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Review

Impacts of PFAS Exposure on Neurodevelopment: A Comprehensive Literature Review

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Abstract: Neurodevelopmental disorders (NDDs) encompass a range of conditions that begin during the developmental stage and cause deficits that lead to disruptions in normal functioning. One class of chemicals that is of increasing concern for neurodevelopmental disorders is made up of per- and polyfluoroalkyl substances (PFAS). In this comprehensive literature review, we investigated data from epidemiological studies to understand the connection between PFAS exposure and neurodevelopmental endpoints such as cognitive function, intelligence (IQ), and memory, along with behavioral changes like Attention-Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD). When we reviewed the findings from individual studies that analyzed PFAS levels in biological samples and their association with NDD, we concluded that there was a correlation between PFAS and neurodevelopmental disorders. The findings suggest that children exposed to higher PFAS levels could potentially have an increased risk of ASD and ADHD along with an inhibitory effect on IQ. While the results vary from one study to another, there is increasing association between PFAS exposure and neurodevelopmental disorders. Importantly, the findings provide valuable insights into the adverse effects associated with PFAS exposure and neurodevelopment.

Keywords: neurodevelopment; PFAS; Intelligence Quotient (IQ); Attention-Deficit Hyperactivity Disorder (ADHD); Autism Spectrum Disorders (ASD); risk assessment

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1. Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), neurodevelopmental disorders (NDD) are defined as a group of conditions with onset in the developmental period, inducing deficits that produce impairments of functioning [1]. Impairments of cellular growth and metabolism during critical periods of prenatal brain development may result from the effects of environmental toxins, nutritional deficits, maternal illnesses, and genetic disorders, alone or in combination [2]. It has been established that the environment plays a crucial role in influencing juvenile health, with an increased risk of negatively affecting neurodevelopment [3]. Additionally, the significant increase in the occurrence of neurodevelopmental disorders suggests that environmental factors could be a major contributing cause [4]. There are approximately 200 chemicals that have been found to be neurotoxic in humans, and there is at least some evidence of neurotoxicity deriving from animal studies for many more [5,6]. However, of over 80,000 chemicals on the market, only a handful (approximately 200) have undergone developmental neurotoxicity testing according to the established guidelines [6,7]. One class of chemicals that is of increasing concern for neurodevelopmental disorders is made up of per- and polyfluoroalkyl substances.

Per- and polyfluoroalkyl substances (PFAS) are a varied collection of synthetic compounds defined by their chemical structure, which includes one or more carbon atoms

bonded to fluorine atoms, forming fully fluorinated groups like −CF3 (perfluorinated methyl) or −CF2− (perfluorinated methylene). These substances differ in their carbon chain lengths, the degree of fluorination, and the types of additional chemical groups that they may contain [8]. The development of PFAS began in the 1930s, and their unique property of interacting with both hydrophobic and hydrophilic substances has driven their widespread adoption in a range of industrial and commercial uses [9]. PFAS are often used for their "non-stick" and surface-tension-lowering properties, which makes them useful for repelling oil and water (preventing stains) and modifying surface chemistry [10]. Humans are exposed to PFAS primarily through consuming contaminated food and water, inhaling or ingesting dust and fumes from PFAS-containing items found in residential and office environments, and through occupational contact in industries that manufacture or utilize PFAS [11,12]. The most significant source of human exposure to PFAS is dietary intake (food and water) [13]. In certain situations, the intake of PFAS through drinking water can be just as significant as dietary sources of these chemicals [14]. Several studies have detected PFAS in surface- and groundwater worldwide, both of which are important sources for drinking water production and as a result, public concern has arisen over human exposure risks to PFAS [15].

Despite the extensive and widespread use of PFAS over recent decades, it was only in recent years that significant attention was paid to human exposure to these chemicals and their potential negative health impacts [16]. PFAS pose numerous environmental and health risks. While some PFAS are regarded as having minimal health impact, others are linked to harmful effects in both humans and wildlife at present environmental exposure levels [17]. PFAS has been associated with adverse effects in many organs and systems, including reproductive [18,19], immune [20,21], endocrine [22–25], hepatic [26], cardiovascular [27,28], and neurodevelopmental effects [29–32]. Neurodevelopment begins shortly after conception, around three weeks into pregnancy, and progresses through the stages of infancy and into puberty [33]. Various pieces of evidence indicate that the nervous system in development may be more vulnerable, or differently affected, by toxic exposures compared to the adult nervous system [34].

Extensive research shows that various PFAS are frequently found in pregnant women [35–37], and that the placenta is a reasonable target for PFAS [38,39]. PFAS accumulate in the placenta and pass the placental barrier, affecting the developing embryo [40]. Studies have shown that PFAS can cross the placental barrier and are associated with fetal growth restriction, immunosuppression, neurotoxicity, and some other health effects [41,42]. The ability of PFAS to pass through the placenta varies depending on factors such as the length of the carbon-fluorine chain, the presence of functional groups, and the overall chemical structure. This process is largely influenced by the interaction of PFAS with serum carrier proteins and placental transport mechanisms [43]. Furthermore, It has been observed that young children tend to reach their highest PFAS concentrations before the age of two [44], possibly due to cumulative exposure via breastfeeding [45,46]. The combination of exposure routes from gestation through adolescence makes PFAS an agent of neurodevelopmental toxicity. Increasing evidence from epidemiological research suggests that exposure to PFAS during pregnancy might influence neurodevelopment in children. This could affect various cognitive functions, including learning, IQ, and memory, and may also be related to behavioral disorders such as ADHD and Autism Spectrum Disorders (ASD) [11,47]. While IQ, ASD, and ADHD constitute prominent endpoints in the study of neurodevelopmental disorders, the broader category of neurodevelopmental disorders encompass a range of complex conditions marked by impairments in cognitive function, communication abilities, behavioral patterns, and motor skills, all stemming from atypical brain development [48].

The US Centers for Disease Control and Prevention (CDC) has reported, based on findings from the National Health and Nutrition Examination Survey (NHANES), that PFAS have been found in the bloodstream of 97% of people in the United States [49]. With the omnipresence of PFAS in humans, there is an increasing concern of PFAS exposure

throughout prenatal and postnatal development. Given the increasing concerns, through this review, we explore epidemiological studies examining the association between early-life PFAS exposure and childhood neurodevelopmental disorders, specifically focusing on IQ, ADHD, and ASD.

