually screened and deleted the repetitive literature. After preliminary screening, the researchers evaluated the titles and abstracts of the included literature, and those not meeting the inclusion criteria were deleted. The full text of each article was further read and evaluated to decide on their inclusion in this meta-analysis. Any differences that arose during the screening process were discussed until a consensus was established; otherwise, the discrepancy was resolved by a third researcher.

2.4. Data extraction

The following information was extracted from each study included in the meta-analysis: country, type of endocrine disruptors, assessment of ADHD, adjustment of covariates, and effect indicator odds ratio (OR) and its 95 % CI. If a study reported the OR and CIs of multiple models simultaneously, the data of the model with the most adjusted covariates were preferred. Data were extracted independently by two researchers,

and any disagreement was resolved by a third researcher.

2.5. Quality evaluation of documents

The Newcastle–Ottawa Scale (NOS) was used to evaluate the final included studies. The NOS scale could simultaneously evaluate case-control and cohort studies, and the total score of all items was 9 points. The overall score of the literature $\geq$ 7 points was identified as high-quality research, 5–6 points as medium-quality research, and $\leq$ 4 points as low-quality research.

2.6. Statistical analysis

Establish a database based on data extracted from literature. A meta-analysis was performed using Stata17.0. The OR and its 95 % CI were used to evaluate the relationship between EEDs and ADHD. Q test and I^2 statistics were used to qualitatively and quantitatively evaluate heterogeneity between the studies. When $I^2 < 50$ %, a fixed-effects model was used to calculate the combined effect, whereas in other cases, a random-effects model was used. A sensitivity analysis was performed to evaluate the stability of the combined results. Publication bias was assessed by Egger's and Begg's tests combined with funnel plots.

3. Results

3.1. Literature search results

In total, 1323 articles were initially retrieved, among which 1204 articles that did not meet the inclusion criteria were excluded, and the effect values used in 119 articles did not meet study summary requirements, or the data could not be extracted. Finally, 19 articles were included in the present meta-analysis (Hansen et al., 2021; Huang et al., 2022; Yoo et al., 2020; Arbuckle et al., 2016; Mortamais et al., 2017; Engel et al., 2018; Chopra et al., 2014; Abid et al., 2014; Perera et al., 2012; Choi et al., 2021; Kamai et al., 2021; Itoh et al., 2022; Vuong et al., 2021; Skogheim et al., 2021; Liew et al., 2015; Strøm et al., 2014; Hoffman et al., 2010; Stein and Savitz, 2011; Ode et al., 2014) (Fig. 1).

3.2. Literature characteristics and quality evaluation

The basic characteristics of the 19 articles are presented in Table 1. All articles investigated the association between exposure to typical EEDs such as BPA, PAEs, PAHs, and PFAS and ADHD risk. The assessment of ADHD was determined through different scales and diagnostic methods selected by different studies. The included study population was from several countries and regions including the United States, Spain, Norway, Denmark, Switzerland, Canada, South Korea, Japan, and China, and the final inclusion effect index was the OR and its 95 % CI. According to the NOS scale evaluation (Details in supplementary materials Table S.1), the quality of the literature included in this meta-analysis was good; 13 (68.42 %) were high-quality and 6 (31.58 %) were medium-quality studies.

3.3. Meta-analysis

3.3.1. Relationship between BPA and ADHD

Five articles were included to determine the association between exposure to BPA and ADHD risk ($I^2 = 0.00$ %). A fixed-effects model was used to merge the data obtained as per the heterogeneity test results. The graph showed that exposure to BPA increased the risk of ADHD in children by 21 % (OR = 1.21, 95 % CI : 1.09–1.34) (Fig. 2).

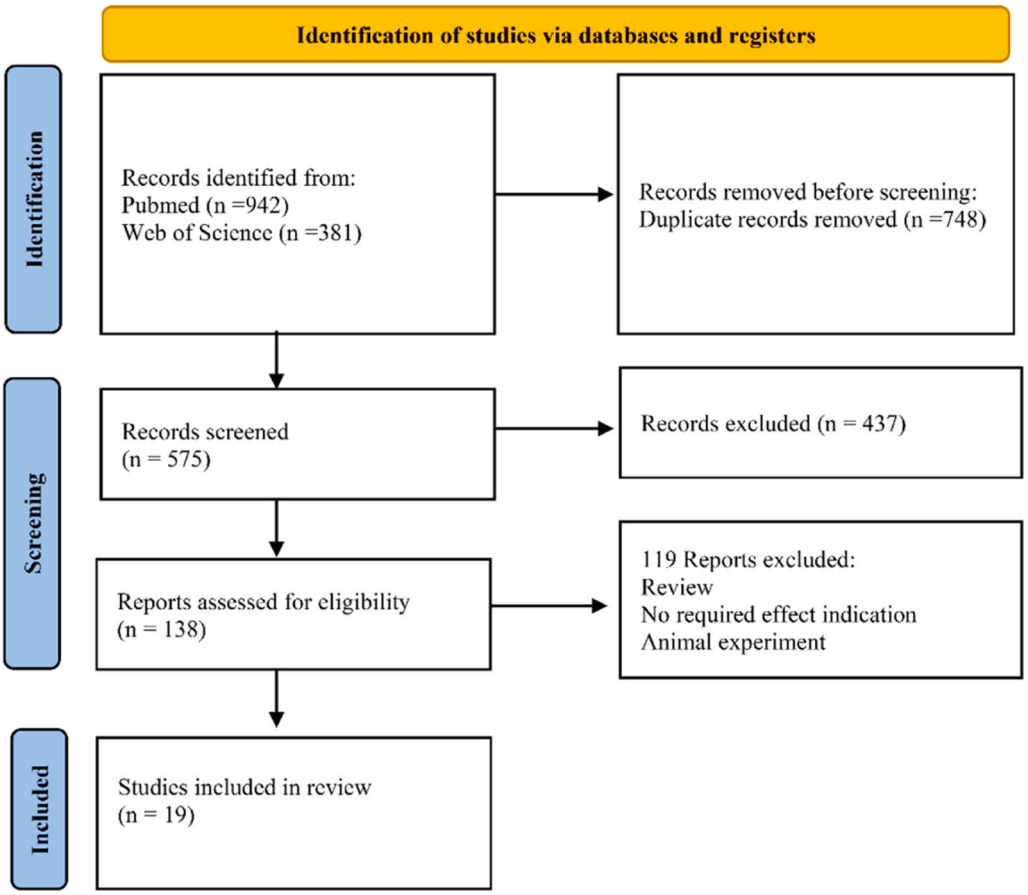

Fig. 1. Prisma Flow Diagram of Study Selection.

