RESEARCH ARTICLE

The association between maternal perfluoroalkyl substances exposure and early attention deficit hyperactivity disorder in children: a systematic review and meta-analysis

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Abstract

Some studies have shown that maternal exposure to perfluoroalkyl substances (PFASs) may be associated with early attention deficit hyperactivity disorder (ADHD) in children. The purpose of this systematic review and meta-analysis is to verify this association by reviewing existing studies and to provide a strong basis for preventing ADHD. The researchers searched electronic databases such as PubMed, Science Direct, Scopus, Google Scholar, Web of Science, and Embase for all studies published before October 2020. Finally, we included nine articles for analysis. Our meta-analysis showed that maternal exposure to PFASs was not significantly associated with the prevalence rate of early childhood ADHD (perfluorooctanoic acid (PFOA), odds ratio (OR) = 1.00, 95% confidence interval (95% CI) = 0.75–1.25; perfluorooctane sulfonate (PFOS), OR = 1.01, 95% CI = 0.88–1.14; perfluorohexane sulfonate (PFHxS), OR = 1.08, 95% CI = 0.80–1.09; perfluorononanoic acid (PFNA), OR = 1.13, 95% CI = 0.99–1.28; perfluorodecanoic acid (PFDA), OR = 1.23, 95% CI = 0.15–2.32). Due to significant heterogeneity, we subsequently performed subgroup analysis and sensitivity analysis. Through subgroup analysis, we found that PFOS concentration of children’s blood and the prevalence rate of early childhood ADHD were statistically positively correlated, and there was also a positive correlation between PFOS exposure and the prevalence rate of early childhood ADHD in the America. Moreover, there was also a statistically positive correlation between PFNA concentration in maternal blood and the prevalence rate of early childhood ADHD. Sensitivity analysis showed that the final results did not change much, the sensitivity was low, and the results were relatively stable. In conclusion, a causal relationship between maternal PFASs exposure and ADHD in children was unlikely. Among them, PFOS, PFNA, and ADHD might have positive associations worthy of further investigation.

Keywords Perfluoroalkyl substances · Attention deficit hyperactivity disorder · Maternal exposure · Children · Systematic review · Meta-analysis

Introduction

Attention deficit hyperactivity disorder (ADHD), commonly known as hyperactivity disorders, is a common neuropsychological development disorder in children and adolescents. The main manifestations of ADHD are inattention, excessive activity, emotional instability, impulsive willfulness, bad self-control ability, etc. A study reported that the incidence rate of ADHD in children worldwide is about 5–8% (Mohr and Steinhausen 2015). The small-scale investigation report of six cities in China found that 5.4% of school-age children suffer from this disease (Zhang et al. 2007), and 30–50% of children’s symptoms can last to adulthood (Comings et al. 2005).
The hyperactivity behavior of adult patients is controlled, which tends to show inner uneasiness and unable to concentrate and complete tasks. ADHD seriously affects children’s academic performance and life and brings a heavy burden to family and society. Although to a large extent, genetics determines the etiology of ADHD (Fernandez-Jaen et al. 2012; Mohr and Steinhausen 2015), some environmental factors, especially environmental endocrine disruptors (EEDs), are also risk factors of ADHD (Banerjee et al. 2007). Perfluorooalkyl substances (PFASs) are a kind of EEDs, which contain thousands of compounds; the most typical and widely used are perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). PFASs, as an excellent surfactant, are widely used in various fields of production and life, such as textile, paper making, tableware coating, food packaging, carpet, antifouling agent, foam extinguishing agent, aviation, and electroplating (Butenhoff et al. 2006; Kantiani et al. 2010). PFASs have stable structure and are not easy to degrade in the environment.

In recent years, PFASs have been tested in a variety of environmental media all over the world, including water, atmosphere, and soil (Zhang et al. 2016; Harrad and Wemken 2019; Shigei et al. 2020). Even the presence of PFASs have been tested in multiple foods including animal-derived foods (aquatic products, meat, eggs, milk), plant-derived foods (Dalahmeh et al. 2018; Szajzner-Katarzyńska et al. 2018; Ghisi et al. 2019), and human biological samples (Boronow et al. 2019; Ingelido et al. 2020). Therefore, enteron is the main way for PFASs to enter human body. People consume many kinds of food in daily life, which will cause certain health risks to the human body. For example, high serum levels of PFASs may affect estrogen homeostasis in pregnant women and fetal growth (Wang et al. 2019a, 2019b). In addition, relevant animal experiments and epidemiological studies have shown that PFASs can produce multiform toxic effects on organisms through a variety of mechanisms, such as hepatotoxicity (Sheng et al. 2018), nephrotoxicity (Liu et al. 2017), immunotoxicity (Zhou et al. 2019), developmental toxicity, and even neurotoxicity (Gaballah et al. 2020). Long et al. demonstrated that PFASs could induce significant apoptosis of hippocampal cells in adult mice, increase glutamate in the hippocampus, increase caspase-3 protein expression, and decrease Bcl-2, Bcl-XL, and survivin proteins expression, which can lead to neurotoxicity (Long et al. 2013).