2. Materials and Methods

2.1. Data Sourcing

To investigate the neurodevelopmental toxicity of per- and polyfluoroalkyl substances, a comprehensive literature search was conducted using PubMed. The search strategy included a combination of keywords related to PFAS and neurodevelopmental outcomes. The primary search terms used were: "PFAS", "per- and polyfluoroalkyl substances", "neurodevelopment", "IQ", "intelligence quotient", "ASD", "autism spectrum disorder", "ADHD", and "attention deficit hyperactivity disorder". These terms were combined using the Boolean operators "AND" and "OR" to form the search string: ("PFAS" OR "per- and polyfluoroalkyl substances") AND ("neurodevelopment" OR "IQ" OR "intelligence quotient" OR "ASD" OR "autism spectrum disorder" OR "ADHD" OR "attention deficit hyperactivity disorder"). Studies had to include clear exposure assessment for PFAS in humans. We included all primary epidemiological studies that presented quantitative measures of the association between at least one type of PFAS and at least one neurodevelopmental disorder. Specifically, this encompassed research that provided statistical estimates of how PFAS exposure correlates with neurodevelopmental outcomes. We excluded studies that were reviews or focused on non-epidemiological aspects, such as mechanistic studies, in vitro experiments, or animal research. Additionally, we did not consider human studies that failed to provide quantitative estimates of the relationship between PFAS and neurodevelopmental disorders. (Figure 1).

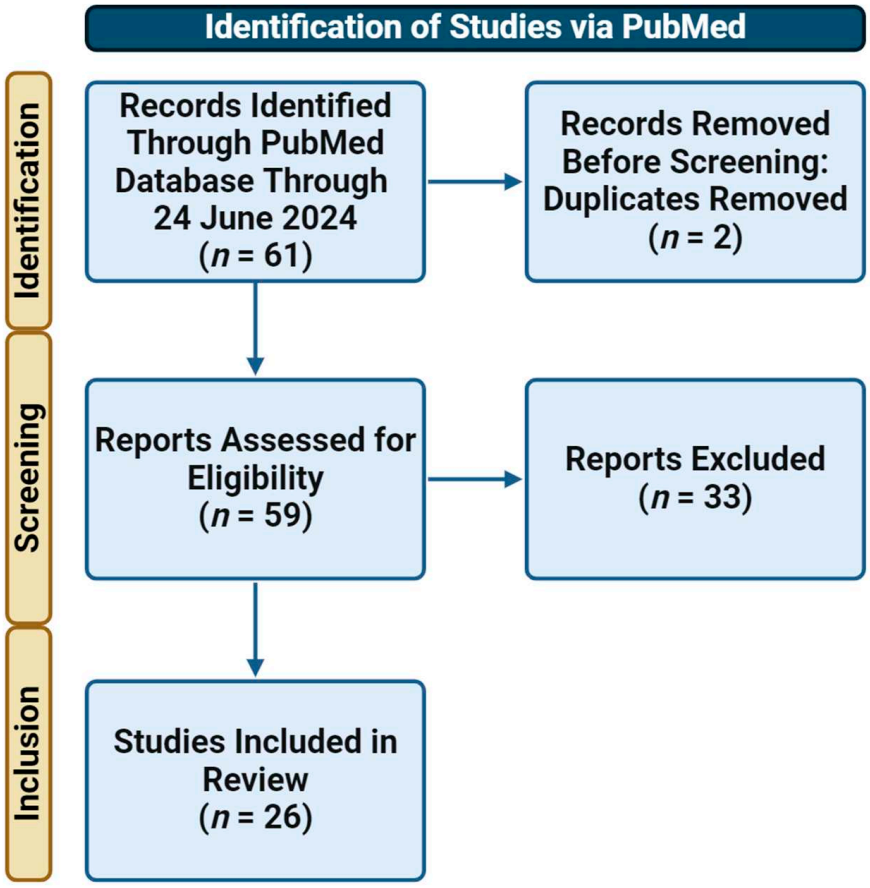

Figure 1. Study Flow Design.

2.2. Exposure Assessment

Exposure assessment in the included studies primarily involved measuring concentrations of PFAS compounds in biological samples, such as serum or plasma, from participants. These measurements were typically obtained through high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC–MS/MS), a highly sensitive and specific analytical method [50,51]. However, a subset of studies employed liquid chromatography (LC), indicating a variability of results. The studies varied in the specific PFAS compounds assessed, with common ones including perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), and perfluorohexanesulfonic acid (PFHxS). Additionally, the timing of exposure assessment ranged from prenatal (e.g., maternal blood or cord blood) to postnatal periods, reflecting critical windows of neurodevelopmental susceptibility [52]. These observations highlight the diversity in methods and compounds analyzed, as well as the broad range of timing the exposure assessments, which collectively contribute to our understanding of PFAS exposure in relation to neurodevelopmental disorders.

2.3. Outcomes

The assessment of neurodevelopmental outcomes such as the Intelligence Quotient (IQ), Autism Spectrum Disorder (ASD), and Attention-Deficit Hyperactivity Disorder (ADHD) in the included studies utilized standard and accepted means of evaluating neurodevelopmental disorders. The Intelligence Quotient (IQ) was evaluated using widely recognized tests including Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) and the Full-Scale Intelligence Quotient (FSIQ) [53,54]. For the diagnosis of ASD, studies often relied on established diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), employing tools like Mullen Scales of Early Learning (MSEL) and the Behavioral Assessment System for Children-2 (BASC-2) [55,56]. Finally, ADHD was assessed and diagnosed using the criteria laid out in the DSM-5. These diagnostic tools included ADHD Rating Scale (ADHD-RS) and the Child Behavior Checklist (CBCL) [57,58]. These assessment tools ensure that the neurodevelopmental outcomes were accurately assessed to allow comparison between studies.

2.4. Covariates

Throughout the various studies between PFAS and neurodevelopment, several covariates were considered to control for potential confounding variables within each study. Commonly adjusted covariates included sociodemographic variables such as child's age, sex, parental education, household income, and maternal age at childbirth. Additionally, studies accounted for smoking, country of birth, and quality of the child's home environment. By controlling for certain covariates, the studies reduced bias and confounding variables to more accurately assess the relationship between PFAS and neurodevelopmental endpoints, such as IQ, ASD, and ADHD.