Table 1
Characteristics of included trials.

Studies	Region	EEDs	Elevator	Exposure	Sample	Assessment of ADHD	Adjusted	NOS (Newcastle-Ottawa Scale)
Hansen et al., 2021 (Hansen et al., 2021)	Denmark	BPA	Parents	Prenatal exposure	Urine samples	CBCL/1½ - 5	Maternal education, maternal age, pre - pregnancy BMI, parity, child age at evaluation, sex	9
Huang et al., 2022 (Huang et al., 2022)	China	BPA	Parents	Prenatal exposure	Blood samples	CABS, C-ASQ, SDQ	Monthly income (RMB), with history of adverse pregnancy outcomes, with gynecological diseases, parity, planning for pregnancy, passive smoking during pregnancy, and blood sample collection time (weeks).	9
Yoo et al., 2020 (Yoo et al., 2020)	Korea	BPA	Doctors	Early school age (6–10 years)	Urine samples	K-ARS, BASC - 2	Age, sex, paternal and maternal educational level, and household income level	7
Arbuckle et al., 2016 (Arbuckle et al., 2016)	Canada	BPA PAEs	Parents	Early school age (6–11 years)	Urine samples	SDQ	NR	9
Mortamais et al., 2017 (Mortamais et al., 2017)	Span	BPA PAHs	Teacher	Early school age (7–10 years)	Air samples	DSM - IV	Age, sex, maternal education and residential neighborhood socioeconomic status; school as nested random effects	7
Engel et al., 2018 (Engel et al., 2018)	Norway	PAEs	Doctors	Prenatal exposure	Urine samples	ICD - 10	Analytic batch, specific gravity, child sex, mother's age, mother's education level, mother's marital status, mother's smoking status, parity, maternal depression during pregnancy, and year of birth.	9
Chopra et al., 2014 (Chopra et al., 2014)	USA	PAEs	Parents	School age (6–15 years)	Urine samples	DSM - IV	Child sex, age, race, household income, blood lead, and maternal smoking during pregnancy.	6
Abid et al., 2014 (Abid et al., 2014)	USA	PAHs	Parents	School age (6–15 years)	Urine samples	Parental report of ever-doctor-diagnosed ADHD	Age, race/ethnicity, sex, creatinine, smokers in the household, PIR, birthweight, and having a routine source of medical care.	6
Perera et al., 2012 (Perera et al., 2012)	USA	PAHs	Parents	Prenatal exposure	Maternal and cord blood samples	DSM - IV	Prenatal ETS, sex of child, gestational age, maternal IQ, HOME inventory, maternal education, ethnicity, prenatal demoralization, age at assessment, and heating season	9
Choi et al., 2021 (Choi et al., 2021)	Norway	PAHs	Parents	Prenatal exposure	Urine samples	ICD - 10	Birth year, child sex, maternal education, maternal depression, maternal urinary log (DEHP), and the season of urine collection.	9
Kamai et al., 2021 (Kamai et al., 2021)	Norway	PAEs	Parents	Prenatal exposure	Urine samples	DSM - IV	Specific gravity, analytic batch, child sex and maternal age, education, parity, depression during pregnancy, and maternal ADHD - like symptoms.	9
Itoh et al., 2022 (Itoh et al., 2022)	Japan	PFAS	Parents	Prenatal exposure	Maternal blood	ADHD - RS	Maternal factors (age at delivery, parity, educational level, pre - pregnancy BMI, alcohol intake during pregnancy, smoking habit during pregnancy) and children's sex	8
Vuong et al., 2021 (Vuong et al., 2021)	USA	PFAS	Parents	Prenatal exposure	Maternal blood	ADHD portion of the DISC-YC	Maternal age, race, education, income, child sex, serum cotinine, maternal depression, parity, HOME score, maternal IQ, and marital status.	9
Skogheim et al., 2021 (Skogheim et al., 2021)	Norway	PFAS	Parents	Prenatal exposure	Maternal blood	ICD - 10	Maternal age, education, parity, seafood intake, child sex and child birth year	7
Liew et al., 2015 (Liew et al., 2015)	Denmark	PFAS	Doctors	Prenatal exposure	Maternal blood	ICD - 10	Maternal age at delivery, socioeconomic status, parity, smoking and drinking during pregnancy, psychiatric illnesses, gestational week of blood drawn, and child's sex and birth year, additionally adjusted including all PFASs in the model.	7
Strøm et al., 2014 (Strøm et al., 2014)	Denmark	PFAS BPA	Doctors	Prenatal exposure	Maternal blood	ICD - 10	Maternal age, pre - pregnancy BMI, parity, maternal smoking during pregnancy, maternal education, maternal cholesterol (except for PFOA and PFOS), maternal triglyc - erides (except for PFOA and PFOS) and offspring sex.	6
Hoffman et al., 2010 (Hoffman et al., 2010)	USA	PFAS	Parents	School age (12–15 years)	Own blood	Parental report of ever - doctor - diagnosed ADHD	NHANES sample cycle, age, sex, race, ETS, and maternal smoking during pregnancy.	5

(*continued on next page*)

Table 1 (*continued*)

