



Effects of Early-life PFAS Exposure on Child Neurodevelopment: A Review of the Evidence and Research gaps

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Abstract

Purpose of Review Per- and polyfluoroalkyl substances (PFAS) are persistent chemicals with many modern applications, leading to widespread contamination and universal human exposure. PFAS exposure during early life is of particular concern, given susceptibility of the developing fetal and infant brain to toxic exposures. This review aims to synthesize current evidence, discuss methodological challenges, and highlight research gaps to guide future studies on the impact of PFAS on neurodevelopment.

Recent Findings Sixty-one studies in total were published from 2008 to March 2024, with 35 in the last five years. Findings primarily link early life PFAS exposure to reduced cognitive, motor, and language development in infancy and increased behavioral issues like hyperactivity in childhood. Large studies have shown mixed results concerning child cognition, executive function, autism, and ADHD, with some indicating no association or unexpected protective findings. Sex-specific associations have been observed, but not consistently. Most research has addressed low-level exposure, suggesting subtle but potentially significant population-wide neurodevelopmental effects. Recent research also highlights concerns about newer, alternative PFAS, suggesting they too might affect neurodevelopment.

Summary The effects of early-life PFAS exposure on neurodevelopment merit further study, particularly the cumulative effects of prenatal and postnatal exposures. Research has not fully explored sensitive subgroups or potential mitigating factors such as breastfeeding and nutrient intake, which will require larger, more diverse samples. Future directions include deeper study of PFAS mixtures, interactions with other neurotoxic environmental chemicals, and effects of newer PFAS types. There is also a need to focus on neuropsychological functioning in later childhood, using direct assessments for more reliable evaluations.

Keywords PFAS · Perfluoroalkyl · Neurodevelopment · Cognition · Neurobehavior · ADHD · Autism

Introduction

Per- and polyfluoroalkyl substances (PFAS) are synthetic chemicals used across various products and industries, including non-stick cookware, food packaging, water and stain repellent fabrics, fire-fighting foams, and semiconductor manufacturing. Distinguished by their carbon-fluorine

bonds, one of the strongest in chemistry, PFAS are extremely resistant to environmental and biological degradation. This durability combined with extensive and historically unregulated use has contributed to substantial environmental contamination worldwide and near-universal human exposure, mostly through contaminated drinking water and food.

Among the thousands of PFAS compounds, PFOA and PFOS have been the most extensively used and studied. Despite their phase out in the early 2000s, these PFAS as well as others that were not discontinued remain highly detectable across the global population due to their persistence and bio-accumulative capacity, earning them the nickname “forever chemicals”. The health implications of PFAS exposures in adults, including cancer, infertility, and diseases of the liver, kidney, and immune system, are well-documented [1]. Developmental effects, including evidence

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linking PFAS to birth defects, reduced birth weight, diminished immune response, and increased risk of cardiometabolic problems in childhood, are also well replicated [2]. Over recent years, concerns regarding potential impacts on neurodevelopmental outcomes has also grown.

Neurodevelopment is a complex process beginning in utero and lasting well into early adulthood. Rapid brain growth and differentiation in the prenatal and early postnatal periods are particularly sensitive to exogenous perturbations, including by environmental chemicals. During pregnancy, PFAS can cross the placenta with varying efficiency and are detectable in breastmilk, posing risks to the developing fetus and infant [3, 4]. The nascent blood brain barrier has greater permeability and lower capacity to metabolize chemicals, making it more sensitive to neurotoxic effects.

Experimental and epidemiological studies indicate multiple pathways through which PFAS could affect early neurodevelopment (reviewed in Cao & Ng 2021 [5]). Studies in adults suggest that PFAS can permeate the brain with varying efficiency, particularly longer chained species. High concentrations have been found in the brain stem, hippocampus, hypothalamus, pons/medulla and thalamus. PFAS impact neuron functioning and neuroendocrine signaling, disrupting calcium homeostasis, calcium-dependent signaling molecules, and dopamine and glutamate signaling. PFAS have also been implicated as endocrine-disrupting, specifically with respect to thyroid and steroid hormones. Prenatal PFAS exposure has been linked to alternately higher androgenic activity and estrogenic activity, depending on the child's sex and exposure dose [6, 7]. Both long and short chain PFAS also show potential to hamper normal thyroid hormone synthesis and signaling, with modification by maternal thyroid autoantibodies and fetal sex [8]. Studies also indicate that PFAS can adversely impact placental function through interactions with peroxisome proliferator-activated receptors (PPARs), nuclear receptors that regulate key pathways of normal placental development including placentation and oxidative and inflammatory responses [9].

Additionally, PFAS can alter transcription of genes during early development through epigenetic mechanisms, affecting genes related to growth, nervous system function, and metabolism [10]. This includes sex-specific methylation changes, with PFOS influencing methylation of genes important for nervous system development specifically in males [11]. Preliminary evidence also suggests that gene-environment interactions may modify susceptibility to PFAS, with some evidence suggesting genetic polymorphisms in genes related to xenobiotic metabolism, estrogen metabolism, and insulin regulation may influence response to PFAS exposure, impacting risk of cancer, diabetes, and neonatal thyroid hormone levels [12–14].

Building from concerns about these potential pathways of neurotoxicity and combined with increased longitudinal

follow-up of birth cohorts established in the 2000s, research on neurodevelopmental effects of PFAS has rapidly accelerated over the past decade. More cohorts exposed in utero have now reached ages when neurodevelopmental deficits can be observed and measured with neuropsychological testing. Despite the growth in literature, motivated by several compelling early studies reporting adverse associations with child attention and cognition [15–20], several recent meta-analyses and reviews have drawn attention to the inconsistent evidence for outcomes such as cognition, ADHD, and autism [2, 21, 22]. The heterogeneity of findings has been attributed to small sample sizes, variable exposure levels, and the variety of neurodevelopmental assessments in use.

The goal of this review is threefold. First, we aim to summarize the current state of evidence, updated with several recent studies and taking a broader scope of neurodevelopmental outcomes from infancy to adolescence. Second, we seek to identify gaps in our understanding of how prenatal and early postnatal exposures to PFAS may affect specific domains of neurodevelopment. Lastly, we explore methodological limitations and innovations, providing insights that may inform future research directions in this area. For example, complex mixture methods are increasingly being used to address the high correlation and/or shared action of co-exposures to multiple PFAS.