PFASs can not only exist in the polluted environment but also accumulate in human serum, breast milk, liver, kidney, and other body fluids and tissues through bioaccumulation effect of the food chain (Antignac et al. 2013; Zafeiraki et al. 2016; Knudsen et al. 2018; Zhou et al. 2018). Since 2000, some developed countries, including the USA, have stopped producing and using compounds such as PFOS and PFOA. In these areas, the concentration of some PFASs in human and animal blood has begun to decrease. However, most PFASs continue to pollute the environment. Moreover, some Asian countries, including China, are still producing and using PFASs.

PFASs have a long half-life and can pass through the placental barrier, and these substances may have adverse effects on the growth and development of the fetus. So PFASs can affect the neurobehavioral function of children and cause the occurrence of ADHD (Chen et al. 2013). More and more attention has been paid to the neurotoxicity caused by exposure to PFASs during pregnancy. The effects during rapid brain development may cause persistent neurobehavioral disorders in the later stage of development. Many studies in the world explored the relationship between the exposure of PFASs during pregnancy and ADHD in offspring. An epidemiological study involving 1526 mothers and infants from Taiwan used inverse probability-weighted linear regression model and found that prenatal exposure to perfluorononanoic acid (PFNA) was associated with ADHD and related neurobehavioral symptoms in Asian 7-year-old children (Lien et al. 2016). Using cross-sectional analysis of 586 children, Hoffman et al. found that for every 1 μg/L increase of PFOS in mother’s serum, the prevalence of ADHD in children increased by 1.03 times. And there was also a significant dose-response relationship between PFOA and perfluorohexane sulfonate (PFHxS) levels and ADHD (Hoffman et al. 2010). A survey from Ohio State showed a moderate correlation between ADHD in children and serum concentration of maternal PFOS and a positive correlation between ADHD in children and serum concentration of maternal PFHxS (Stein and Savitz 2011; Stein et al. 2013). However, Oder et al., using Wilcoxon paired test, did not find any association between prenatal exposure to PFASs and ADHD in Swedish children (Ode et al. 2014). As a result, the relationship between pregnancy exposure to PFASs and children’s ADHD is not consistent. Therefore, we performed a comprehensive systematic review and meta-analysis to explore the relationship between them. So we can provide a scientific basis for the prevention of children’s ADHD and also provide a theoretical basis for the prevention and control of PFASs pollution.

Methods

Search strategy

We searched the electronic databases including PubMed, Science Direct, Scopus, Google Scholar, Web of Science, and Embase to find all studies published before October 2020. We used the following keywords: “Perfluorinated,” “Alkanesulfonic Acids,” “Fluorine,” “Fluorine Compounds,” “Halothane,” “Perfluorooctane sulfonate,” “Perfluorooctanoate,” “Polyfluoroalkyl compounds,” “Polyfluoroalkyl chemicals,” “Perfluorinated chemicals,” “Perfluoroalkyl sulfonate,” “Perfluorooctanoic acid.”
“Perfluorooctanoic acid,” “Perfluorooctane sulfonic acid,” “Perfluorinated acid,” “Fluorocarbons,” “Perfluorinated alkyl substances,” “Perfluorohexane sulfonate,” “Perfluoroalkyl acids,” “Fluorinated organic compounds,” “PFOA,” “PFOS,” “PFAA,” “PFNA,” “PFC,” “PFHxS,” “PFOSA,” “Attention Deficit Disorders with Hyperactivity,” “Attention Deficit Hyperactivity Disorders,” “Attention Deficit-Hyperactivity Disorder,” “Attention Deficit-Hyperactivity Disorders,” “Deficit-Hyperactivity Disorder, Attention,” “Deficit-Hyperactivity Disorders, Attention,” “Disorder, Attention Deficit-Hyperactivity,” “Disorders, Attention Deficit-Hyperactivity,” “Hyperkinetic Syndrome,” “Syndromes, Hyperkinetic,” “ADHD,” “Attention Deficit Hyperactivity Disorder,” “Attention Deficit Disorder,” “Attention Deficit Disorders,” “Deficit Disorder, Attention,” “Disorder, Attention Deficit,” “Disorders, Attention Deficit,” “Brain Dysfunction, Minimal,” “Dysfunction, Minimal Brain,” “Minimal Brain Dysfunction.”