Studies	Region	EEDs	Elevator	Exposure	Sample	Assessment of ADHD	Adjusted	NOS (Newcastle-Ottawa Scale)
Stein & Savitz, 2011 (Stein and Savitz, 2011)	USA	PFAS	Parents	School age (5–18 years)	Own blood	C10 Health Project questionnaire	Age and sex	6
Ode et al., 2014 (Ode et al., 2014)	Sweden	PFAS	Doctors	Prenatal exposure	Cord blood samples	DSM - IV	Maternal active smoking, parity, and gestational age at birth.	5

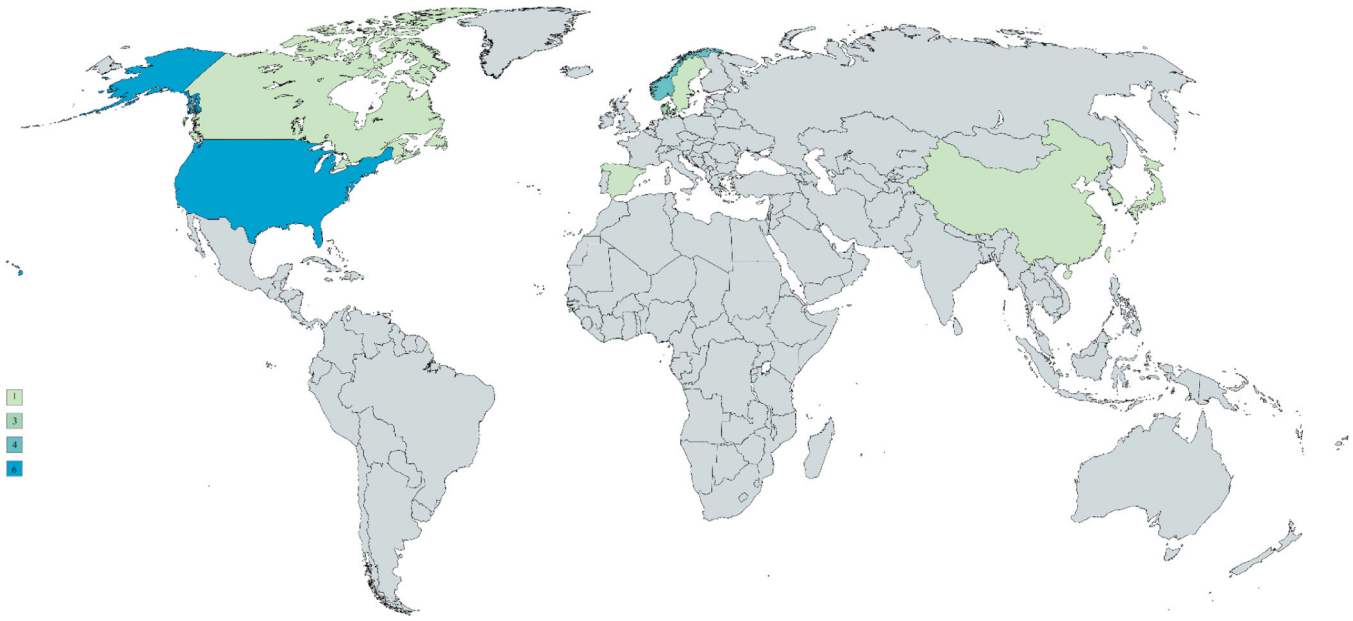

Fig. 2. The distribution and quantity of different countries included in the study.

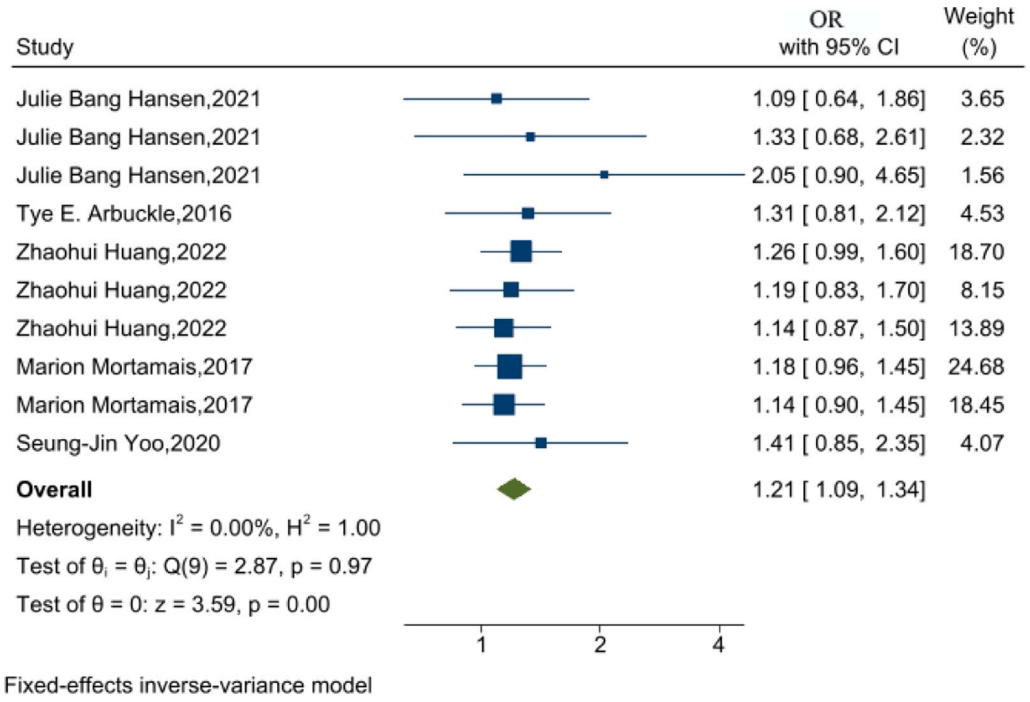

Fig. 3. The forest plot of BPA and ADHD.