Methods

We conducted searches on PubMed and Google Scholar with the search terms (Per- and Polyfluorinated Alkyl Substances OR Perfluorinated Compounds OR PFAS) AND (neurodevelopment OR neuropsychological functioning OR executive functioning OR cognition OR neurobehavior OR hyperactivity OR ADHD OR autism). We included all full-text articles in English published or ahead of print prior to April 2024. We focused on studies with biomarker-based measures of PFAS exposure. References of all articles were reviewed to identify additional matching articles. Our search compiled 61 articles published between 2008 and 2024 across three continents: Asia, Europe, and North America (Fig. 1). Most studies of prenatal PFAS exposure implemented prospective cohort designs. Studies of postnatal exposure were fewer and included a mix of prospective and cross-sectional designs. The participants in these cohorts were born across several decades, with 33 studies focused on children born during peak use of PFOA and PFOS (1999–2003), 27 during the phase out period (2003–2010), and 23 during the replacement PFAS era (2010–2018). We summarize PFAS levels across these studies by both time, geography, and biospecimen assayed. Further, we structure our review of the evidence following a neurodevelopmental testing framework adapted from White et al. 2022 [23], characterizing

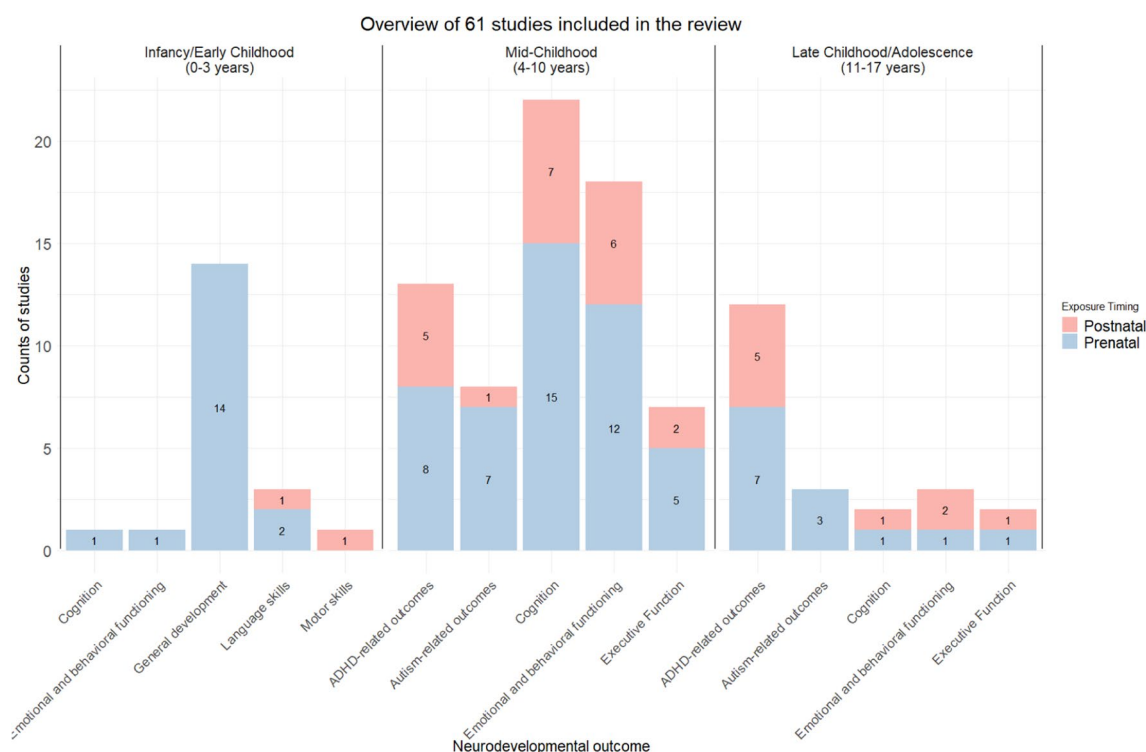


Fig. 1 Overview of studies included in the review

domain-specific results as well as omnibus or broader test results, but acknowledging that the neurodevelopmental domains targeted by psychometric testing often show overlap and are not mutually exclusive. For example, executive functioning is related but distinct from general cognition in that it represents higher-order cognitive processes that allow a person to regulate and organize cognitive skills of working memory, cognitive flexibility, and inhibitory control to set and achieve goals. These skills are also predictive of adaptive function, which is itself distinguished as the ability to manage and cope with demands of everyday life, often requiring social communication, conceptual skills, and practical behaviors for independent living and personal care.

Given that PFAS are hypothesized endocrine disruptors, impacting physiological systems that tend to be sexually dimorphic, we also evaluated evidence of sex-specific associations.

PFAS Exposures Across Studies

Most studies estimated prenatal PFAS using measurements in maternal blood, cord blood, or neonatal bloodspots (Fig. 2). Estimates of postnatal exposure mostly used child blood with some studies sampling breastmilk. PFAS exposures varied across cohorts by birth year, geography, and biospecimen. While blood concentrations of PFOS, PFOA, and PFHxS appear to have declined in North American and

European populations, they remain elevated in Asia, especially in mothers. Other legacy PFAS such as PFNA have increased over time with the highest contemporary exposures observed in both mothers and children from Asian cohorts.

Evidence Within Each of the Neurodevelopmental Domains

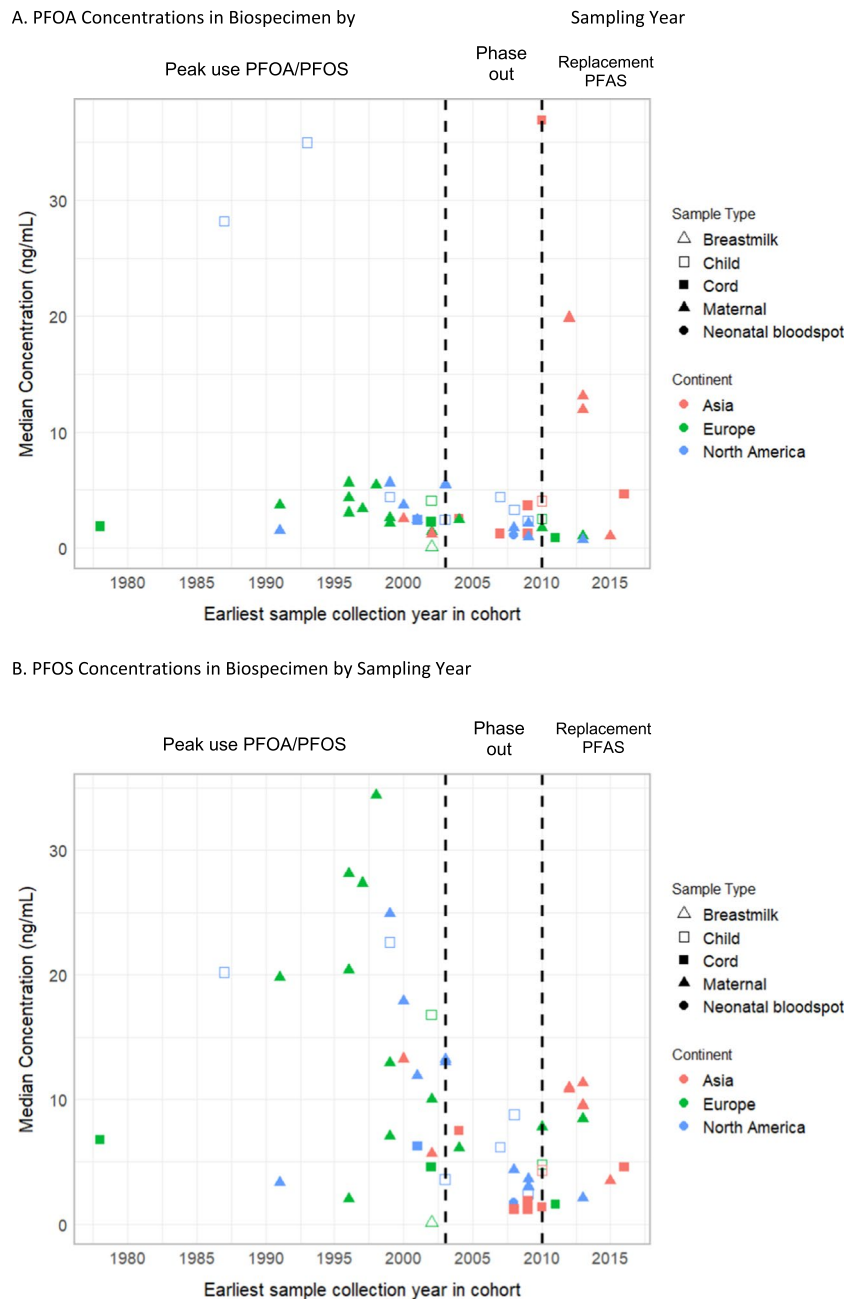
Early Developmental Milestones

Prenatal Exposure

We identified 17 studies from Asia, Europe, and North America investigating the impact of prenatal PFAS exposure on global scales of early development in infants and toddlers (children 3 and under) (Table 1). These studies utilized various assessment tools, described below. Overall, 13 of these reported adverse associations with early developmental milestones, 1 null association, and 4 positive associations, though most studies reported a mix of these across different PFAS. Seven studies examined PFAS using complex mixture approaches.