2.5. Data Extraction

Data extraction was conducted systematically using a standardized form to ensure consistency and comprehensiveness across all included studies. Key information collected included the following: authors' names, publication year, study design, sample size, and population characteristics such as age, sex, and geographic location. PFAS exposure assessment was recorded, including the types of PFAS compounds measured, biological sample type, and concentration levels. For neurodevelopmental outcomes, data on assessment methods for IQ, ASD, and ADHD were extracted, specifying the tools/criteria used for evaluation, such as standardized intelligence tests, diagnostic interviews, and rating scales. Further, sample sizes, confidence intervals, and significance were also noted. Finally, any covariates that were adjusted for throughout the studies were recorded. Using a systematic data extraction process, all necessary information was collected in detail for accurate comparison between studies.

3. Results

3.1. The Intelligence Quotient (IQ)

Within a literature search (Table 1), ten studies focusing on the association between PFAS exposure throughout childhood and the Intelligence Quotient were included [11,59–67]. In total, 14 individual PFAS were included, but only PFOS, PFHxS, and PFOA were seen in every study. Cognitive assessments were performed using various standardized tests, primarily the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and the Full-Scale Intelligence Quotient (FSIQ). Most studies used either one of these main tests or a combination of them. However, Harris et al., 2018 chose to use the Kaufman Brief Intelligence Test (KBIT-2), while Skogheim et al., 2020 employed the Stanford–Binet Intelligence Test. While each study has different testing parameters, an extensive body of research has demonstrated that IQs obtained from different intelligence tests substantially correlate at the group level [68]. The results of the included studies showed conflicting results, but some studies indicated that there was some significant evidence that PFAS could have an inhibitory effect on the Intelligence Quotient. Some of the inconsistent results could be associated with the several covariates such as PFAS exposure levels, child's age, and child's sex.

Table 1. Summary of articles, results, and evidence on PFAS exposure to the Intelligence Quotient (IQ).

First Author/ Year/Country	Design	Sample Size	Age of Children	PFAS	Sample/ Measuring Method	Exposure Measure	Test Type and Indicator	Adjustment of Covariates	Conclusion
Carly V Goodman/2023/ Canada [59]	Cohort Study	*n* = 522	Between 3 and 4	PFOA, PFOS, and PFHxS	Plasma/ UHPLC–MS/MS	PFOA: 1.68 (1.10–2.50), PFOS: 4.97 (3.20–6.20), PFHxS: 1.09 (0.67–1.60) (μg/L)	Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III), composite full-scale IQ (FSIQ), performance IQ (PIQ), and verbal IQ (VIQ) scores	Gestational week of blood sampling, maternal age, pre-pregnancy BMI, country of birth (Canadian born, foreign born), maternal level of education (trade school diploma or lower, bachelor's degree or higher), parity (0, 1, 2+), maternal smoking during pregnancy (current smoker, former smoker, never smoked), study site, and the Home Observation Measurement of the Environment (HOME) score, a continuous measure of the quality of the child's home environment	Each doubling of PFHxS levels corresponded to a reduction of 2.0 points (95% CI: −3.6, −0.5) in FSIQ and 2.9 points (95% CI: −4.7, −1.1) in PIQ in males. However, in females, PFHxS showed no association with FSIQ or PIQ. PFOA and PFOS were also linked to lower PIQ scores in males (PFOA: B = −2.8, 95% CI: −4.9, −0.7; PFOS: B = −2.6, 95% CI: −4.8, −0.5), while in females, they were slightly positively associated with PIQ, but not FSIQ
Iben Have Beck/2023/ Denmark [60]	Cohort Study	*n* = 967	7 years old	PFOS, PFOA, PFHxS, PFNA, and PFDA	Serum/ LC–MS	PFOS: 4.61 (3.08–7.08), PFOA: 2.48 (1.58–3.49), PFHxS: 0.33 (0.21–0.50), PFNA: 0.57 (0.40–0.78), PFDA: 0.18 (0.13–0.24) (ng/mL)	Abbreviated version of the Danish WISC-V, Full-Scale Intelligence Quotient (FSIQ) score, and Verbal Comprehension Index (VCI) score	Maternal educational level, BMI, and sex	PFOS and PFNA exposure and FSIQ remained significant, with β coefficients of −1.7 (95% CI: −3.0, −0.3) and −1.7 (95% CI: −3.0, −0.4)
Ann M Vuong/2019/ United States [69]	Cohort Study	*n* = 221	3 and 8 years old	PFOA, PFOS, PFHxS, and PFNA	Serum/ HPLC–MS/MS	PFOA: 2.4, PFOA: 3.9, PFHxS: 1.4, PFNA: 0.8 (ng/mL)	Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) and Full Scale IQ (FSIQ)	Maternal sociodemographic, behavioral factors, and biological measurements of environmental chemical	Findings do not support that PFAS are adversely associated with cognitive function
Hui Wang/2023/ China [62]	Cohort Study	*n* = 2031	4 years old	PFOA, PFOS, PFNA, PFUA, PFDA, PFHxS, PFBS, PFDoA, PFHpA, and PFOSA	Plasma/ HPLC–MS/MS	PFOA: 13.12 (9.36–15.50), PFOS: 11.3 (6.66–13.68), PFNA: 2.05 (1.27–2.49), PFDA: 2.16 (1.18–2.67), PFHxS: 0.62 (0.42–0.69) (ng/mL)	Wechsler Preschool and Primary Scales of Intelligence-Fourth Edition (WPPSI-IV)	Maternal age at delivery, maternal educational level, maternal pre-pregnancy body mass index, parity, maternal folic acid intake during pregnancy, maternal place of birth, maternal active/passive smoking status during pregnancy, maternal freshwater fish intake during pregnancy, and self-reported economic status	No significant associations between ln-transformed nine individual PFAS and child full scale IQ (FSIQ) or subscale IQ after adjusting for potential confounders
Zeyan Liew/2018/ Norway [63]	Cohort Study	*n* = 1592	5 years old	PFOS, PFOA, PFHxS, PFNA, PFHpS, PFDA, and PFOSA	Plasma/ LC–MS/MS	PFOS: 28.10 (21.60–35.80), PFOA: 4.28 (3.51–5.49), PFHxS: 1.07 (0.76–1.38), PFNA: 0.46 (0.36–0.57), PFHpS: 0.37 (0.27–0.49), PFDA: 0.17 (0.14–0.22), PFOSA: 2.32 (1.38–4.16) (ng/mL)	Wechsler Primary and Preschool Scales of Intelligence–Revised (WPPSI-R)	Maternal age at delivery, parity, maternal IQ, socioeconomic status, maternal smoking during pregnancy, maternal alcohol consumption during pregnancy, maternal prepregnancy BMI, child's sex	There is no reliable evidence establishing a connection between prenatal exposure to PFAS and IQ scores in children at the age of five