3.3.2. Relationship between PAEs and ADHD

Five articles were included to determine the association between exposure to PAEs and ADHD risk. The heterogeneity of the combined results was low ($I^2 = 42.90\ \% < 50\ \%$); thus, a fixed-effects model was used for data consolidation. The combined results are shown in the Fig. 3. Exposure to diethylhexyl phthalate (DEHP) and monobenzyl phthalate (MBzP) in PAEs increased ADHD risk. The OR and 95 % CI was 1.67 and 1.37–2.03 for DEHP, and 1.30 and 1.07–1.58 for MBzP, respectively. Other phthalates such as DiNp, DnBP, MCPP, MEP, MiBP, and MnBP were not significantly associated with ADHD risk. Overall, exposure to PAEs increased ADHD risk by 13 % (OR = 1.13, 95 % CI: 1.05–1.21) (Fig. 3).

3.3.3. Relationship between PAHs and ADHD

Four articles were included to determine the association between exposure to PAHs and ADHD risk. The heterogeneity of the combined results was low ($I^2 = 48.56\ \% < 50\ \%$); thus, a fixed-effects model was used to combine the data. However, no correlation was found between PAHs and ADHD risk (OR = 1.02, 95 % CI: 0.94–1.10) (Fig. 4).

3.3.4. Relationship between PFAS and ADHD

Eight articles were included to determine the association between exposure to PFAS and ADHD risk. The combined results were highly heterogeneous ($I^2 = 95.64\ \% > 50\ \%$); thus, a random-effects model was used to merge the data. The combined results showed no correlation between PFAS and ADHD, and only PFDA in PFAS was negatively correlated with ADHD (OR = 0.58, 95 % CI: 0.45–0.76) (Fig. 5).

3.3.5. Correlation between EEDs and ADHD (stratified by sex)

A subgroup analysis showed that ADHD was positively correlated with exposure to BPA (OR = 1.35, 95 % CI : 1.14–1.60), PAEs (OR = 1.11, 95 % CI : 1.03–1.18) and PAHs (OR = 1.40, 95 % CI : 1.13–1.76) in boys and was negatively correlated with exposure to PFAS (OR = 0.75, 95 % CI : 0.65–0.94) in girls (Table 2).

3.3.6. Correlation between EEDs and ADHD (stratified by exposure window: prenatal vs. postnatal)

This study defined prenatal exposure as occurring during gestation and postnatal exposure as after birth. Due to data limitations, exposure windows were not further stratified. BPA exposure was significantly associated with an increased risk of ADHD, regardless of whether the exposure occurred prenatally (OR = 1.22, 95 % CI : 1.05–1.42) or postnatally (OR = 1.18, 95 % CI : 1.01–1.36), while phthalates showed effects only prenatally (OR = 1.13, 95 % CI : 1.01–1.26). No significant associations were observed for other pollutants. Although PFAS were not significantly linked to ADHD, high heterogeneity across studies suggests variability in exposure assessment and population characteristics.

3.3.7. Sensitivity analysis and publication bias

The results of the present meta-analysis of different types of EEDs did not change significantly after the literature was successively deleted, indicating the stability of the results (Details in Supplementary Materials Fig. S.1). The results of Egger's and Begg's tests showed that only the PAH group exhibited publication bias ($P < 0.05$) (Table 4).

4. Discussion

We are the first to comprehensively review and analyze the varying outcomes observed in studies performed over the past 15 years regarding the association between EEDs and ADHD risk. Herein, we found that exposure to EEDs was associated with ADHD risk, among which BPA and PAEs increased the risk. PAHs and PFAS did not correlate with ADHD. Additionally, boys were potentially more vulnerable to ADHD than girls. This study provides empirical evidence for environmental hazards associated with ADHD and offers a pertinent theoretical basis for future studies on the correlation between ADHD risk and exposure to EEDs.

4.1. BPA and ADHD

Exposure to BPA affects the behavioral patterns of children (Rodríguez-Carrillo et al., 2019). A study involving 292 participants revealed a remarkable relationship between increased urinary BPA levels and ADHD in children, particularly in boys (Harley et al., 2013). Combined with epidemiological studies and the present results, we postulated that exposure to BPA increases the susceptibility to ADHD in children, with notable differences in sexes, showing a more pronounced correlation in boys than in girls. We found that BPA exposure during both prenatal and postnatal periods was associated with increased ADHD risk, suggesting persistent neurotoxic effects of BPA, with underlying mechanisms potentially active across developmental stages. Given the ubiquitous presence of BPA as a conventional plastic additive, there is a pressing need to reduce the usage of BPA-containing plastic commodities, be discerning in selecting food storage vessels, and refrain from subjecting plastic items to high-temperature conditions.

4.2. PAEs and ADHD

Numerous epidemiological studies have investigated the potential relationship between phthalate exposure and ADHD. However, the findings are inconsistent; thus, reaching a definitive conclusion is challenging (Praveena et al., 2020). Gascon et al. demonstrated that the multiple assessments of exposure to phthalates and various neuropsychological aspects across different age groups showed that exposure to phthalate at a prenatal stage did not negatively affect the cognitive, psychomotor, and behavioral development of children (Gascon et al., 2015). Conversely, Park et al. suggested a possible relationship between phthalate metabolite levels and ADHD risk, emphasizing the need for further prospective and epigenetic studies to investigate the causal association and elucidate pathophysiological mechanisms underlying this association (Park et al., 2014). Moreover, a case-control study showed that after adjusting for covariates, increased total phthalate levels were consistently associated with a higher risk of major ADHD-related behavioral issues. Among the phthalate metabolites studied, mono-n-butyl phthalate exhibited the most robust adverse correlation, with a relative risk (RR) of 1.45 (Shoaff et al., 2020). Furthermore, the issue of hyperactivity was more strongly correlated to exposure to phthalate than inattention (Shoaff et al., 2020). Maternal exposure to low levels of MCPP, a phthalate metabolite, was markedly related to lower ADHD symptom scores in children, especially in girls (Munk Andreasen et al., 2023). Additionally, a correlation was identified between PAE concentrations and attention deficit in critically ill children after exposure to medical supplies (Dyer, 2016).