We used two types of retrieval: the first is (Fluorocarbons or “Alkanesulfonic Acids” or Fluorine or “Fluorine Compounds” or Halothane) and (“Attention Deficit Disorder with Hyperactivity” or “ADHD”). The second is (Perfluorinated or “Perfluoroctane sulfonate” or Perfluoroctanoate or “Polyfluoroalkyl compounds” or “Polyfluoroalkyl chemicals” or “Perfluorinated chemicals” or “Perfluoroctanoic acid” or “Perfluorooctane sulfonic acid” or “Perfluorinated acid” or Fluorocarbons or “Perfluorinated alkyl substances” or “Perfluorohexane sulfonate” or “Perfluoroalkyl acids” or “Fluorinated organic compounds” or PFOA or PFOS or PFNA or PFC or PFHxS or PFOSA) and (“Attention Deficit Disorder with Hyperactivity” or “Attention Deficit Disorders with Hyperactivity” or “Attention Deficit Hyperactivity Disorders” or “Attention Deficit-Hyperactivity Disorder” or “Attention Deficit-Hyperactivity Disorders” or “Deficit-Hyperactivity Disorder, Attention” or “Deficit-Hyperactivity Disorders, Attention” or “Disorder, Attention Deficit-Hyperactivity” or “Disorders, Attention Deficit-Hyperactivity” or “Hyperkinetic Syndrome” or “Syndromes, Hyperkinetic” or ADDH or “Attention Deficit Hyperactivity Disorder” or “Attention Deficit Disorder” or “Attention Deficit Disorders” or “Deficit Disorder, Attention” or “Deficit Disorders, Attention” or “Disorder, Attention Deficit” or “Disorders, Attention Deficit” or “Brain Dysfunction, Minimal” or “Dysfunction, Minimal Brain” or “Minimal Brain Dysfunction”).

Exclusion criteria are as follows: (a) the research with no full text; (b) the research unavailable to extract data; (c) the research with no original data or incomplete data; (d) duplicated publication or used of the same data in publications; and (e) low-quality research.

Quality assessment

The researchers used the Newcastle-Ottawa Scale (NOS) to assess the study. The total score of NOS is 0–9. Studies with a total score higher than or equal to six were of high quality. However, studies with NOS score below six were considered to be of low quality (Table 1).

Data extraction

The data was extracted from the publication by the researchers in a standard format. We collected the following information from each eligible article: first author, year of publication, country, sample size, type of pollutant, exposure type, OR, RR or HR, and its 95% confidence interval (95% CI). For studies dividing PFASs concentration into three or four levels, the researchers used the fixed-effect model to merge the data and then adopted the final merge results for meta-analysis (Table 2).

Data analysis

The aim of this meta-analysis was to examine the relationship between PFASs and ADHD in children, and we used OR, RR, or HR to evaluate the effect of these associations. The study data were analyzed using Stata version 11 for windows.

We performed a subgroup analysis of the exposure types of PFASs (maternal serum and children’s serum) and regions (America and Europe). According to the heterogeneity of the study, if $P < 0.05$ or heterogeneity index ($I^2$) >50%, the analysis was performed using the random effect model. Otherwise, the fixed-effect model should be chosen. To eliminate publication bias, Begg’s test and Egger’s regression asymmetry tests were used and presented in the form of funnel plots. In order to observe the stability of the comprehensive results, we performed a sensitivity analysis.