Table 1. *Cont.*

First Author/ Year/Country	Design	Sample Size	Age of Children	PFAS	Sample/ Measuring Method	Exposure Measure	Test Type and Indicator	Adjustment of Covariates	Conclusion
Yan Wang/2015/ United States [64]	Cohort Study	*n* = 120	5 years old	PFHxS, PFOA, PFOS, PFNA, PFDeA, PFUnDA, PFDoDA, PFHpA, and PFHxA	Serum/ HPLC–MS/MS	PFHxS: 0.45 (0.35–0.57), PFOA: 2.00 (1.72–2.33), PFOS: 11.5 (10.2–13.07), PFNA: 1.33 (1.12–1.59), PFDeA: 0.39 (0.34–0.44), PFUnDA: 3.05 (2.37–3.94), PFDoDA: 0.29 (0.25–0.34) (ng/mL)	Full-Scale Intelligence Quotient (FSIQ), verbal IQ (VIQ) and performance IQ (PIQ)	Maternal age, maternal education, previous live births, family income, and maternal fish consumption during pregnancy	Exposure to two types of long-chain PFAS during pregnancy has been linked to lower IQ scores in children
Maria H Harris/2018/ United States [65]	Cohort Study	*n* = 1226	3 years old	PFOA, PFOS, PFHxS, PFNA, MeFOSAA, and PFDeA	Plasma/ HPLC–MS/MS	PFOA: 4.4 (3.1–6.0), PFOS: 6.2 (4.2–9.7), PFHxS: 1.9 (1.2–3.4), PFNA: 1.5 (1.1–2.3), MeFOSAA: 0.3 (<LOD −0.6), PFDeA: 0.3 (0.2–0.5) (ng/mL)	Peabody Picture Vocabulary Test (PPVT-III), Wide Range Assessment of Visual Motor Abilities (WRAVMA), Kaufman Brief Intelligence Test (KBIT-2), and Visual Memory Index of the Wide Range Assessment of Memory and Learning (WRAML2)	Child sex, age at cognitive testing, maternal race/ethnicity, age, maternal and paternal education, socioeconomic status and maternal intelligence scores	Prenatal PFAS were associated with both better and worse cognitive scores
Miranda J. Spratlen/2020/ United States [11]	Cohort Study	*n* = 110	Children ages 3–7 years	PFOS, PFOA, PFHxS, PFNA, PFDS, PFBS, PFOSA, PFHxA, PFHpA, PFDA, PFUnDA, and PFDoDA	Plasma/ HPLC–MS/MS	PFOS: 6.27 (1.05, 33.7), PFOA: 2.37 (0.18, 8.14), PFNA: 0.45 (<LOQ, 10.3), PFHxS: 0.69 (<LOQ, 15.8), PFDS: 0.13 (<LOQ, 0.64) (ng/mL)	Bayley Scales of Infant Development (BSID-II), Mental Development Index (MDI), Psychomotor Development Index (PDI), and Wechsler Preschool and Primary Scale of Intelligence (WPPSI)	Maternal age; material hardship during pregnancy; pre-pregnancy BMI; maternal IQ; maternal race; maternal education; home smoking exposure; marital status; parity; child's gestational age at birth; exact child age on test date; child's sex; maternal demoralization score; and child breastfeeding history	Findings on prenatal PFAS exposure and child neurodevelopment are inconsistent
Thea S. Skogheim/2020/ Norway [66]	Longitudinal Prospective Study	*n* = 944	3.5 years old	PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFHpS, and PFOS	Plasma/ LC–MS/MS	PFOA: 2.50 (1.77–3.21), PFNA: 0.41 (0.29–0.53), PFDA: 0.15 (0.10–0.23), PFUnDA: 0.22 (0.14–0.32), PFHxS: 0.65 (0.46–0.88), PFHpS: 0.15 (0.10–0.20), PFOS: 11.51 (8.77–14.84) (ng/mL)	The Preschool Age Psychiatric Assessment interview, Child Development Inventory and Stanford–Binet (5th revision)	Maternal age, maternal education, maternal fish intake, parity, maternal ADHD symptoms, child sex, premature birth, birth weight, maternal BMI, maternal smoking, maternal alcohol consumption, maternal anxiety/depression and maternal iodine intake	No consistent evidence to conclude that prenatal exposure to PFAS are associated with cognitive dysfunctions in preschool children aged three and a half years
Boya Zhang/2024/ China [67]	Cohort Study	*n* = 327	7 years old	PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFBS, PFHxS, PFHpS, PFOS, PFDS, and PFOSA	Serum/ UHPLC–MS/MS	PFHpA: 0.27 (0.23–0.30), PFOA: 3.51 (3.29–3.75), PFNA: 0.32 (0.28–0.36), PFDA: 0.86 (0.76–0.96), PFUnDA: 0.61 (0.57–0.65), PFDoDA: 0.13 (0.12–0.14), PFBS: 0.08 (0.07–0.09), PFHxS: 0.09 (0.08–0.10), PFHpS: 0.06 (0.05–0.07), PFOS: 2.10 (1.98–2.22) (ng/mL)	Wechsler Intelligence Scale for Children-Chinese Revised (WISC-CR)	Maternal age at delivery, parity, maternal educational level, child's sex, annual household income, pet ownership, changes in marital status, pre-pregnancy BMI	Increased prenatal exposure to PFAS negatively affected the IQ of school-aged children

3.2. Attention-Deficit Hyperactivity Disorder (ADHD)

As a results of the literature search (Table 2), nine primary research studies were identified that focused on PFAS exposure on Attention-Deficit Hyperactivity Disorder (ADHD) [61,66,70–76]. While eleven PFAS were examined throughout the different studies, PFOS and PFOA were the only PFAS that were included in every study. While there is not a current standardized ADHD test, various tests with the main ADHD criteria being outlined in the Diagnostic and Statistical Manual of Mental Disorders were utilized in the different studies. These include commonly used diagnostic exams such as Attention Syndrome Scale of the Child Behavior Checklist (CBCL-ADHD) and Behavioral Assessment System for Children-2 (BASC-2). Most studies did not show any association between PFAS exposure and ADHD. However, a few studies showed conflicting results. Skogheim et al., 2021 [74] and Itoh et al., 2022 [75] indicated that there could be an inverse, protective effect of PFAS. Furthermore, Kim et al., 2023 [72] and Vuong et al., 2021 [61] indicated that there could be an positive association between PFAS exposure and ADHD. These conflicting results could be associated with the inability to conduct consistent ADHD diagnosis.