The present results indicated that exposure to PAEs increased ADHD risk by 14 %, and this association was observed in boys per the sex difference analysis performed. PAEs were associated with ADHD risk only during prenatal exposure, thus highlighting the fetal period as a critical window for neurotoxicity, possibly due to high placental permeability and limited fetal metabolism. However, the existing literature provides scarce evidence regarding the adverse effects of phthalates on neurodevelopmental domains because of challenges such as exposure misclassification, critical sensitivity periods, sex-specific effects, and the combined effects of phthalate mixtures (Radke et al., 2020). Watkins et al. suggested that intrauterine exposure to phthalate might exert detrimental effects on attention, potentially manifesting during puberty, a crucial period for neurodevelopment. Additionally, exposure during adolescence could contribute to inattention. Thus, future studies should investigate the enduring effects of intrauterine and childhood exposure to phthalate on attention and ADHD during adolescence, along with elucidating potential underlying mechanisms (Watkins et al., 2021).

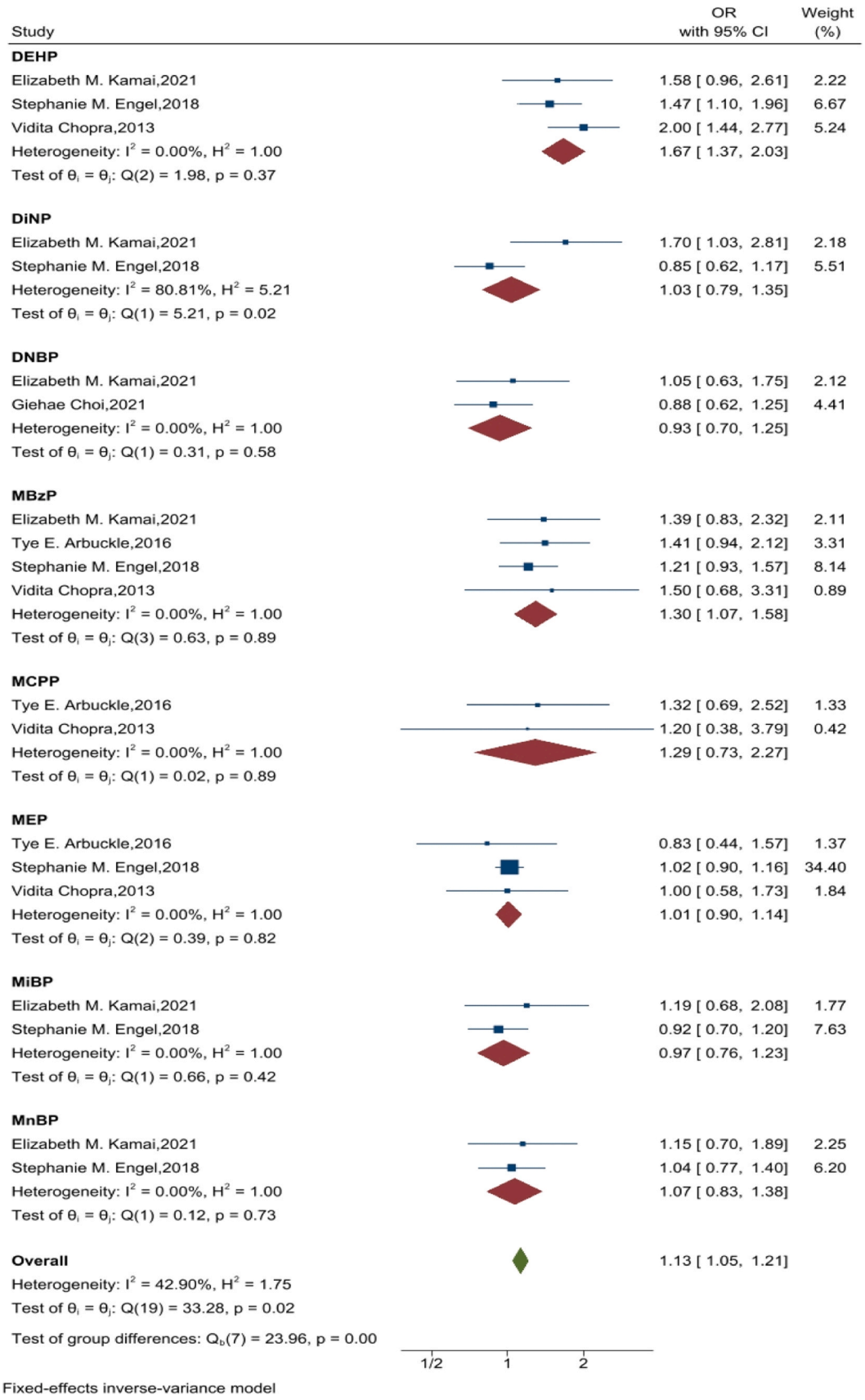

Fig. 4. The forest plot of PAEs and ADHD.