Bayley Scales of Infant and Toddler Development (BSID), Editions II and III The BSID is a task and observation-based

Fig. 2 Concentrations by sampling year, biospecimen type, and country for (A) PFOA, (B) PFOS, (C) PFHxS, and (D) PFNA



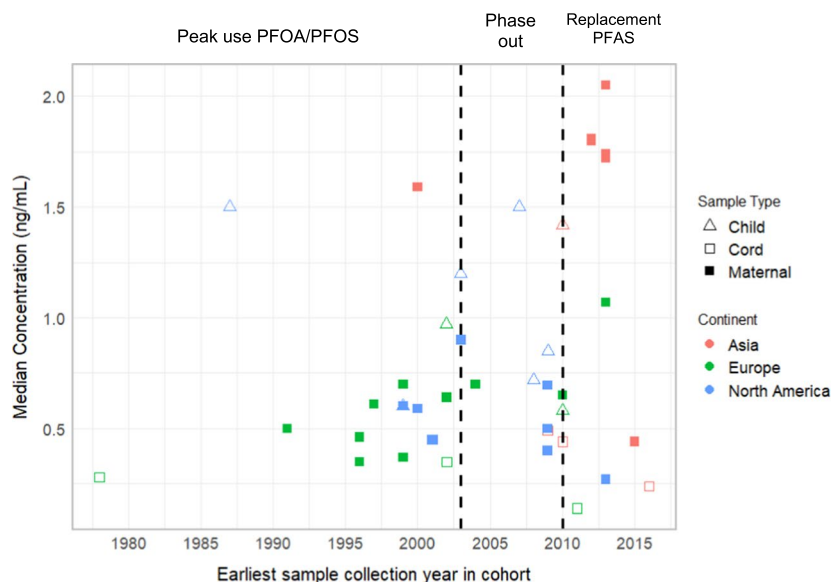
assessment administered by a trained professional that measures performance on five scales – Cognitive, language, motor, socio-emotional, adaptive behavior – to identify developmental delays. The largest study ($n = 2557$), from the Shanghai Birth Cohort, found adverse, monotonic associations between early pregnancy levels of PFOS, PFNA, PFDeA, and PFUnDA and cognitive scores; PFNA, PFDeA, PFUnDA PFHxS and language scores; and PFNA and PFUnDA and motor scores on at age 2 [24]. Conversely, PFOA, PFHxS, PFBS (an alternative PFAS), and PFDoA showed positive associations (e.g., improved function with higher levels) with cognition and adaptive behavior. In

mixture analyses using quantile G-computation, the overall PFAS mixture of 9 analytes was associated with poorer cognition, language, and motor scores. A study in Canada ($n = 490$), with lower background exposures, found adverse monotonic associations between PFHpA and PFDoA and cognitive composite scores; PFHpA and social-emotional composite scores; and non-monotonic associations between PFOS isomers and poorer language scores that were consistent in BKMR mixture analyses [25].

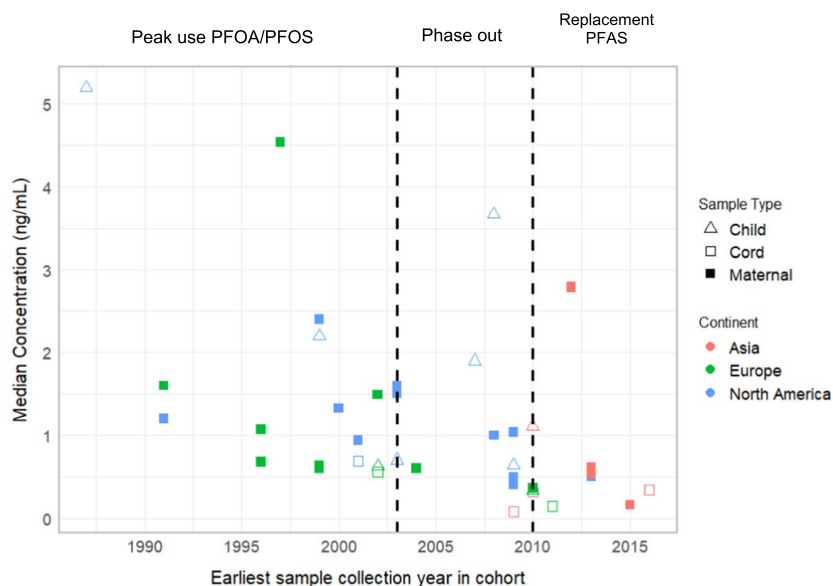
BSID-II The largest study ($n = 1240$) reported an inverse relationship between PFHxS and motor development in

Fig. 2 (continued)

C. PFNA Concentrations in Biospecimen by Sampling Year



D. PFHxS Concentrations in Biospecimen by Sampling Year



European children at 14 months [26]. In two smaller studies, PFOA and PFOS were not associated with outcomes at 18 months or earlier [27, 28]. However, PFOA and PFHxS were associated with better mental and psychomotor development at 2 and 3 years [28]. Mixture analysis with PCA supported the positive relationship between PFOA and PFHxS and psychomotor skills at these ages and suggested a negative relationship for PFNA.

Ages and Stages Questionnaire(ASQ) The ASQ is a developmental screening survey completed by the caregiver that assesses developmental delays in communication, gross

motor, fine motor, problem solving, and personal-social skills. Three Chinese birth cohorts examined the ASQ, finding somewhat consistent results. The largest ($n = 1285$), from Shanghai, found that long chain (PFOA, PFOS), short-chain (PFHxS), and alternative PFAS (6:2Cl-PFESA) were all associated with poorer communication scores at 6 months and PFHxS and 6:2Cl-PFESA were additionally associated with trajectories of low communication and gross motor skills between ages 2–24 months [29]. The second study also used repeated ASQ administrations between 3 and 36 months, finding that PFHxS was associated with persistently low trajectories for problem solving and communication;

Table 1. Summary of studies examining early developmental milestones (red denotes adverse association, green denotes beneficial association, blue denotes mix of adverse and beneficial associations, and no color denotes null association)