3.3. Autism Spectrum Disorder (ASD)

Through a systematic literature review (Table 3), six primary clinical studies were identified that focus on associating PFAS exposure with Autism Spectrum Disorder (ASD) [31,74,77–80]. While ten different PFAS were analyzed, PFOA PFOS, PFHxS, and PFNA appeared in every study. The diagnosis of Autism Spectrum Disorder was conducted through several different standardized exams. The Mullen Scales of Early Leaning (MSEL) or the International Classification of Diseases (ICD)-8 were used in diagnosis in every study, except for Lyall et al., 2018 [80], which used the DSM-5 criteria for diagnosis. Additionally, the Vineland Adaptive Behavioral Scale (VABS) and the Autism Diagnostic Observation Schedule (ADOS) were utilized in corroborating the results of the MSEL and the ICD-8. A majority of the studies showed significant association between PFAS exposure and increased odds of ASD. However, two studies that showed a low protective effect were Lyall et al., 2018 [80] and Skogheim et al., 2021 [74]. This conflicting result could be due to the difference in diagnostic method utilized in the study. The results of these studies indicate that PFAS could have an inhibitory effect on neurodevelopment leading to ASD.

Table 2. Summary of articles, results, and evidence on PFAS exposure to Attention-Deficit Hyperactivity Disorder (ADHD).

First Author/ Year/Country	Design	Sample Size	Age of Children	PFAS	Sample/ Measuring Method	Exposure Measure	Test Type and Indicator	Adjustment of Covariates	Conclusion
Joan Forns/2020/ Norway [70]	Cross-Sectional Study	*n* = 518	3, 6, 12, and 24 months of age	PFOS and PFOA	Serum/ HPLC–MS/MS	PFOS: 20.19 (4.1–87.3), PFOA: 1.83 (0.5–5.1) (ng/mL)	Attention Syndrome Scale of the Child Behavior Checklist (CBCL-ADHD), Hyperactivity/Inattention Problems subscale of the Strengths and Difficulties Questionnaire (SDQ-Hyperactivity/Inattention), and ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (ADHD-DSM-IV)	Maternal prepregnancy body mass index, maternal age at delivery, maternal education, maternal smoking during pregnancy, maternal parity, duration of total breastfeeding, and child sex	Exposure to PFOS or PFOA early in life was not linked to ADHD during childhood, with odds ratios (ORs) varying between 0.96 (95% CI: 0.87, 1.06) and 1.02 (95% CI: 0.93, 1.11). Analysis using stratified models indicates that the impact of PFAS may vary based on the child's sex and the mother's level of education
Louise Dalsager/2021/ Denmark [71]	Cohort Study	*n* = 1138	2.5–5 years old	PFHxS, PFOS, PFOA, PFNA, and PFDA	Serum/ LC–MS/MS	PFOS: 4.65 (11.22), PFOA: 2.43 (6.40), PFHxS: 0.32 (0.81), PFNA: 0.58 (1.24), PFDA: 0.18 (0.37), Median (95th percentile) (ng/mL)	Child Behavior Checklist 1.5–5	Parity, maternal educational level, parental psychiatric diagnosis, child sex	No correlation has been found between PFAS levels in mothers or children and symptoms of ADHD
Johanna Inhyang Kim/2023/South Korea [72]	Prospective Cohort Study	*n* = 521	2, 4, and 8 years old	PFOA, PFNA, PFDA, PFUnDA, PFHxS, and PFOS	Serum/ HPLC–MS/MS	PFOA: 3.61 (1.91–6.72), PFNA: 0.99 (0.45–2.96), PFDA: 0.34 (0.12–0.94), PFUnDA: 0.45 (0.17–0.94), PFHxS: 1.01 (0.54–1.95), PFOS: 3.94 (1.80–7.47) (ng/mL	ADHD Rating Scale IV (ARS)	Mother's age during pregnancy, mother's educational attainment, father's educational background, socioeconomic conditions, maternal smoking during pregnancy, use of assisted reproductive technologies, maternal stress levels during pregnancy	PFAS exposure at age 2 was associated with ADHD development at age 8
Ann M Vuong/2021/ United States [61]	Cohort Study	*n* = 240	5 and 8 years old	PFOA, PFHxS, PDNA, and PFOS	Serum/ HPLC–MS/MS	PFOA: 5.3 (1.7), PFOS: 12.8 (1.7), PFHxS: 1.5 (0.8), PFNA: 0.90 (1.5), mean (SD) (ng/mL)	The Behavioral Assessment System for Children-2 (BASC-2) and the Diagnostic Interview Schedule for Children–Young Child (DISC-YC) were used to evaluate ADHD symptoms and diagnostic criteria	Maternal age, race/ethnicity, education, family income, ln-maternal serum cotinine (ng/mL), maternal depression, marital status, maternal IQ, parity, and child sex	PFOS and PFNA were consistently linked to hyperactive-impulsive ADHD traits across two validated assessment tools