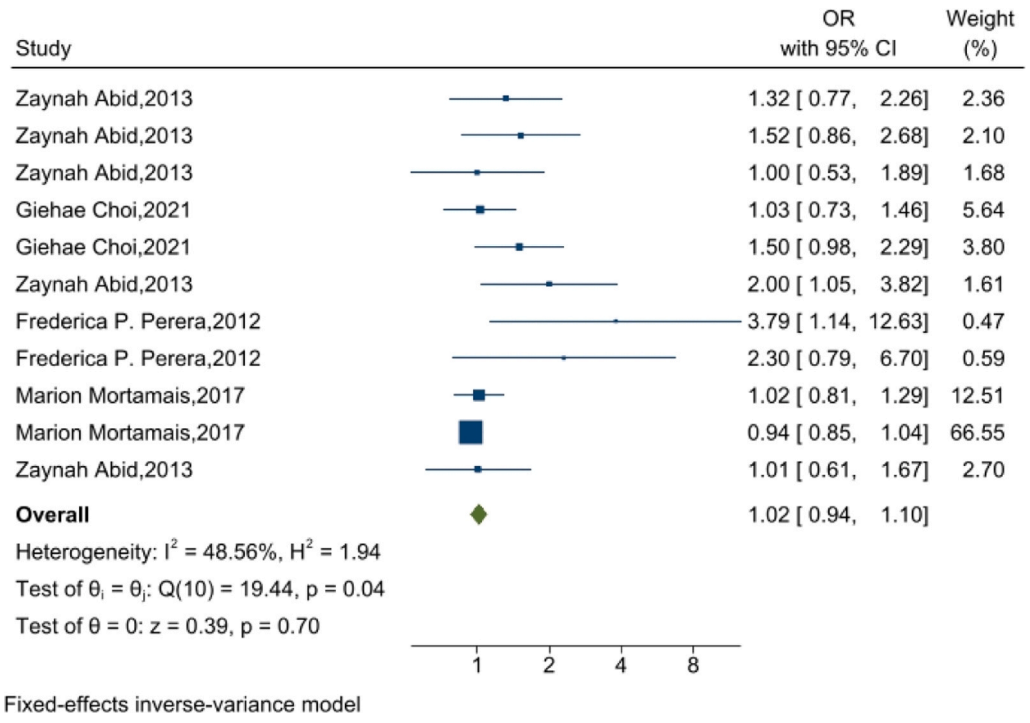

Fig. 5. The forest plot of PAHs and ADHD.

4.3. PAHs and ADHD

A study conducted in New York City from 1998 to 2006 revealed that children with high prenatal exposure to PAHs usually showed more ADHD symptoms than children with less exposure to PAH, as evidenced by higher ADHD scores. The findings were consistent across various families with varying economic statuses (Perera et al., 2018). Roshanak et al. revealed a notable positive correlation between PAH and ADHD in a meta-analysis, thus underlining the predominant role of PAH ADHD development in children (Rezaei Kalantary et al., 2020). Conversely, no substantial relationship was reported between exposure to PAHs and increased ADHD risk (RR: 0.98 and 95 % CI: 0.82–1.17). However, these results should be interpreted with caution, given the limited number of epidemiological studies focusing on the issue (Zhang et al., 2022b). Furthermore, the present results indicated no direct association between exposure to PAHs and ADHD risk, except for a discernible association in boys based on the sex subgroup analysis. Hence, we believed that the association between exposure to PAHs and ADHD risk was weak, and boys were more prominently affected by the exposure than were girls. Subgroup analyses by exposure window (prenatal vs. postnatal) revealed no significant association between PAH exposure and ADHD. Collectively, the current evidence remains inadequate to establish causality, therefore, future studies should address this gap through rigorous designs.

4.4. PFAS and ADHD

A comprehensive analysis of multiple pollutants encompassing four types of chemicals revealed that early exposure to β-hexachlorocyclohexane and PFOS was associated with increased ADHD risk, suggesting a sex-based difference in the effect of PFOS on ADHD (Lenters et al., 2019). Concurrently, a positive association was observed between exposure to PFOA and ADHD, whereas exposure to PFOS was negatively associated with ADHD (Yao et al., 2023). Quaak et al. showed that exposure to PFAS was inversely associated with behavioral problems in children (Quaak et al., 2016). This reverse correlation should not be considered a protective effect; however, the presence of unknown confounding factors should be clarified (Skogheim et al., 2021). It is imperative to consider the previously reported adverse effects of PFAS on health in this context.

Herein, no correlation was observed between exposure to PFAS and ADHD risk; however, exposure to PFDA in PFASs was negatively correlated with ADHD risk. Additionally, a meta-analysis encompassing nine European population studies could not find a remarkable association between early exposure to PFOS and PFOA and ADHD during childhood (Forns et al., 2020). Lien et al. observed that exposure to PFNA was negatively correlated with SNAP-IV scale-defined inattention and opposition-defined disorders and SDQ scale-defined hyperactivity and inattention; however, no association was observed between exposure to PFOA, PFOS, or PFUA and ADHD symptoms (Lien et al., 2016). These findings align with the present outcomes. Overall, previous results did not show the adverse effects of exposure to PFOA on behavior; however, the results were sex-specific, which increased the likelihood of a sex-based difference pattern (Stein et al., 2014).

This study showed a negative correlation between ADHD and exposure to PFAS in girls. Additionally, subgroup analyses by exposure window (prenatal vs. postnatal) revealed no significant association between PFAS exposure and ADHD. This indicated that the existing evidence was insufficient to confirm the adverse effects of PFAS exposure on ADHD, despite a probable association between PFAS exposure and ADHD risk. Investigation or data collection is warranted in the future to determine the precise relationship between PFAS exposure and ADHD.

4.5. Other EEDs and ADHD

Yu et al. revealed that children in Taiwan exhibited increased levels of exposure to NP compared with those reported previously in developed nations. Nevertheless, no correlation was found between urinary NP concentration and ADHD, and the probability of ADHD in children with higher urinary NP levels was not high. Therefore, exposure to NP may not promote ADHD in children (Yu et al., 2016). Because studies on the association between exposure to NP and ADHD development are limited and concentrated in Taiwan and China, future investigations should include diverse samples to further elucidate this association.