Inclusion and exclusion criteria

First, we screened articles by title and abstract. Studies that did not involve PFASs exposure and early childhood ADHD were excluded.
| Cohort studies               | Selection | Comparability | Outcome | Score |
|-----------------------------|-----------|---------------|---------|-------|
|                             | Representativeness of the exposed cohort | Control for important factor or additional factor | Follow-up long enough for outcome to occur | Adequacy of follow-up of cohorts |
|                             | Selection of the unexposed cohort | Outcome assessment | |
|                             | Ascertainment of exposure | |
|                             | Outcome of interest not present at start of study | |
| Birgit Bjerre Hoyer et al. 2015 | * | * | * | 8 |
| Chunyuan Fei and Olsen 2011 | * | * | * | 8 |
| Chunyuan Fei et al. 2008 | * | * | * | 8 |
| Virissa Lenters et al. 2019 | * | * | * | 8 |
| Birgit Bjerre Hoyer et al. 2018 | * | * | * | 8 |
| Cross-sectional studies     | Selection | Comparability | Outcome | Score |
|                             | Representativeness of the sample | Control for important factor or additional factor | Outcome assessment | Statistical test |
|                             | Sample size | Confounding factors are controlled | Outcome assessment | |
|                             | Non-respondents | Case-definition of the exposure | |
|                             | Ascertainment of the exposure | |
| Cheryl R. Stein and Savitz 2011 | * | * | * | 7 |
| Kate Hoffman et al. 2010 | * | * | * | 7 |
| Case-control studies        | Selection | Comparability | Exposure | Score |
|                             | Case definition | Control for important factor or additional factor | SAME METHOD OF ASCERTAINMENT FOR CASES AND CONTROLS | Non-response rate |
|                             | Representativeness | Control definition | Ascertained of exposure | |
|                             | Control selection | |
|                             | Control definition | |
| Zeyan Liew et al. 2015      | * | * | * | 8 |
| Amanda Ode et al. 2014      | * | * | * | 8 |
| Author               | Year  | Country  | Study size | Exposure type | Exposure substances | Result                        |
|---------------------|-------|----------|------------|---------------|---------------------|-------------------------------|
| Zeyan Liew          | 2015  | Denmark  | 220        | Maternal blood | PFOA, PFOS, PFHxS, PFNA, PFDA | RR=1.28(0.74,2.20)<sup>a</sup> |
|                     |       |          |            |               |                     | RR=1.54(0.82,2.87)<sup>b</sup> |
|                     |       |          |            |               |                     | RR=2.02(0.95,4.27)<sup>c</sup> |
|                     |       |          |            |               |                     | RR=0.89(0.52,1.51)<sup>d</sup> |
|                     |       |          |            |               |                     | RR=0.79(0.40,1.54)<sup>e</sup> |
|                     |       |          |            |               |                     | RR=0.63(0.28,1.42)<sup>f</sup> |
|                     |       |          |            |               |                     | RR=0.85(0.52,1.39)<sup>g</sup> |
|                     |       |          |            |               |                     | RR=0.75(0.44,1.29)<sup>h</sup> |
|                     |       |          |            |               |                     | RR=0.54(0.29,1.01)<sup>i</sup> |
|                     |       |          |            |               |                     | RR=1.23(0.75,2.02)<sup>j</sup> |
|                     |       |          |            |               |                     | RR=1.57(0.91,2.70)<sup>k</sup> |
|                     |       |          |            |               |                     | RR=1.52(0.77,3.03)<sup;l</sup> |
|                     |       |          |            |               |                     | RR=0.79(0.50,1.26)<sup;m</sup> |
|                     |       |          |            |               |                     | RR=1.01(0.58,1.78)<sup>n</sup> |
|                     |       |          |            |               |                     | RR=0.59(0.29,1.18)<sup,o</sup> |
| Birgit Bjerre Hoyer | 2015  | Greenland| 1106       | Maternal blood | PFOA, PFOS          | OR=0.80(0.40,2.00)<sup>a</sup> |
|                     |       | Ukraine  |            |               |                     | OR=3.10(1.30,7.20)<sup>b</sup> |
|                     |       | Poland   |            |               |                     | OR=1.60(0.90,2.80)<sup>c</sup> |
|                     |       |          |            |               |                     | OR=1.20(0.50,2.50)<sup>d</sup> |
|                     |       |          |            |               |                     | OR=1.40(0.40,4.90)<sup>e</sup> |
|                     |       |          |            |               |                     | OR=1.70(0.90,3.20)<sup>f</sup> |
| Cheryl R.Stein      | 2011  | Ohio     | 10546      | Children's blood | PFOA, PFOS, PFHxS, PFNA | OR=1.20(0.94,1.53)<sup>a</sup> |
|                     |       |          |            |               |                     | OR=1.04(0.81,1.32)<sup>b</sup> |
|                     |       |          |            |               |                     | OR=0.72(0.55,0.94)<sup>c</sup> |
|                     |       |          |            |               |                     | OR=1.15(0.89,1.50)<sup>d</sup> |
|                     |       |          |            |               |                     | OR=1.14(0.87,1.48)<sup>e</sup> |
|                     |       |          |            |               |                     | OR=1.27(0.99,1.64)<sup>f</sup> |
|                     |       |          |            |               |                     | OR=1.41(1.09,1.90)<sup>g</sup> |
|                     |       |          |            |               |                     | OR=1.55(1.19,2.04)<sup>h</sup> |
|                     |       |          |            |               |                     | OR=1.59(1.21,2.08)<sup>i</sup> |
|                     |       |          |            |               |                     | OR=1.02(0.78,1.34)<sup>j</sup> |
|                     |       |          |            |               |                     | OR=1.06(0.82,1.36)<sup>k</sup> |
|                     |       |          |            |               |                     | OR=1.16(0.90,1.49)<sup;l</sup> |
| Kate Hoffman        | 2010  | America  | 571        | Children's blood | PFOA, PFOS          | OR=1.19(0.95,1.49)<sup>a</sup> |
|                     |       |          |            |               |                     | OR=1.05(1.02,1.08)<sup>b</sup> |
|                     |       |          |            |               |                     | OR=1.07(1.03,1.11)<sup>c</sup> |
|                     |       |          |            |               |                     | OR=1.57(0.67,3.64)<sup>d</sup> |
| Amanda Ode          | 2014  | Sweden   | 206        | Cord blood     | PFOA, PFOS, PFHxS, PFNA | OR=1.07(0.67,1.70)<sup>a</sup> |
|                     |       |          |            |               |                     | OR=0.81(0.50,1.32)<sup>b</sup> |
|                     |       |          |            |               |                     | OR=1.10(0.75,1.70)<sup>c</sup> |
| Chunyuan Fei        | 2011  | Denmark  | 1313       | Maternal blood | PFOA, PFOS          | OR=0.51(0.28,0.94)<sup>a</sup> |
|                     |       |          |            |               |                     | OR=0.39(0.20,0.76)<sup>b</sup> |
|                     |       |          |            |               |                     | OR=0.62(0.32,1.19)<sup>c</sup> |
|                     |       |          |            |               |                     | OR=1.05(0.59,1.88)<sup>d</sup> |
|                     |       |          |            |               |                     | OR=0.51(0.26,1.00)<sup>e</sup> |
|                     |       |          |            |               |                     | OR=0.92(0.50,1.69)<sup>f</sup> |
| Chunyuan Fei        | 2008  | Denmark  | 1381       | Maternal blood | PFOA, PFOS          | OR=0.85(0.56,1.29)<sup>a</sup> |
|                     |       |          |            |               |                     | OR=0.75(0.49,1.16)<sup>b</sup> |
|                     |       |          |            |               |                     | OR=0.76(0.48,1.18)<sup>c</sup> |
|                     |       |          |            |               |                     | OR=1.13(0.75,1.69)<sup>d</sup> |
|                     |       |          |            |               |                     | OR=1.05(0.69,1.59)<sup>e</sup> |
|                     |       |          |            |               |                     | OR=0.94(0.61,1.44)<sup>f</sup> |
| Chunyuan Fei        | 2019  | Norway   | 1199       | Breast milk    | PFOA, PFOS          | OR=1.35(0.87,2.11)<sup>a</sup> |
|                     |       |          |            |               |                     | OR=1.75(1.11,2.76)<sup>b</sup> |
| Virissa Lenters     | 2018  | Greenland| 1023       | Maternal blood | PFHxS, PFNA, PFDA   | OR=1.10(0.50,2.20)<sup>a</sup> |
|                     |       | Ukraine  |            |               |                     | OR=0.90(0.40,2.00)<sup>b</sup> |
|                     |       |          |            |               |                     | OR=1.10(0.70,1.80)<sup>c</sup> |
|                     |       |          |            |               |                     | OR=1.20(0.60,2.70)<sup>d</sup> |
|                     |       |          |            |               |                     | OR=1.70(0.80,3.70)<sup>e</sup> |
|                     |       |          |            |               |                     | OR=1.80(1.00,3.20)<sup>f</sup> |
Results