Table 2. *Cont.*

First Author/ Year/Country	Design	Sample Size	Age of Children	PFAS	Sample/ Measuring Method	Exposure Measure	Test Type and Indicator	Adjustment of Covariates	Conclusion
Thea S. Skogheim/2021/ Norway [74]	Cohort Study	*n* = 821	3 years old	PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFHpS, and PFOS	Plasma/ LC–MS/MS	PFOA: 2.46 (3.46–2.86), PFNA: 0.42 (0.20–0.49), PFDA: 0.19 (0.15–0.23) (ng/mL)	Adult ADHD Self-Report Scale (ASRS screener)	Child sex, birth weight, and small for gestational age (SGA); maternal age at delivery, education, parity, pre-pregnancy body mass index (BMI, kg/m^2), self-reported smoking and alcohol intake during pregnancy, as well as FFQ-based estimates of seafood (g/day), and dietary iodine intake (µg/day)	Several PFAS (PFUnDA, PFDA, and PFOS) were inversely associated with odds of ADHD and/or ASD
Sachiko Itoh/2022/ Japan [75]	Prospective Cohort Study	*n* = 770	8 years old	PFHxS, PFOS, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, and PFTeDA	Plasma/ UHPLC–MS/MS	PFHxS: 0.32 (0.22–0.41), PFOS: 6.66 (4.92–8.31), PFOA: 2.48 (1.50–3.00), PFNA: 1.16 (0.79–1.38), PFDA: 0.53 (0.34–0.62), PFUnDA: 1.37 (0.73–1.73), PFDoDA: 0.18 (0.12–0.23), PFTrDA: 0.35 (0.24–0.44) (ng/mL)	ADHD Rating Scale (ADHD-RS)	Age of the mother at delivery, number of previous pregnancies, level of education, body mass index before pregnancy, alcohol consumption during pregnancy, smoking habits during pregnancy, and the sex of the child	Higher the maternal PFAS levels, lower the risk of ADHD symptoms at 8 y of age
Ilona Quaak/2016/The Netherlands [76]	Cohort Study	*n* = 76	18 months	PFOA, PFOS, PFHxS, PFHpS, PFNA, PFDA, and PFUnDA	Plasma/ LC–MS/MS	PFOA: 905.6 (437.1), PFOS: 1583.6 (648.3), PFHxS: 140.0 (69.2), PFHpS: 35.6 (21.3), PFNA: 140.0 (61.8), PFDA: 52.2 (20.9), PFUnDA: 32.05 (11.9), Mean (SD) (ng/L)	Child Behavior Checklist 1.5–5 (CBCL)	Family history, educational level, smoking, alcohol use and illicit drug use during pregnancy	Prenatal exposure to PFAS showed no significant associations with ADHD scores
Thea S. Skogheim/2020/ Norway [66]	Cohort Study	*n* = 944	3.5 years old	PFHpS, PFOS, PFHxS, PFOA, PFDA, PFUnDA, and PFNA	Plasma/ LC–MS/MS	PFOA: 2.61 (1.77–3.21), PFNA: 0.45 (0.29–0.53), PFDA: 0.19 (0.10–0.23), PFUnDA: 0.25 (0.05–0.32), PFHxS: 0.79 (0.46–0.88), PFHpS: 0.16 (0.10–0.20), PFOS: 12.32 (8.77–14.84), (ng/mL)	The Preschool Age Psychiatric Assessment interview, Child Development Inventory and Stanford–Binet (5th revision)	Maternal age, maternal education, maternal fish intake, parity, maternal ADHD symptoms, child sex, premature birth, birth weight, maternal BMI, maternal smoking, maternal alcohol consumption, maternal anxiety/depression and maternal iodine intake	Consistent evidence was not found to link prenatal PFAS exposure with ADHD symptoms or cognitive impairments in preschool children around three and a half years old

Table 2. *Cont.*

First Author/ Year/Country	Design	Sample Size	Age of Children	PFAS	Sample/ Measuring Method	Exposure Measure	Test Type and Indicator	Adjustment of Covariates	Conclusion
Zeyan Liew/2015/ United States [73]	Cohort Study	n = 220	Average 10.7 years old	PFOS, PFOA, PFHxS, PFHpS, PFNA, and PFDA	Plasma/ LC–MS/MS	PFOS: 26.80 (19.20, 35.00), PFOA: 4.06 (3.08, 5.50), PFHxS: 0.84 (0.61, 1.15), PFHpS: 0.30 (0.20, 0.40), PFNA: 0.42 (0.34, 0.52), PFDA: 0.15 (0.11, 0.20), (ng/mL)	ICD-10 codes F90.0	Maternal age at delivery, socioeconomic status, maternal smoking, alcohol drinking during pregnancy, mother's self-reported psychiatric illnesses, child's birth year, child's sex	Evidence does not consistently support a link between prenatal PFAS exposure and an increased risk of ADHD

Table 3. Summary of articles, results, and evidence on PFAS exposure to Autism Spectrum Disorder (ASD).

First Author/ Year/Country	Design	Sample Size	Age of Children	PFAS	Sample/ Measuring Method	Exposure Measure	Test Type and Indicator	Adjustment of Covariates	Conclusion
Thea S. Skogheim/2021/ Norway [74]	Cohort Study	n = 400	3 years old	PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFHpS, and PFOS	Plasma/ LC–MS/MS	PFOA: 2.46 (3.46–2.86), PFNA: 0.42 (0.20–0.49), PFDA: 0.19 (0.15–0.23) (ng/mL)	Diagnoses of "pervasive developmental disorders" were identified using ICD-10 codes F84.0, F84.1, F84.5, F84.8, or F84.9	Child's sex, birth weight, and status as small for gestational age (SGA); maternal age at delivery, education level, number of previous births, pre-pregnancy body mass index (BMI, kg/m^2), self-reported smoking and alcohol consumption during pregnancy, as well as estimates of seafood intake (g/day) and dietary iodine intake (µg/day) based on a food frequency questionnaire (FFQ).	An increased risk of Autism Spectrum Disorder (ASD) was observed in the second quartile of PFOA exposure [OR = 1.71 (95% CI: 1.20, 2.45)]. Conversely, PFUnDA, PFDA, and PFOS were associated with a reduced likelihood of ADHD, and the overall PFAS mixture showed a decreased risk of ASD [OR = 0.76 (95% CI: 0.64, 0.90)].