Author	Year	Sample size/ Population	Cohort name	Country	Birth years	PFAS exposure assessment	Neurodevelopmental outcome	Age at neuro assessment	Primary findings
Prenatal PFAS Exposure									
Beck et al	2023a	999	Odense cohort	Denmark	2010-2012	Prenatal	MacArthur Bates Communicative Development Inventories	18-36 months	No associations with PFAS.
Carrizosa et al	2021	1240	INMA	Spain	2004-2008	Prenatal	Bayley Scales of Infant and Toddler Development, 2 nd Edition (BSID-II)	14 months	Higher PFAS exposure was associated with worse motor development, especially in the case of PFHxS and to a lesser extent PFOS.
Chen et al	2013	239	Taiwan Birth Panel Study	Taiwan	2004-2005	Prenatal	Comprehensive Developmental Inventory for Infants and Toddlers	2 years	PFOS associated with poorer performance on overall test and the domains related to gross-motor development.
Donauer et al	2016	349	HOME	USA	2003-2006	Prenatal	NICU Network Neurobehavioral Scale (NNS)	5 weeks	PFOA associated with nearly 4-fold increase in being categorized as hypotonic vs. social/easy-going.
Enright et al	2023	326	Chemicals in Our Bodies (CIOB) and Illinois Kids Development Study (IKIDS)	USA	2013-present	Prenatal	visual recognition memory task using an infrared eye tracker	7.5 months	PFNA, PFOA, PFOS, PFHxS, PFDeA, and PFUdA associated with an increase in shift rate, reflecting better visual attention. Overall mixture association consistent in BKMR.
Fei et al	2008	1400	Danish National Birth Cohort	Denmark	1996-2002	Prenatal	Apgar and structured developmental milestones survey	6 and 18 months	No associations with Apgar. PFOS associated with slight delay in starting to sit without support.
Goudarzi et al	2016	133-173	Hokkaido Birth Cohort	Japan	2002-2005	Prenatal	Bayley Scales of Infant and Toddler Development, 2 nd Edition (BSID-II)	6 and 18 months	PFOA associated with lower MDI scores at 6 months in females only. No significant associations with PFOS.
Jeddy et al	2017	432	Avon Longitudinal Study of Parents and Children (ALSPAC) - girls only	UK	1991-1992	Prenatal	MacArthur Communicative Development Inventories for Infants and Toddlers	15 and 38 months	In daughters of younger mothers (< 25 years of age), PFOS was associated with lower vocabulary score at 15 months and lower language score at 38 months
Li et al	2023	718	Chinese Maoming Birth cohort	China	2015-2020	Prenatal	Ages and Stages Questionnaire (ASQ-3)	3, 6, 12, 18, 24, and 36 months	PFHxS, associated with persistently low ASQ trajectory for problem solving and communication. PFOS, PFUNDA, and PFDA associated with persistently low ASQ gross motor. PFoDA associated with low problem solving. Similar adverse findings in legacy but not alternative PFAS

Table 1. (continued)

									mixture using group-weighted WQS.
Luo et al	2022	2257	Shanghai Birth Cohort	China	2013 - 2016	Prenatal	Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III)	2 years	PFOS, PFNA, PFDeA, PFUnDA associated with lower cognitive scores; PFNA, PFDeA, PFUnDA PFHxS with lower language scores; and PFNA and PFUnDA with lower motor scores. Consistent findings with PFAS mixture using quantile-based G-Comp.
Niu et al	2019	533	Shanghai-Minhang Birth Cohort	China	2012	Prenatal	Ages and Stages Questionnaire (ASQ)	4 years	PFNA and PFDA associated with development problems in personal-social skills.
Oh et al	2022	598	Hamamatsu Birth Cohort	Japan	2007-2012	Prenatal	Mullen Scales of Early Learning (MSEL)	4-40 months	PFOA adversely associated with MSEL at 18 mo but PFOA and PFOS associated with improvement in scores between 4 and 40 months.
Reardon et al	2023	490	APRON study	Canada	2009-2012	Prenatal	Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III)	2 years	PFHpA, PFDoA associated with lower cognitive composite scores. PFHpA associated with lower social-emotional composite. Non-linear association with PFOS isomers and lower language scores. Findings consistent in BKMR.
Spratlen et al	2020	302	World Trade Center Cohort	USA	2001-2002	Prenatal	Bayley Scales of Infant and Toddler Development, 2nd Edition (BSID-II)	1, 2 and 3 years	PFOA, PFHxS, and a principal component mixture of PFAS associated with higher MDI at 2 and 3 years.
Yao et al	2022	274	Laizhou Wan Birth Cohort	China	2010 to 2013	Prenatal	Gesell Developmental Schedules	1 year	PFBS and PFHxS associated with poorer gross motor and adaptive scores.
Zhang et al	2023	716	Sheyang Mini Birth Cohort Study	China	2009-2010	Prenatal	Developmental Screen Test (DST) for Children; Gesell Developmental Schedules (GDS)	1,2, and 3 years	PFOA associated with lower Developmental quotient z-score. PFBS and PFHpA associated with higher odds of being in low score trajectory group. Results consistent in BKMR.
Zhou et al	2023	1285	Shanghai Maternal-Child Pairs (MCPC)	China	2016-2017	Prenatal	Ages and Stages Questionnaire (ASQ)	2, 6, 12, and 24 months	Most PFAS were associated with poorer scores in the communication domain, especially at 6 months of age. PFOS drove the mixture association in Quantile G-Comp.
Postnatal PFAS exposure									
Beck et al	2023a	999	Odense cohort	Denmark	2010-2012	Postnatal	Macarthur Bates Communicative Development Inventories	18-36 months	No association with language development.
Varsi et al	2022	114	Healthy women in Bergen OB-GYN clinic	Norway	Not specified	Postnatal	Alberta Infant Motor Scale (AIMS)	6 months	PFOA, PFNA, and sum of PFCA, PFSA and PFAS associated with poorer gross motor development

PFOS, PFUNDA, and PFDA with low trajectories of gross motor development; and PFoDA with low trajectories of problem solving [30]. These studies used different mixture approaches (quantile g-comp and group-based WQS, respectively) but found that legacy PFAS drove the mixture associations, with little contribution from alternative PFAS. The third study reported an association between PFNA and poorer personal-social development at age 4 [31].

Gesell Developmental Schedules (GDS) The GDS, still commonly used in China, is an observer and parent-reported checklist assessment of motor skills, social behavior, language development and adaptive behavior. Two Chinese birth cohorts used the GDS. The first study found decrements in gross motor skills associated with PFBS and PFHxS in cord blood [32]. PFBS was additionally associated with lower adaptive skills. In the second study, which took repeated measures of the GDS, PFOA was associated with poorer overall performance on the screener at age 1 and PFBS and PFHpA were associated with a low overall score trajectory between ages 2 and 3 [33].

Macarthur Bates Communicative Development Inventories (MBCDI) Two studies examined early language development with the MBCDI, a parent-reported instrument assessing early language, specifically vocabulary comprehension, language production, gestures, and grammar. One study among girls in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort found only PFOS to be consistently associated with lower vocabulary and language scores across infancy [34] while the other in the Odense Cohort (Denmark) found no association but did not present analyses stratified by sex [35].