Research characteristic

The systematic retrieval scheme of literature was shown in Fig. 1. According to the search strategy, we retrieved 1779 articles from the PubMed, Science Direct, Scopus, Google Scholar, Web of Science, and Embase databases. After excluding the duplicate items, we retrieved the remaining 600 articles. Next, 38 articles were obtained by screening the titles and abstracts. And then a total of nine articles were included according to the inclusion and exclusion criteria. Moreover, 29 articles were excluded, of which four articles did not have the full text, 15 articles were reviews, four articles did not have complete data, four articles used linear regression models, one article used Cox proportional hazards regression models, and one article used multivariable regressions and structural equations models. Finally, the researchers conducted a meta-analysis of data from nine literatures (Fei et al. 2008; Hoffman et al. 2010; Fei and Olsen 2011; Stein and Savitz 2011; Ode et al. 2014; Hoyer et al. 2015; Lie we et al. 2015; Hoyer et al. 2018; Lenters et al. 2019). The specific characteristics of the literature included in the study were shown in Table 2. These studies were all of the high quality.

PFASs exposure and prevalence rate of ADHD in children

PFOA exposure and prevalence rate of ADHD in children

In the analysis of eight studies on the relationship of PFOA exposure and the prevalence rate of ADHD in children, the researchers found no statistical significance between them (OR = 1.00, 95% CI = 0.75–1.25). Heterogeneity was significant in the study, and a random effect model was applied ($I^2 = 54.7\%, P = 0.031$). The result was shown in Fig. 2. Due to exploring the source of heterogeneity, the researchers conducted a subgroup analysis of PFOA exposure type and the region. The results showed that exposure type and regional differences were all sources of heterogeneity. There was a positive correlation between PFOA concentration in children’s blood and the prevalence rate of ADHD (OR = 1.05, 95% CI = 1.02–1.08), and the heterogeneity was not significant ($I^2 = 48.7\%, P = 0.163$). In America, there was a positive correlation between PFOA exposure and the prevalence rate of ADHD in children (OR = 1.05, 95% CI = 1.02–1.08), and the heterogeneity was not significant ($I^2 = 48.7\%, P = 0.163$). The result was shown in Figs. 5 and 6.

PFOS exposure and prevalence rate of ADHD in children

In the analysis of eight studies on the relationship of PFOS exposure and the prevalence rate of ADHD in children, the researchers found no statistical significance between them (OR = 1.00, 95% CI = 0.88–1.14). Heterogeneity was significant in the study, and a random effect model was applied ($I^2 = 54.7\%, P = 0.031$). The result was shown in Fig. 2. Due to exploring the source of heterogeneity, the researchers conducted a meta-analysis of data from nine literatures (Fei et al. 2008; Hoffman et al. 2010; Fei and Olsen 2011; Stein and Savitz 2011; Ode et al. 2014; Hoyer et al. 2015; Lie we et al. 2015; Hoyer et al. 2018; Lenters et al. 2019). The specific characteristics of the literature included in the study were shown in Table 2. These studies were all of the high quality.