Table 3. *Cont.*

First Author/ Year/Country	Design	Sample Size	Age of Children	PFAS	Sample/ Measuring Method	Exposure Measure	Test Type and Indicator	Adjustment of Covariates	Conclusion
Jiwon Oh/2022/ United States [31]	Case–control Study	*n* = 551	2–5 years old	PFOS, PFHxS, PFNA, PFDA, PFPeA, PFUnDA, PFBS, PFHxA, MeFOSAA, and EtFOSAA	Serum/ HPLC–MS/MS	PFOA: 2.20 (0.91, 6.30), PFOS: 2.01 (0.81, 8.01), PFHxS: 0.59 (0.20, 3.05), PFNA: 0.71 (0.26, 2.49), PFDA: 0.14 (0.06, 0.49), PFPeA: 0.51 (0.20, 1.33), PFHpA: 0.23 (0.03, 1.00), PFUnDA: 0.03 (<LOD, 0.13), PFBS: <LOD (<LOD, 0.10), PFHxA: <LOD (<LOD, 0.43), MeFOSAA: 0.10 (<LOD, 1.56), EtFOSAA: <LOD (<LOD, 0.06) (ng/mL)	Mullen Scales of Early Learning (MSEL) and Vineland Adaptive Behavior Scales (VABS) are combined to generate an Early Learning Composite (Composite) score	Child's sex, age at sampling, recruitment regional center; sampling year; gestational age at delivery, maternal factors, parity, breastfeeding duration, race/ethnicity, and socioeconomic status.	PFOA was linked to higher odds of ASD, with an odds ratio (OR) of 1.99 per log ng/mL increase (95% CI: 1.20, 3.29). PFHpA also showed increased odds of ASD with an OR of 1.61 (95% CI: 1.21, 2.13). Conversely, perfluoroundecanoic acid (PFUnDA) was associated with lower odds of ASD, showing an OR of 0.43 (95% CI: 0.26, 0.69). Additionally, mixtures of PFAS were associated with increased odds of ASD, with an average OR of 1.57 and a range from the 5th to 95th percentile of 1.16 to 2.13.
Jiwon Oh/2021/ United States [77]	Cohort Study	*n* = 57	3 years old	PFOA, PFOS, PFHxS, PFNA, PFDA, PFUnDA, PFDoDA, MeFOSAA, and EtFOSAA	Serum/ Reverse-Phase LC–MS/MS	PFOA: 0.9 (0.3–2.3), PFOS: 3.0 (1.1–6.8), PFHxS 0.4 (0.2–1.6), PFNA 0.5 (0.2–1.0), PFDA 0.1 (<LOD −0.4), PFUnDA 0.1 (<LOD −0.3), PFDoDA: <LOD (<LOD −0.1), MeFOSAA: 0.1 (<LOD −0.8), EtFOSAA <LOD (<LOD-<LOD) (ng/mL)	Autism Diagnostic Observation Schedule (ADOS) and Mullen Scales of Early Learning (MSEL)	Child's sex, birth year, maternal vitamin intake in the first month of pregnancy, maternal education, and homeownership.	PFOA and PFNA were positively associated with ASD risk, with relative risks (RR) of 1.20 (95% CI: 0.90, 1.61) and 1.24 (95% CI: 0.91, 1.69), respectively, for each 2-fold increase in concentration. In contrast, PFHxS was negatively associated with ASD risk, showing an RR of 0.88 (95% CI: 0.77, 1.01).

Table 3. *Cont.*

First Author/ Year/Country	Design	Sample Size	Age of Children	PFAS	Sample/ Measuring Method	Exposure Measure	Test Type and Indicator	Adjustment of Covariates	Conclusion
Jeong Weon Choi/2024/ United States [78]	Cohort Study	*n* = 280	3 years old	PFHxS, PFOS, PFOA, PFNA, and PFDA	Serum/ Reverse-Phase LC–MS/MS	PFHxS: 0.45 (0.2–1.60), PFOS: 2.93 (1.10–7.00), PFOA: 0.87 (0.35–2.10), PFNA: 0.48 (0.20–1.00), PFDA 0.14 (<LOD −0.40) (ng/mL)	Autism Diagnostic Observation Schedule and Mullen Scales of Early Mullen Scales of Early Learning	Child sex, child age at assessment, year of birth, gestational age at delivery, maternal age at delivery, parity, maternal pre-pregnancy BMI, maternal race/ethnicity, maternal education, breastfeeding duration, homeownership, maternal smoking status during pregnancy, and child ASD outcome group.	PFOS, PFNA, and PFDA were associated with several behavioral problems among children diagnosed with ASD.
Hyeong-Moo Shin/2020/ United States [79]	Case–control Study	*n* = 239	2–5 years old	PFOA, PFOS, PFHxS, and PFNA	Plasma/ Reverse-Phase HPLC–MS/MS	PFOA: 1.07 (0.37–3.40), PFOS: 3.10 (1.08–10.03), PFHxS: 0.50 (0.20–1.63), PFNA: 0.50 (<LOD −1.23) (ng/mL)	Mullen Scales of Early Learning (MSEL), the Vineland Adaptive Behavior Scales (VABS), Autism Diagnostic Interview-Revised (ADI-R), Autism Diagnostic Observation Schedules-Generic (ADOS-G)	Age and sex of the child at the time of assessment, year of birth, regional center of recruitment, number of previous pregnancies, gestational age at birth, maternal race/ethnicity, place of maternal birth, mother's age at delivery, maternal BMI before pregnancy, vitamin intake around conception, duration of breastfeeding.	Increases in PFHxS and PFOS levels were tentatively connected to a higher risk of ASD diagnosis in children. For each nanogram per milliliter increase, PFHxS had an odds ratio of 1.46 (95% CI: 0.98, 2.18) and PFOS had an odds ratio of 1.03 (95% CI: 0.99, 1.08).
Kristen Lyall/2018/ United States [80]	Case–control Stude	*n* = 553	15–19 weeks gestational age	Et-PFOSA, Me-PFOSA, PFDeA, PFHxS, PFNA, PFOA, PFOS, PFOSA	Serum/ Negative-ion Turbo Ion Spray–tandem mass spectrometry	Et-PFOSA: 0.68 (0.63, 0.73), Me-PFOSA: 1.14 (1.07, 1.23), PFDeA: 0.17 (0.16, 0.18), PFHxS: 1.39 (1.29, 1.49), PFNA: 0.60 (0.57, 0.63), PFOA: 3.58 (3.41, 3.76), PFOS: 17.5 (16.8, 18.3), PFOSA: 0.11 (0.10, 0.11) (ng/mL)	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR) criteria	Child sex, month and year of birth, maternal age, country of maternal birth, maternal race/ethnicity, parity, and maternal education.	While most PFAS prenatal concentrations were not significantly linked to ASD, notable inverse associations were observed for perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS). Specifically, the adjusted odds ratios for the highest versus lowest quartiles were 0.62 (95% CI: 0.41, 0.93) for PFOA and 0.64 (95% CI: 0.43, 0.97) for PFOS.