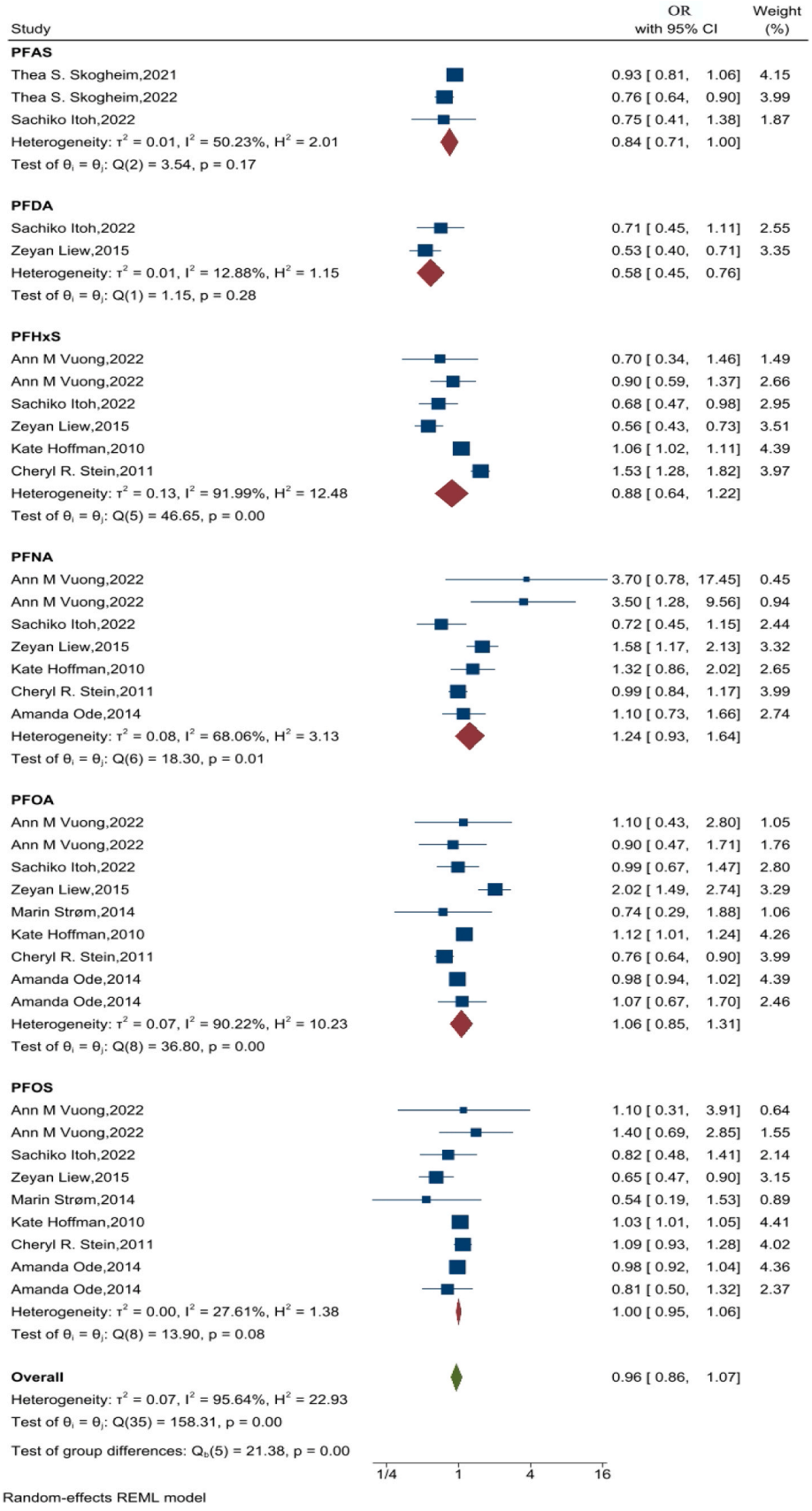

Fig. 6. The forest plot of PFAS and ADHD.

Table 2
Gender subgroup analysis of the association between EEDs and ADHD.

Types of EEDs	Number of literatures	Gender	OR (95 % CI)	I^2	P of Heterogeneity
BPA	3	Boys	1.35 (1.14–1.60)	46.09 %	0.08
		Girls	1.15 (0.85–1.55)	0.00 %	0.60
PAEs	4	Boys	1.11 (1.03–1.18)	0.36 %	0.45
		Girls	1.06 (0.97–1.15)	18.56 %	0.39
PAHs	2	Boys	1.40 (1.13–1.76)	4.44 %	0.39
		Girls	1.18 (0.87–1.59)	0.00 %	0.82
PFAS	1	Boys	0.81 (0.82–1.06)	15.76 %	0.31
		Girls	0.75 (0.65–0.94)	0.00 %	0.89

Table 3
Exposure window subgroup analysis of the association between EEDs and ADHD.

Types of EEDs	Number of literatures	exposure window	OR (95 % CI)	I^2	P of Heterogeneity
BPA	5	Prenatal exposure	1.22 (1.05–1.42)	0.00 %	0.84
		Postnatal Exposure	1.18 (1.01–1.36)	0.00 %	0.96
PAEs	6	Prenatal exposure	1.13 (1.01–1.26)	34.54 %	0.13
		Postnatal Exposure	1.01 (0.75–1.36)	63.55 %	0.00
PAHs	4	Prenatal exposure	1.52 (0.96 – 2.41)	55.08 %	0.10
		Postnatal Exposure	1.07 (0.91–1.26)	33.76 %	0.04
PFAS	8	Prenatal exposure	0.91 (0.79–1.05)	89.09 %	0.00
		Postnatal Exposure	1.08 (0.94 – 1.23)	95.62 %	0.00

Table 4
Egger & Begg test results of included studies.

Types of EEDs	P (Egger)	P (Begg)
BPA	0.647	0.750
PAE	0.261	0.152
PAHs	**0.032**	0.253
PFAS	0.486	0.586

Prenatal exposure to hexachlorobenzene and polychlorinated biphenyls (PCBs) may result in cognitive decline in preschool children (Kyriklaki et al., 2016). Eubig et al. conducted a retrospective analysis supporting the notion that PCBs potentially affect children with ADHD (Eubig et al., 2010). Additionally, Sioen et al (Sioen et al., 2013). and Sagiv et al (Sagiv et al., 2012). supported the association between organochlorines, especially PCBs, and a series of neurobehavioral problems including ADHD; however, these associations should be further investigated in the context of sex specificity of the effects of organochlorines. Hence, sex-based effects must be considered when studying environmental pollutants and behavioral problems. Xu et al. found positive correlations between maternal exposure to pesticides and ASD and ADHD. Additionally, maternal exposure to organochlorine pesticides was a risk factor for ADHD in offspring (Xu et al., 2023). Further, Canadian prospective data supported the possibility that prenatal exposure to persistent organic pollutants could be a modifiable risk factor for ADHD phenotypes. Moreover, sex-based differences should be considered when assessing the effects of environmental pollutants on behavioral issues (Sussman et al., 2022).