PFHxS exposure and prevalence rate of ADHD in children

In the analysis of four studies on the relationship of PFHxS exposure and the prevalence rate of ADHD in children, the researchers found no statistical correlation between them (OR = 1.08, 95% CI = 0.80–1.36). Heterogeneity was significant in the study, and a random effect model was applied ($I^2 = 87.2\%, P < 0.001$). The result was shown in Fig. 2. To explore the source of heterogeneity, the researchers conducted a subgroup analysis of PFHxS exposure type and the region. The result showed that neither exposure type nor regional differences were the sources of heterogeneity. The result was shown in Figs. 3 and 4.
Heterogeneity was not significant in the study, and a fixed-effect model was applied ($\hat{I}^2 = 0.00\%, P = 0.549$). The result was shown in Fig. 2. To further explore whether exposure type and region had an impact on the results, the researchers conducted a subgroup analysis of PFNA exposure type and the region. The results showed a positive correlation between PFNA concentration in maternal blood and the prevalence rate of ADHD (OR = 1.42, 95% CI = 1.04–1.81), and the heterogeneity was not significant ($\hat{I}^2 = 0.00\%, P = 0.703$). Regional differences were not observed. The result was shown in Figs. 8 and 9.

**PFDA exposure and prevalence rate of ADHD in children**

In the analysis of two studies on the relationship of PFDA exposure and the prevalence rate of ADHD in children, the researchers found no statistical correlation (OR = 1.23, 95% CI = 0.15–2.32). Heterogeneity was significant in the study, and a random effect model was applied ($\hat{I}^2 = 81.4\%, P = 0.020$). The result was shown in Fig. 2.

**Publication bias and sensitivity analysis**

We used Begg’s regression asymmetry test to assess publication bias, and there was no prominent asymmetry in the funnel plot by visual inspection. Data results showed that the P-value of Begg’s test for PFASs exposure and the prevalence of ADHD in children were both greater than 0.05, and there was no publication bias. The result was shown in Fig. 10.

Because of the significant heterogeneity of PFOA, PFOS, PFHxS, and PFDA exposure, the researchers conducted a sensitivity analysis. The results showed that the results did not change much after excluding each study in turn. The sensitivity of the results was low, and the results were relatively stable. The result was shown in Fig. 11.
Discussion

The results of the meta-analysis showed that there was no statistical significance between maternal prenatal exposure to PFASs and the prevalence rate of early childhood ADHD. Subgroup analysis showed that there was a positive association between PFOS concentration in children’s blood and ADHD in children (OR = 1.05, 95% CI = 1.02–1.08), and there was also a positive association between PFNA level in maternal blood and ADHD in children (OR = 1.42, 95% CI = 1.04–1.81). In America, there was also a positive association between PFOS level and ADHD in children (OR = 1.05, 95% CI = 1.02–1.08). The results indicated no correlation between maternal prenatal exposure to PFASs and the prevalence rate of early childhood ADHD, and researchers need to conduct more relevant studies for further certification. But this paper was also suggestive. Our research was the first meta-analysis of the relationship between maternal prenatal exposure to PFASs and the prevalence rate of early childhood ADHD which provides a reference for future studies. It also suggested that different exposure types of PFASs and regions of exposure might have different effects on the prevalence rate of ADHD in children.

Relevant epidemiological studies have shown that PFASs can produce multifarious toxicities to humans, such as immunotoxicity, hepatotoxicity, nephrotoxicity, and...
developmental toxicity. Pennings et al. used the Norwegian BraMat cohort to investigate the association between prenatal PFASs exposure and depressed immune function in early childhood. They found that PFASs could affect the expression of immune regulatory genes (CYTL1, IL27) as well as other immune-related genes (e.g., EMR4P, SHC4, ADORA2A), which result in immunotoxicity (Pennings et al. 2016). Stratakis et al. used data from the European Human Early-Life Exposome cohort to explore the association between prenatal PFASs exposure and liver injury in children. Their result demonstrated that PFASs could increase serum levels of alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltransferase, thus, it caused liver damage in children (Stratakis et al. 2020). Wang et al. used a cohort in

**Fig. 3** Association between PFOA exposure and the prevalence of ADHD in children with different exposure

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Zeyan Liew (2015) | 1.44 (0.88, 2.00) | 18.84 |
| Birgit Bjerre Hoyer (2015) | 1.21 (0.61, 2.41) | 17.83 |
| Chunyuan Fei (2011) | 0.48 (0.28, 0.87) | 31.92 |
| Chunyuan Fei (2008) | 0.78 (0.58, 0.99) | 31.00 |
| Subtotal (I-squared = 79.9%, p = 0.002) | 0.88 (0.53, 1.44) | 100.00 |