Other Assessments Two studies, one in Taiwan and one in Denmark, found PFOS to be associated with poorer gross motor skills, using structured surveys of mental and motor developmental milestones in infants [36, 37]. One small Norwegian study ($n = 114$) specifically examined motor development in infancy, finding no association between prenatal PFAS and the Alberta Infant Motor Scale (AIMS) [38], an examiner-rated assessment of the infant or toddler's ability to complete a comprehensive battery of motor tasks in various positions. A Japanese study assessed cognitive outcomes with repeated administrations of the Mullen Scales of Early Learning (MSEL), a task-based measure of early cognitive functioning, including visual reception, fine and gross motor, receptive language, and expressive language scales, across 4 and 40 months. They reported generally longitudinal improvements in cognitive development with PFAS exposure [39]. However, at specific ages, they found that PFOA was associated with modest decreases in visual reception and receptive language scores at 10 months, lower

composite scores at 18 months, and greater fine motor scores at 4 and 24 months. PFOS, on the other hand, was linked to small increases in expressive language scores at 24 and 32 months. A US study, using eye-tracking technology to obtain an objective measure of infant visual memory at 7.5 months of age [40], found that PFNA, PFOA, PFOS, PFHxS, PFDeA, and PFUdA, both individually and in BKMR were associated with better visual attention. A second US study found PFOA to be associated with nearly a 4-fold increase in the likelihood of an infant being hypotonic at 5 weeks [41].

Postnatal Two Scandinavian studies examined PFAS levels in infant blood (Table 1). One found that infants with higher infant sum PFCA, PFSA and PFAS at 6 months had worse gross motor development [38]. The other found no cross-sectional association between PFAS and language development at 18–36 months [35].

Sex Differences Nine of these studies examined sex differences, reporting mixed results. Among girls compared to boys, two studies reported stronger associations between PFAS exposures and positive early neurodevelopment, including adaptive behavior and cognitive development [25, 28] while two others reported poorer personal-social skills [31] and cognitive scores [27]. Two studies reported adverse associations between PFAS exposures (biomarker-based and geographic proxy) with delayed language development in girls [34, 42]. Five studies reported adverse associations between PFAS and early development, including overall developmental z-scores, gross-motor skills, communication, and social and adaptive function, unique to boys [29, 31–33, 36]. One study saw no evidence of sex differences [26].

Summary Overall, most studies found adverse associations between early-life PFAS exposure and early developmental milestones, including poorer cognitive, language, motor, and socio-emotional outcomes. However, a variety of assessment tools were used and there was some variability based on the specific PFAS and mixtures examined.

Cognition

Prenatal Fifteen studies examined childhood cognitive functioning in relation to levels of PFAS in pregnancy or cord blood samples (Table 2). Most studies assessed outcomes when the children were between 5 and 8 years old. Overall, 4 of these reported adverse associations with cognition, 6 null associations, and 6 positive associations, though most studies reported a mix of these across different PFAS. Six studies examined mixtures of PFAS.

Table 2. Summary of studies examining cognition (red denotes adverse association, green denotes beneficial association, blue denotes mix of adverse and beneficial associations, and no color denotes null association)

Author	Year	Sample size/ Population	Cohort name	Country	Birth years	PFAS exposure assessment	Neurodevelopmental outcome	Age at neuro assessment	Primary findings
Prenatal									
Beck et al	2023b	967	Odense Child Cohort	Denmark	2010-2020	Prenatal	WISC-V	7 years	PFOS and PFNA concentrations associated with a lower FSIQ score. PFNA associated with lower Verbal Comprehension.
Carrizosa et al	2021	1240	INMA	Spain	2004-2008	Prenatal	Cognitive Index of the McCarthy Scales of Children's Abilities (MSCA) and N-back task (non-verbal working memory)	4-5, and 7 yrs	PFOS and PFNA had marginal positive association with cognitive development at 4-5 years.
Goodman et al	2023	522	MIREC	Canada	2008-2011	Prenatal	Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III)	3-4 years	PFOA, PFOS, and PFHxS adversely associated with performance IQ, among males only. Results consistent in mixture analysis using repeated-holdout WQS.
Harris et al	2018	631-971	Project Viva	USA	1999-2002	Prenatal	Peabody Picture Vocabulary Test (PPVT-III), Wide Range Assessment of Visual Motor Abilities (WRAVMA), Kaufman Brief Intelligence Test (KBIT-2), Visual Memory Index of the Wide Range Assessment of Memory and Learning (WRAML2)	7-8 years	PFAS associated with better visual motor abilities in early childhood and non-verbal IQ and visual memory in mid-childhood.
Kearns et al	2024	1097	HELIX	Europe	1999-2010	Prenatal	Raven's Coloured Progressive Matrices, Attention Network Test, N-back Test, and Trail Making Test	8 years	No association between joint exposure to PFAS and cognitive abilities using mixture approach quantile-based g-computation
Liew et al	2018	1592	Danish National Birth Cohort	Denmark	1996-2001	Prenatal	WPPSI-R	4 years	No association between PFAS and IQ
Spratlen et al	2020	302	World Trade Center Cohort	USA	2001-2002	Prenatal	WPPSI-R	Ages 4 and 6	No association between individual PFAS and PFAS PCA components and IQ
Stein et al	2013	320	C8 Cohort	USA	Late 90s/early 00s	Prenatal (estimated)	Wechsler Abbreviated Scale of Intelligence, Wechsler (WISC), Individual Achievement Test-II, NEPSY-II	3-4 years and 6-12 years	No association between PFAS and cognitive outcomes
Skogheim et al	2020	944	MoBA	Norway	2004-2008	Prenatal	Child Development Inventory (CDI) and Stanford Binet Intelligence scales (5th edition)	3.5 years	PFOA, PFNA, PFHxS, PFHpS and PFOS associated with poorer nonverbal working memory. PFOA, PFNA, PFDA and PFUnDA associated with better verbal working memory. No associations with language skills or IQ. Results consistent in mixture models using PFAS components from PCA.
Vuong et al	2018a	218	HOME	USA	2003-2006	Prenatal	Virtual Morris Water Maze (VMWM)	8 years	Higher prenatal PFHxS was associated with better performance on VMWM.

Table 2. (continued)

Vuong et al	2019	221	HOME	USA	2003-2006	Prenatal	WISC-IV	8 years	PFOA and PFNA associated with increases in working memory
Xie et al	2023	449	Shanghai-Minhang Birth Cohort	China	2012	Prenatal	WISC	6 years	No association between PFAS and WISC in single pollutant and BKMR models.
Wang et al	2023	2031	Shanghai Birth Cohort	China	2013-2016	Prenatal	WPPSI-IV	4 years	No association between PFAS and PFAS mixture and IQ in single-chemical and quantile g-comp models, respectively.
Wang et al	2015	120	Taiwan Maternal and Infant Cohort	Taiwan	2000-2001	Prenatal	WPPSI-R and WISC-III	5 and 8 years	PFUNDA adversely associated with PIQ at age 5. PFNA adversely association with VIQ at age 8.
Zhang et al	2018	167	HOME	USA	2003-2006	Prenatal	Woodcock-Johnson Tests of Achievement III and Wide Range Achievement Test	5 and 8 years	PFOA, PFOS and PFNA associated with better reading skills at ages 5 and 8 years
Postnatal									
Beck et al	2023b	967	Odense Child Cohort	Denmark	2010-2020	Postnatal	WISC-V	7 years	Most PFAS associated with a higher FSIQ and Verbal Comprehension scores. However, PFAS levels and breastfeeding duration highly correlated and could not be disentangled.
Harris et al	2018	631-971	Project Viva	USA	1999-2002	Postnatal	Peabody Picture Vocabulary Test (PPVT-III), Wide Range Assessment of Visual Motor Abilities (WRAVMA), Kaufman Brief Intelligence Test (KBIT-2), Visual Memory Index of the Wide Range Assessment of Memory and Learning (WRAML2)	7-8 years	PFHxS, PFOA, and PFOS adversely associated with visual motor scores.
Oh et al	2022	551 (case-control)	CHARGE	USA	2004-2015	Postnatal	Mullen Scales of Early Learning (MSEL)	2-5 years	PFOA and PFPeA adversely associated with MSEL scores. PFAS mixture using repeated holdout WQS also associated with lower MSEL scores, driven by PFHpA, PFPeA, and PFOA.
Stein et al	2013	320	C8 Cohort	USA	Late 90s/early 00s	Postnatal	Wechsler Abbreviated Scale of Intelligence, Wechsler Individual Achievement Test-II, NEPSY-II	3-4 years and 6-12 years	Highest quartile of PFOA associated with higher IQ.
Vuong et al	2018a	218	HOME	USA	2003-2006	Postnatal	Virtual Morris Water Maze (VMWM)	8 years	PFNA at 3 years was associated with longer (poorer) VMWM completion times while PFHxS at 8yrs associated with shorter times.
Vuong et al	2019	221	HOME	USA	2003-2006	Postnatal	WISC-IV	8 years	PFNA at 3 years associated with increases in FSIQ and perceptual reasoning
Zhang et al	2018	167	HOME	USA	2003-2006	Postnatal	Woodcock-Johnson Tests of Achievement III and Wide Range Achievement Test	5 and 8 years	PFOA, PFOS and PFNA associated with better reading skills at ages 5 and 8 years