4. Discussion

In this review, we systematically gathered the current available evidence on the effects of early development PFAS exposure with respect to the outcome of neurobehavioral defects in children. Our results indicated that there is a potential effect of PFAS exposure throughout development on the Intelligence Quotient, but the results are inconclusive. Furthermore, recent evidence (since 2022) highlights that PFAS exposure throughout gestation and early childhood has significant adverse effects on both ASD and ADHD. Although some studies have produced conflicting results, the latest research underscores the serious impact of PFAS on these neurodevelopmental disorders, emphasizing the importance of continued investigation to better understand these associations.

Within the past decade, researchers have considered PFAS exposure during gestation and childhood and its association with a variety of neurodevelopmental disorders. There are data supporting the plausibility of PFAS exposure as a risk factor on neurodevelopment through various routes of exposure. Initial exposure of PFAS begins with exposure of the developing fetus [81]. This is due to the ability for PFAS to cross the placenta barrier from a pregnant woman to her fetus [82–84]. PFAS has also been shown to expose developing children through breast milk [85–88]. These early exposure pathways have been positively associated with cardiovascular [89], immunologic [90,91], sexual maturation [92,93], thyroid function [94–96], kidney function [97,98], and neurodevelopment outcomes [99–101]. Neurodevelopmental Disorders are a class of disorders affecting brain development and function and are characterized by wide genetic and clinical variability [102]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), NDDs comprise of Autism Spectrum Disorder, attention-deficit/hyperactivity disorder, and intellectual disabilities [103].

Environmental chemicals and toxins have been correlated with a higher risk of neurodevelopmental impairments [104]. Epidemiological research supports these conclusions by documenting higher rates of birth defects, developmental disabilities, and reduced IQ levels in areas where mothers and children are exposed to various environmental pollutants [105]. The Intelligence Quotient (IQ) is a measure of the progress an individual had made in mental or cognitive development compared to same-aged peers [106]. For groups with neurodevelopmental disorders, mean IQ scores are generally below the population normative mean [107]. The Intelligence Quotient was utilized to assess generalized intellectual disabilities to PFAS exposure. Studies using the Wechsler Preschool and Primary scales of Intelligence (WPPSI) and the Full-Scale Intelligence Quotient (FSIQ) showed conflicting results on early PFAS exposure to intelligence disabilities. Some studies indicated that there was no association between PFAS and inhibition of IQ [11,62,63,66,69]. However, other studies found associations with multiple PFAS and their adverse effects on intelligence [59,60,64,65,67]. There were a few confounding variables that adjusted the association. Goodman et al., 2023 noted that there was a significant association difference between the sex of the child with intellectual deficiencies and that this could be due to sex-specific effect by one or more mechanisms. This suggests that sex could act as an effect modifier rather than just a confounder. While some studies controlled for sex, they may have missed important variations by not examining how sex modifies the association between PFAS exposure and neurodevelopmental outcomes. Future studies should consider stratified analyses or interaction terms to better understand how sex influences these associations.

Attention-Deficit Hyperactivity Disorder (ADHD) is among the most prevalent neurodevelopmental disorders in children, marked by difficulties with attention, excessive activity, and impulsive behavior [108]. Various epidemiological studies have explored the link between early exposure to PFAS and the onset of ADHD during childhood [61,66,70–76]. Early studies did not find any associations between PFAS and ADHD, however more recent studies have discovered that there is a significant association. In 2022, there were significant changes within the DSM-5 for the diagnosis of ADHD to make the diagnosis more accurate [109]. It was previously presumed that any symptoms of inattention and/or

hyperactivity–impulsivity was secondary to ASD and not due to an additional ADHD diagnosis [110]. This could lead to misdiagnosis in ADHD diagnosis, potentially distorting the results of earlier studies on the link between PFAS and ADHD. However, newer research has found a relationship between PFAS exposure at age 2 and the risk of developing ADHD by age 8 [72].

Over the past two decades, the prevalence of Autism Spectrum Disorders has progressively increased [111]. Autism Spectrum Disorder (ASD), characterized by deficits in social communication and restricted, repetitive behaviors or interests, affects approximately 2.3% of 8-year-old children in the US [112]. Studies using the Mullen Scales of Early Learning (MSEL) determined that PFOA had the strongest association with risk of ASD with an odds ratio [OR] per ng/mL increase: 1.99 (95% confidence interval [CI]: 1.20–3.29) [31]. PFOS and PFHxS exhibited borderline associations with elevated risks of Autism Spectrum Disorder (ASD). Specifically, PFOS had an odds ratio of 1.46 (95% CI: 0.98–2.18), suggesting a potential increase in risk, while PFHxS had an odds ratio of 1.03 (95% CI: 0.99–1.08), indicating a similar, though less pronounced, association [79]. However, the remaining PFAS investigated did not show any significant relationship with ASD. The inability to determine association between some PFAS and ASD could be due to the inability to measure PFAS in biological samples over the limit of detection (LOD). Furthermore, evaluating co-occurring conditions in Autism Spectrum Disorder (ASD) is difficult due to the overlap of symptoms with other disorders, the risk of diagnostic overshadowing, and the often unclear presentation of symptoms. These factors make it challenging to accurately assess and differentiate additional conditions in individuals with ASD [113].

Previous studies have considered neurodevelopment as one of the most sensitive endpoints for PFAS exposure. The findings of this extensive review have found significant associations between early-life PFAS exposure and the prevalence neurodevelopmental disorders. Given there is a ubiquitous exposure to PFAS, investigating the association between early-life exposure and neurodevelopmental disorders provides valuable information in understanding PFAS toxicity. Furthermore, the increasing prevalence and improved diagnostic techniques for neurodevelopmental disorders makes it essential to understand the detrimental impacts of environmental pollutants on human health.

5. Conclusions

In this review, PFAS exposure through neurodevelopment was strongly associated with neurodevelopmental disorders, such as ADHD and ASD, and potentially an inhibitory effect on IQ. Importantly, these findings indicate that the ubiquitous exposure of PFAS throughout gestation and into early childhood development could lead to neurodevelopmental disorders. However, there are notable data gaps that need addressing. For instance, high limits of detection (LODs) may have hindered the identification of associations between PFAS and NDD. Developing more sensitive analytical methods for detecting PFAS in biological matrices could enable the identification of lower levels of PFAS and provide crucial data. Further investigation using larger prospective cohort studies with standardized diagnostic methods is essential to confirm these results and elucidate the relationships between PFAS structures and associated risks. Expanding research to fill these data gaps will offer valuable insights into the potential biological mechanisms underlying these adverse effects and guide future studies in this field.

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