**PFOA in the children's blood**

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Cheryl R. Stein (2011) | 0.97 (0.68, 1.36) | 46.99 |
| Kate Hoffman (2010) | 1.19 (0.95, 1.49) | 50.01 |
| Subtotal (I-squared = 15.6%, p = 0.276) | 1.09 (0.87, 1.30) | 100.00 |

NOTE: Weights are from random effects analysis

**Fig. 4** Association between PFOA exposure and the prevalence of ADHD in children in different regions

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Europe |
| Zeyan Liew (2015) | 1.44 (0.88, 2.00) | 13.82 |
| Birgit Bjerre Hoyer (2015) | 1.21 (0.61, 2.41) | 12.94 |
| Chunyuan Fei (2011) | 0.48 (0.28, 0.87) | 23.04 |
| Chunyuan Fei (2008) | 0.78 (0.58, 0.99) | 22.82 |
| Amanda Ode (2014) | 1.07 (0.67, 1.70) | 14.06 |
| Vrissa Lentes (2019) | 1.35 (0.87, 2.11) | 12.53 |
| Subtotal (I-squared = 75.7%, p = 0.001) | 0.97 (0.66, 1.44) | 100.00 |

| America |
| Cheryl R. Stein (2011) | 0.97 (0.68, 1.36) | 46.99 |
| Kate Hoffman (2010) | 1.19 (0.95, 1.49) | 50.01 |
| Subtotal (I-squared = 15.6%, p = 0.276) | 1.09 (0.87, 1.30) | 100.00 |

NOTE: Weights are from random effects analysis
Shenyang, China, to investigate the relationship between PFOA and PFOS isomers and renal function in humans. The result confirmed that PFASs could lead to nephrotoxicity by reducing the glomerular filtration rate (Wang et al. 2019a, b, c). Kishi et al. investigated the relationship between prenatal PFASs exposure and birth weight of offspring by using the Hokkaido cohort. They found that PFOS could reduce polyunsaturated fatty acid concentrations in maternal blood and cause lower birth weight of offspring (Kishi et al. 2015).

At present, several studies had proposed the possible mechanism of PFASs affecting neural development, but they had limitations. For example, through toxicological genomic analysis, Martin et al. found that exposure to PFOA and PFOS could cause interference of thyroid hormone metabolism...
genes and decrease serum thyroid hormone level (Martin et al. 2007). Similarly, a cross-over study of rats exposed to PFOS in uterus and lactation showed that prenatal and postnatal exposure to PFOS might reduce thyroid hormone levels in the offspring (Yu et al. 2009). Study has verified that PFASs can cause changes in thyroid function, which resulted in neurodevelopmental disorders (Boas et al. 2012). However, the effects of PFASs environmental level were still lack of widely research in human, animal, and in vitro experiments. It was necessary to conduct human and animal studies of the thyroid interference effect in fetal or infancy. Furthermore, cross-foster model research showed that PFOS exposure increased $[\text{Ca}^{2+}]$ in a dose-dependent in both continuous and prenatal exposure groups (Wang et al. 2015). A recent study
demonstrated that the release of intracellular calcium could change the calcium homeostasis of neurons and increased the risk of developmental neurotoxicity of fetal exposure to PFOS (Wang et al. 2019a, b, c). PFOS also could cause neurotoxicity by affecting apoptosis. A study by Li et al. reported that in primary cultured neurons, astrocytes could protect the PFOS-inhibited neurite growth, however, PFOS might also result in astrocytes apoptosis, which could lead to neurotoxicity of PFOS (Li et al. 2017; Liu et al. 2017). At present, studies exploring the impact of PFASs in human mainly focus on animal experiments. But in a recent study, Guo et al. used the human neuroblastoma cell line, SK-N-SH, to examine the role of epigenetics in the neurotoxicity guided by PFOS. And they looked into the influences of PFOS on the Brain-derived neurotrophic factor (BDNF) expression in SK-N-SH cells. The results suggested that methylated regulation of the BDNF gene promoter and increased BDNF-associated microRNA may form the basis for the mechanism of PFOS-guided neurotoxicity, which might lead to ADHD in early childhood (Guo et al. 2017). The mechanism of PFASs on human needs further be explored.

PFASs contain many substances. This paper mainly studied five substances, among which PFNA exposure had no heterogeneity. To clarify the sources of heterogeneity in PFOA, PFOS, PFHxS, and PFDA, the researchers performed subgroup analysis, but it is divided by exposure type and region. For PFOS, exposed type and region were all the sources of heterogeneity. Unfortunately, the sources of heterogeneity of the other three substances were not found. The heterogeneity may be due to the lack of completeness of the research outcome report, the lack of rigor in the statistical methods of the study itself, or the existence of genetic diversity among different races. In a word, we cannot eliminate heterogeneity.