Wechsler Preschool and Primary Scale of Intelligence (WPPSI)

The WPPSI is an administered, task-based test of cognitive development in children 2.5–7 years old that includes 5 subscales: verbal comprehension, visual spatial skills, fluid reasoning, working memory, and processing. Four studies, across Canada, the USA, Denmark, and China, found no associations between PFAS and the WPPSI administered during ages 3–6 [28, 43–45]. Two of these studies were relatively large ($n = 1591$ – 2031). A fifth study, in a small Taiwanese cohort ($n = 120$) found PFUNDA to be inversely associated with performance IQ at age 5 [20].

Wechsler Intelligence Scale for Children (WISC) Five studies collected the WISC, an administered test of general cognitive ability for children aged 6–16 years old which consists of 4–5 primary scales, depending on the version: verbal comprehension, visual spatial, working memory, fluid reasoning, and processing speed. The largest study, from Denmark ($n = 967$), found PFOS and PFNA to be associated with lower full scale IQ and PFNA to be associated with lower verbal comprehension scores [46]. A small study in Taiwan ($n = 120$), found similar findings, with nearly all PFAS examined being associated with lower cognitive scores, though only PFNA was statistically significant [20]. Two studies in the US reported better cognitive scores among children with higher exposures to PFOA and PFNA [47, 48]. However, the second largest study, in China ($n = 449$), reported no association with PFAS [49].

Other Assessments Across diverse neurocognitive assessments, studies found both positive and complex associations with PFAS exposure. The European INMA cohort reported slight positive associations on the McCarthy Scales of Children's Abilities (MSCA), an administered task-based test of general cognition comprised of subscales on verbal, perceptual-performance, quantitative, memory, and motor skills, among 4–5 year olds [26]. The US-based Project Viva Cohort reported associations between PFOA and MeFOSA with improved visual-motor skills on the administered Wide Range Assessment of Visual Motor Abilities (WRAVMA) and language improvements on the Peabody Picture Vocabulary Test (PPVT), respectively, at age 3 [50]. However, by age 8, PFOA, PFOS and PFHxS were non-linearly associated with lower visual motor abilities on the WRAVMA. In Denmark, several PFAS were associated with poorer nonverbal working memory but better verbal working memory on the Stanford Binet Scales [51], an administered intelligence test featuring scales of fluid reasoning, knowledge, quantitative reasoning, visual-spatial processing and working memory. The large European HELIX consortium ($n = 1097$) found no association between PFAS and cognitive performance on a comprehensive assessment battery in mid-childhood [52]. Lastly, the HOME study offers similarly mixed

findings. One study linked higher reading scores among 5 and 8 year olds to greater exposure to PFOA, PFOS, and PFNA [53]. However, PFNA was also found to be associated with poorer performance on the Virtual Morris Water Maze (VMWM), a computerized test of spatial learning and short-term memory, at age 3 while PFHxS was associated with improved performance at age 8 [54].

Postnatal Seven studies investigated relationships either prospectively or cross-sectionally between child PFAS levels and cognitive outcomes (Table 2), reporting conflicting results. One study implemented a complex mixture approach. Three studies found PFAS levels to be associated with higher IQ scores [46–48], though PFAS levels in early childhood are strongly correlated with breastfeeding duration (neuroprotective) [46]. In a cross-sectional study, PFOA, PFOS, and PFHxS were correlated with lower visual-motor scores but not IQ or visual memory [50]. In a California autism case-control sample, PFOA and PFPeA, as well as a WSQ index of the PFAS mixture, were associated with lower MSEL scores [55]. In the HOME study, PFOA, PFOS, and PFNA at age 3 were associated with lower reading skills at age 8. PFNA at age 3 was also associated with poorer performance on the VMWM while PFHxS at ages 3 and 8 were associated with better performance [54].

Sex Differences Most of these studies examined effect modification by child sex, with equivocal results. Four studies found no consistent differences by sex [26, 44, 45, 50]. Among boys, two studies observed prenatal PFOS exposure was associated with lower IQ scores on the WPPSI [28, 43] while others noted better cognitive performance between childhood PFOS, PFDA, PFOA, and PFHxS levels and MSEL scores [55], perceptual reasoning [45], mathematical skills [47], and visual spatial learning [54]. Among girls, poorer cognitive performance was noted between prenatal PFOA and childhood PFDA and MSEL scores and also between childhood PFOA and math skills. In Norway, associations between prenatal PFAS and better verbal working memory were observed among boys only [51]. One study noted a positive relationship between prenatal PFOA and verbal IQ among girls [28].

Summary Taken together, findings were mixed about the potential relationship between early-life PFAS exposure and cognition. Assessments using gold standard instruments such as the WPPSI and WISC did not show consistent patterns, though some studies highlighted potential sex differences and complex mixture associations with cognitive outcomes.

Table 3. Summary of studies examining executive functioning (red denotes adverse association, green denotes beneficial association, blue denotes mix of adverse and beneficial associations, and no color denotes null association)