Organophosphate flame retardants (OPFRs) are used as substitutes for brominated flame retardants; they undergo transplacental transfer into the fetal microenvironment (Doherty et al., 2019). Their metabolites, such as BDCIPP, are consistently detected in umbilical cord blood (Liu et al., 2021), with exposure levels during critical developmental periods significantly exceeding those in adults (Doherty et al., 2019). Developmental exposure inhibits the tryptophan–serotonin metabolic axis, inducing abnormal accumulation of neuroactive metabolites and facilitating excessive outgrowth of 5-HTR3A$^+$ neurites in the male fetal forebrain (Rock et al., 2020). Concurrently, it selectively impairs the dopaminergic system, manifested by reduced volume of dopamine (DA) cell clusters in the embryonic midbrain (particularly in men) and disruption of dorsoventral patterning in TH$^+$ axonal projections (Newell et al., 2023). This exposure further perturbs neurotransmission homeostasis by impairing D1/D2 dopamine receptor signaling (Oliveri et al., 2018). Additionally, OPFRs activate astrogliosis. This elevates the levels of neurotoxic biomarkers including GFAP and S100B, with male fetuses exhibiting greater susceptibility than female ones (Hogberg et al., 2021; Hernández et al., 2025). Epidemiological studies corroborate these findings: prenatal chlorinated alkyl OPE exposure significantly reduces psychomotor and mental indices in boys (Liu et al., 2021), whereas gestational DnBP exposure increases ADHD risk in childhood by 71 %, demonstrating sex-dependent associations (Hall et al., 2023). Collectively, OPFRs preferentially impair male neurodevelopment through interfering with placental monoamine metabolism, causing targeted disruption of dopaminergic development, and activating neuroinflammation (Doherty et al., 2019).

4.6. *Neurodevelopmental mechanisms of EEDs*

EED exerts synergistic control over gene transcription through epigenetic modifications (including DNA methylation, histone modifications, and non-coding RNA). These modifications can be transmitted across generations via alterations in germ cell DNA, thereby impacting the neurodevelopment of offspring (Ghassabian et al., 2022). Yesildemir and Celik examined the relationship between prenatal and postnatal exposure to EED and birth/neurodevelopmental outcomes. They showed that BPA might increase the risk of ADHD by disrupting catecholaminergic and adrenergic systems. Phthalates compromise the homeostasis of sex hormones and thyroid hormones, subsequently impacting the dopaminergic system and calcium signaling pathways. They also exert adverse neurodevelopmental effects by inducing oxidative stress and lipid peroxidation (Yesildemir and Celik, 2024). PCBs can impair hypothalamic function, alter the expression of sex hormones and brain-derived neurotrophic factor (BDNF), interfere with the dopaminergic system, and impact neurodevelopment through aryl hydrocarbon receptor (AhR)-mediated signaling pathways. PFASs influence neuronal differentiation, alter the levels of neuronal proteins, and induce neurotoxic effects by disrupting synaptic formation, promoting cell death, and generating reactive oxygen species. They also interfere with the expression of calcium signaling molecules in the hippocampus, the cholinergic system, and thyroid homeostasis (Yesildemir and Celik, 2024; Bell, 2014). Organochlorine pesticides disrupt thyroid hormone function and impair neurodevelopment by causing oxidative stress and DNA damage. Dioxins and furans influence neurodevelopment via AhR-mediated signaling pathways (Yesildemir and Celik, 2024).

4.7. *Study advantages and limitations*

This study systematically summarized the inconsistent results of the association between EEDs and ADHD during the last 15 years, thereby

providing valuable evidence for the environmental etiology of ADHD and proposing a theoretical framework for future mechanistic exploration. However, the variations in ADHD diagnostic protocols across countries/regions and inconsistent covariate adjustment strategies may introduce inherent heterogeneity and residual confounding bias. Furthermore, currently available evidence is limited to the independent effects of single EEDs, thus lacking systematic evaluation of co-exposure to multiple pollutants (e.g., EEDs-metals/particulate matter interactions). Also, methodological heterogeneity and deficiency of co-exposure data constrain the application of interaction models. Prospective cohorts with standardized covariate collection and diagnostic procedures should be conducted to elucidate the combined neurotoxic effects of environmental pollutants.

5. Conclusion

The present meta-analysis is the first to reveal that exposure to EEDs is associated with ADHD risk, and BPA and PAEs remarkably increase this risk. Exposure to PAHs and PFAS shows no noticeable correlation with ADHD. Additionally, boys may be potentially more ADHD-sensitive than girls. However, this study provides limited evidence to show the adverse effects of exposure to EEDs on ADHD in children. Various countries and regions have already formulated numerous relevant policies to mitigate the adverse effects of EEDs on humans. However, the long-term accumulation of EEDs in the environment can potentially harm human health. Therefore, preventive measures should be exercised to protect pregnant women and young children from exposure to these chemicals.

Author contributions

Jie Yu and Jie Xu designed the study. Yuzhu Xu, Jie Xu, Ahmad Zaharin Aris, Chang Peng, Kai Pan, Chengxing Wang, Yingxi Zeng, and Jie Yu analyzed and interpreted the data. Yuzhu Xu, Kai Pan, Jie Xu and Jie Yu conducted the literature screening. Yuzhu Xu wrote the manuscript, Jie Yu and Jie Xu revised the manuscript. All the authors read and approved this paper.

CRediT authorship contribution statement

Jie Yu: Supervision, Writing – review & editing, Conceptualization. **Yuzhu Xu:** Writing – original draft, Software. **Jie Xu:** Writing – review & editing, Conceptualization. **Ahmad Zaharin Aris:** Data curation. **Chang Peng:** Data curation. **Kai Pan:** Data curation. **Chengxing Wang:** Data curation. **Yingxi Zeng:** Data curation.

Consent for publication

All the authors read and approved this paper.

Ethics Approval statement

No Ethics Approval

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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.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.118845.

Data availability

Data will be made available on request.

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