Through the subgroup analysis of PFASs exposure type, this study found that PFOS exposure to children’s blood was more likely to cause ADHD, while PFNA exposure to mother’s blood was more likely to cause ADHD. Lien et al. reported that PFNA concentration in cord blood was associated with ADHD in children (Lien et al. 2016). The reason for the different in results may be due to the different regions of the study population. At the same time, the subjects of this study selected premature children, which was the main reason for the difference in results. Besides, Hoyer et al. concluded a certain degree of correlation between PFOS level in maternal blood and hyperactivity of children (Hoyer et al. 2015). Different regression models of data analysis or the influence of regional differences may cause the difference of results. According to the existing research, which exposure type has a significant correlation with the occurrence of ADHD has not been unified, which needs researchers to further explore.

Although the results of this study indicated a positive correlation between PFOS exposure in American and the prevalence of ADHD in children, however, due to the small number of research papers and the lack of convincing power to a certain extent, more relevant articles need to be included for further proof. Most of the research areas we entered were located in Europe (Strom et al. 2014; Oulhote et al. 2016; Quaak et al. 2016). Also, some studies (Stein et al. 2013; Stein et al. 2014) only observed the relationship between

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Europe   |             |        |
| Zeyan Liew (2015) | 1.37 (0.90, 1.95) | 39.96 |
| Birgit Bjerring Hoyer (2018) | 1.53 (0.86, 2.29) | 20.08 |
| Amanda Ode (2014) | 1.10 (0.75, 1.70) | 39.96 |
| Subtotal (I-squared = 0.0%, p = 0.545) | 1.29 (0.99, 1.59) | 100.00 |
| American |             |        |
| Cheryl R. Stein (2011) | 1.08 (0.91, 1.24) | 90.78 |
| Kate Hoffman (2010) | 1.57 (0.67, 3.64) | 1.22 |
| Subtotal (I-squared = 0.0%, p = 0.520) | 1.09 (0.92, 1.25) | 100.00 |
PFOA exposure and ADHD in American children, not PFOS. Due to various limiting factors, the number of articles about PFOS exposure in America was too small, and the conclusion was not universal.

For overall results, there was no association between maternal PFASs exposure and early childhood ADHD. This was not consistent with previous research results (Hoyer et al. 2015; Lien et al. 2016; Hoyer et al. 2018). But our study had many advantages. Firstly, the included studies were cross-sectional, case-control, or cohort studies. They included both prospective and retrospective studies, and they were all of the high quality. Secondly, the included studies all used logistic regression, which reduced the source of heterogeneity and could efficiently explore whether PFASs exposure was a risk factor for ADHD in children. Thirdly, there was no publication bias in this study, and the results of sensitivity analysis were also very stable and reliable.

We believed that this discovery had research significance, but we also noticed some limitations. Firstly, our analysis included a small number of studies may be one of the reasons...
for the meaningless results. Secondly, most of the studies were from Europe, and others were from the Americas. The lack of data from Asia and Africa made the results may not be universal. Thirdly, some studies reported that maternal PFASs exposure was related to ADHD but did not report its data. The reported data were incomplete and cannot be combined, which may also lead to the deviation of results. Fourthly, to reduce the impact of confounding factors, we extracted data from the adjusted model, which meant that our results might be prone to over adjustment.

The results of this meta-analysis had certain scientific value and significance. Our research was the first meta-analysis of the relationship between maternal PFASs exposure and the prevalence of early childhood ADHD. It provided first-level evidence to verify whether there was a correlation between the two and used statistical methods to solve inconsistent results in relevant studies. Furthermore, this study suggested that clinical data on the relationship between PFASs exposure and ADHD in children should continue to be collected, which will provide data support for qualitative or quantitative studies in the future. Meanwhile, this paper also supplied reference for future-related research and provided ideas for reducing the prevalence of ADHD in children.

Due to the limitation of this study, there were still many problems to be solved. We should further explore whether gender differences impacted maternal PFASs exposure and the prevalence of ADHD in children. At the same time, researchers could extend further study to Asia and Africa to explore the impact of regional differences between them. Future studies need to further expand the sample size to make the results more reliable.

**Conclusion**

This study showed that maternal exposure to PFASs was not associated with the prevalence rate of ADHD in children. Researchers observed that exposure type and regional factor may influence the occurrence of ADHD. More epidemiological studies should be encouraged, especially on the exposure type of PFASs, to understand the pathogenesis of ADHD in more depth. Further research should be carried out widely in different regions. Most importantly, in order to reduce the harm of PFASs to people, the country should cut down the use of PFASs in industry and develop new alternatives to PFASs with green, low toxicity and low accumulation. Finally, researchers should vigorously develop techniques that can effectively degrade PFASs and lessen the concentration of PFASs in the environment. This is the crucial measure for the protection of ecological environments and other species.
Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contribution Conceived and designed the experiments, XLZ, XHL, and SJS; performed the experiments, XLZ, WJW, RL, XW, and YXX; analyzed the data, ABQ and TRC; contributed analysis tools, XLZ; wrote the paper, XHL, ABQ, and TRC. All authors read and approved the final manuscript.

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Declarations

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