Author	Year	Sample size/ Population	Cohort name	Country	Birth years	PFAS exposure assessment	Neurodevelopmental outcome	Age at neuro assessment	Primary findings
Prenatal									
Bach et al	2022	1593	Danish National Birth Cohort	Denmark	1996-2002	Prenatal	Test of Everyday Attention for Children at Five (TEAch-5) and BRIEF	5 years	PFOSA associated with reduced selective attention. PFOA, PFHpS, PFHxS, PFOS, and PFOSA were associated with greater executive function difficulties, specifically with greater issues with meta-cognition
Goodman et al	2023	522	MIREC	Canada	2008-2011	Prenatal	BRIEF-P	3-4 years	No association with executive function in either single-pollutant or WQS mixture models.
Harris et al	2021	693-921	Project Viva	USA	1999-2002	Prenatal	Parent and Teacher-rated Behavior Rating Inventory of Executive Function (BRIEF)	6-10 years	No association with PFAS
Reimann et al	2024	92	Flemish Environment and Health Study (FLEHS)	Netherlands	2002-2004	Prenatal	Stroop test	15 years	No association with mean reaction time and PFAS mixture modeled with quantile g-comp
Vuong et al	2016	256	HOME	USA	2003-2006	Prenatal	Behavior Rating Inventory of Executive Function (BRIEF)	5 and 8 years	PFOS associated with poorer behavior regulation, metacognition, and global executive functioning
Yang et al	2024	1765	Shanghai Birth Cohort	China	2013-2016	Prenatal	Behavior Rating Inventory of Executive Function (BRIEF-P)	4 years	No association with BRIEF-P scores in single-chemical or BKMR mixture models.
Postnatal									
Harris et al	2021	693-921	Project Viva	USA	1999-2002	Postnatal	Parent and Teacher-rated Behavior Rating Inventory of Executive Function (BRIEF)	6-10 years	PFOS associated with greater executive function problems as assessed by parents, while PFHxS associated with greater problems as assessed by teachers
Stein et al	2014	321	C8 Health Study	USA	Late 90s/early 00s	Postnatal	Parent and Teacher-rated Behavior Rating Inventory of Executive Function (BRIEF)	3-4 and 6-12 years	No consistent associations between PFAS and BRIEF scores

Executive Functioning

Prenatal We found six studies that examined prenatal PFAS exposure in relation to executive functioning in childhood (Table 3). Two of these reported adverse associations and

four null associations. Three studies examined mixtures of PFAS.

Behaviour Rating Inventory of Executive Function (BRIEF) Five studies collected the BRIEF, a survey instrument of executive function and self-regulation completed

by mothers, and occasionally by teachers. The largest study ($n = 1765$), in the Shanghai Birth Cohort, found no association between executive function scores at age 4 and PFAS exposure [56]. The next largest study, conducted in the National Danish Birth Cohort ($n = 1593$), observed an association between PFOA and poorer scores in parent-rated, but not pre-school teacher-rated, meta-cognition at age 5 [57]. Conversely, a study in the US reported poorer behavior regulation, metacognition, and global executive functioning at ages 5–8 in relation to prenatal PFOS but not PFOA [19]. Two studies, conducted in children aged 3–8, found null or no clear pattern of association between PFAS and executive functioning [43, 58].

Stroop Color and Word Test In a small sample ($n = 99$) of 15 year olds, a Flemish study did not find associations between PFAS and the Stroop test, which measures executive function in a scenario of quickly processing incongruent information (i.e., cognitive interference), i [59].

Postnatal Two studies investigated childhood exposures to PFAS and executive function cross-sectionally (Table 3). One study found no clear association [18] while the other found PFOS and PFhXS to be associated with greater executive function problems in parent-report and teacher-report, respectively [58].

Sex Differences Two US-based studies noted consistent sex differences. PFOS and PFOA were found to have adverse associations with parent-reported executive functioning among girls but not boys, in the HOME study and C8 Health Study, respectively [18, 19]. The four other studies did not see consistent patterns of sex differences [43, 56–58].

Summary Most studies, including large studies from China and Denmark, used the BRIEF and reported mixed results with respect to PFAS exposure. Sex differences were noted in some studies with adverse associations reported in girls for certain PFAS but overall the findings were inconsistent.

Motor Skills

Prenatal We found three studies that examined prenatal PFAS exposure and motor coordination in mid-childhood (Table 4). Two of these studies used the Developmental Coordination Disorder Questionnaire (DCDQ), a survey completed by the parent/caregiver about gross and fine motor skills in the child. Neither study found an association between PFOS and PFOA, the only two PFAS analyzed in both studies, and motor difficulties in children aged 5–9 years [15, 60]. The third study, which examined pregnancy exposures to a mixture of persistent pollutants, found an association between the overall mixture and reduced performance on the finger tapping test, a direct assessment of fine motor function and psychomotor speed [52]. PFAS, specifically PFOA, appeared to be a major contributor to the mixture effect.

Postnatal No studies examined postnatal PFAS exposure in relation to motor coordination in children.

Sex Differences Only the INUENDO study ($n = 1106$) investigated sex differences, finding no evidence of effect modification by child sex [15].

Table 4. Summary of studies examining motor skills (red denotes adverse association, green denotes beneficial association, blue denotes mix of adverse and beneficial associations, and no color denotes null association)

Author	Year	Sample size/ Population	Cohort name	Country	Birth years	PFAS exposure assessment	Neurodevelopmental outcome	Age at neuro assessment	Primary findings
Fei & Olsen et al	2011	526	Danish National Birth Cohort	Denmark	1998–2002	Prenatal	Developmental Coordination Disorder Questionnaire 2007 (DCDQ)	7 years	No association with motor difficulties
Hoyer et al	2015	1106	INUENDO	Greenland, Ukraine, Poland	2002–2004	Prenatal	Developmental Coordination Disorder Questionnaire 2007 (DCDQ)	5–9 years	No association with motor difficulties
Kearns et al	2024	1097	HELIX	Europe	1999–2010	Prenatal	Finger Tapping Test	8 years	A quartile increase in all the chemicals in the overall mixture was associated with worse fine motor function, with PFAS contributing strongly to the association. PFAS mixture using quantile-based g-computation associated with slower fine motor speed.

Table 5. Summary of studies examining emotional and behavioral functioning (red denotes adverse association, green denotes beneficial association, blue denotes mix of adverse and beneficial associations, and no color denotes null association)

Author	Year	Sample size/ Population	Cohort name	Country	Birth years	PFAS exposure assessment	Neurodevelopmental outcome	Age at neuro assessment	Primary findings
Prenatal									
Choi et al	2024	177	MARBLES	USA	2009-2015	Prenatal	CBCL 1.5-5	3 years	PFNA associated with more externalizing and aggressive behavior. PFNA and PFOS associated with sleep problems, particularly among children with atypical development. PFAS mixtures, modeled with WQS, showed similar associations, primarily driven by PFNA and PFDA.
Fei & Olsen et al	2011	787	Danish National Birth Cohort	Denmark	1998-2002	Prenatal	SDQ (parent)	7 years	No consistent associations with SDQ.
Ghassabian et al	2018	650	Upstate KIDS Study	USA	2008-2010	Prenatal	SDQ (parent)	7 years	PFOS associated with greater behavioral difficulties, especially conduct and emotional problems. PFOA associated with greater difficulties in prosocial behavior.
Harris et al	2021	713-933	Project Viva	USA	1999-2002	Prenatal	SDQ (parent and teacher)	6-10 years	No consistent associations with SDQ.
Hoyer et al	2015	1106	INUENDO	Greenland, Ukraine, Poland	2002-2004	Prenatal	SDQ (parent)	5-9 years	PFOA associated with greater hyperactivity symptoms.
Hoyer et al	2018	1023	INUENDO	Greenland, Ukraine, Poland	2002-2004	Prenatal	SDQ (parent)	5-9 years	PFHxS and PFNA associated with higher SDQ-total (more problem behaviour). PFNA and PFDA associated with greater hyperactivity symptoms.
Kornvig et al	2021	102	ACCEPT	Greenland	2013-2015	Prenatal	SDQ (parent)	3-5 years	No consistent associations with SDQ.
Oulhote et al	2016	539	Faroe Islands Cohort	Denmark	1997-2000	Prenatal	SDQ (parent)	7 years	No consistent associations with SDQ.
Quaak et al	2016	76	LINC cohort	Netherlands	2011-2013	Prenatal	Child Behavior Checklist 1.5-5 (CBCL)	18 months	No association with externalizing behaviors and ADHD subscales.
Skogheim et al	2020	944	MoBA	Norway	2004-2008	Prenatal	Preschool Age Psychiatric Assessment (PAPA) interview	3.5 years	No association with inattention, hyperactivity, and impulsivity symptoms. PFAS components

Summary One study reported adverse associations between PFAS and motor function. However, the literature is limited to only three studies, prenatal exposures, and a small subset of PFAS chemicals.

Emotional and Behavioral Functioning

Prenatal We found fourteen studies that examined prenatal PFAS exposure in relation to emotional and behavioral functioning in childhood (Table 5). Overall, seven of these reported adverse associations and seven null associations. Five studies examined PFAS using complex mixture approaches.

Strengths and Difficulties Questionnaire (SDQ) Eight studies, all but two in European samples, assessed behavior with the SDQ, a survey instrument completed by a caregiver or teacher to screen for problems with the child's emotional symptoms, conduct, hyperactivity/inattention, peer relationships, and prosocial behavior. Four of these studies, including two large studies in the INUENDO multi-country cohort ($n = 1106$), found associations between prenatal PFOA, PFNA, PFHxS, PFDA, and PFOS and total behavior problems [58, 61], child externalizing behaviors [58, 62], and hyperactivity [15, 61, 62] in either mid-childhood or early adolescence. Three other studies in mid-childhood participants, generally found no consistent associations [17, 60, 63]. The eighth study, which was based in the US and used

Table 5. (continued)

									from PCA not associated.
Tillaut et al	2023	444	PELAGIE	France	2002-2006	Prenatal	Strengths and Difficulties Questionnaire (SDQ), Dominic Interactive for Adolescents (DIA) (parent)	12 years	PFOA and PFNA associated with externalizing behaviors and hyperactivity. PFDA associated with greater depressive and internalizing symptoms. PFDA and PFNA associated with higher anxiety symptoms. No association with overall PFAS mixture in BKMR.
Vuong et al	2021	240	HOME	USA	2003-2006	Prenatal	Behavioral Assessment System for Children-2 (BASC-2)	5 and 8 years	PFOS, PFHxS, and PFNA associated with greater externalizing behaviors, including hyperactivity. PFHxS also associated with greater internalizing problems and somatization.
Xie et al	2022	614	Shanghai-Minhang Birth Cohort	China	2012	Prenatal	CBCL 1.5-5	2 and 4 years	No consistent associations with CBCL in BKMR models, though sex differences observed.
Xie et al	2023	449	Shanghai-Minhang Birth Cohort	China	2012	Prenatal	CBCL 6-18	6 years	PFDoA associated with more somatic complaints. PFOA associated with greater attention problems. Consistent results in BKMR models.
Postnatal									
Gump et al	2011	83	Oswego, NY	USA	Not specified	Postnatal	Differential Reinforcement of Low Rates of Responding (DRL) Task.	9-11 years	PFOS, PFNA, PFDA, PFHxS, and PFOSA were associated with greater impulsivity.
Harris et al	2021	713-933	Project Viva	USA	1999-2002	Postnatal	SDQ (parent and teacher)	6-10 years	PFOA, PFOS, PFHxS, PFNA, and PFDA associated with greater behavioral problems on parent-rated SDQ. No associations with teacher-rated SDQ scores.
Oh et al.	2022a	551 (case-control)	CHARGE	USA	2004-2015	Postnatal	Vineland Adaptive Behavior Scales (VABS)	2-5 years	PFPeA associated with lower adaptive functioning. PFAS mixture using repeated holdout WQS also associated with lower adaptive functioning, driven by PFHpA, PFPeA, and PFOA.
Oulhote et al	2016	491-508	Faroe Islands Cohort	Denmark	1997-2000	Postnatal	SDQ (parent)	7 years	PFOA, PFNA, and PFDA at 5 years was adversely associated with increases in total behavior problems, hyperactivity, peer relationships, conduct problems, internalizing and externalizing behaviors.
Stein et al	2014	321	C8 Health Study	USA	1993-2000	Postnatal	Mother- and teacher-reported Behavioral Assessment System for Children-2 (BASC-2)	3 to 4 years and 6-12 years	No consistent associations with Mother or Teacher BASC
Vuong et al	2021	208	HOME	USA	2003-2006	Postnatal	Behavioral Assessment System for Children-2 (BASC-2)	8 years	PFAS were not associated with Externalizing or Internalizing Problems.

neonatal blood spots as a proxy for prenatal exposure, found higher PFOS and PFOA levels were associated with greater problems with conduct, emotional regulation, and prosocial behavior at age 7 [64].

Child Behavior Checklist (CBCL) Findings were mixed among four studies that used the CBCL, a comprehensive survey completed by the caregiver about their child's behavior in the last six months. The CBCL has eight syndrome scales (e.g., somatic complaints, attention problems) and several DSM diagnostic subscales (e.g., ADHD, conduct problems). In two studies that assessed children ages 5 and younger, no associations between PFAS and behavioral problems were observed [65, 66], however one of these studies only analyzed the CBCL's externalizing behaviors and ADHD subscales [65]. In MARBLES, a cohort enriched with familial autism, PFNA and PFOS were associated with more externalizing and aggressive behavior, and sleep problems in 3 year-olds, particularly among participants with atypical neurodevelopment [67]. In the Shanghai birth cohort, which assessed outcomes at age 6, the oldest age among the CBCL studies, PFDoA and PFOA were associated, in single pollutant and BKMR models, with more somatic complaints and attention problems, respectively [49].

Other Assessments The HOME study, which used the *Behavior Assessment System for Children (BASC)*, a short rating scale of child behavior and emotion completed by the parent, found that PFOS, PFHxS, and PFNA were associated with greater behavioral problems, including externalizing behaviors and hyperactivity at age 8. PFHxS was additionally linked to internalizing problems and somatization [68]. The Norwegian MoBA study found no association between PFAS and inattention, hyperactivity, and impulsivity symptoms on the Pre-School Age Psychiatric Assessment [51], an interview-based structured diagnostic interview completed with the parent.

Postnatal Among six studies that assessed postnatal PFAS exposure, four found adverse associations and two found null associations (Table 5). Only one examined PFAS using mixture methods.

SDQ The largest study ($n = 628$) in the US found that PFOA, PFOS, PFHxS, PFNA and PFDA were cross-sectionally associated with internalizing and externalizing behaviors in mid-childhood [58]. This was consistent with another study finding PFOA, PFNA, and PFDA concentrations at age 5 to be associated with increases in total behavior problems and multiple subscales including hyperactivity, peer relationships, and internalizing and externalizing behaviors [17].

Vineland Adaptive Behavior Scale (VABS) The VABS is an interview-based assessment, typically administered to the caregiver to measure three major domains of adaptive functioning – communication, daily living skills, and socialization. PFPeA at ages 2–5 was cross-sectionally correlated with lower adaptive behavior in a case-control study of autism [55].

BASC In the HOME and C8 studies, childhood PFAS levels were generally not associated with behavior problems [18, 68], with the exception of PFNA which was found to be associated with poorer activities of daily living at 8 years old [68].

Other Assessments One study observed that PFOS, PFNA, PFDA, PFHxS, and PFOSA were associated with poorer impulse control at age 10 using a computerized differential reinforcement of low rates of responding (DRL) task [69].

Sex Differences These studies reported mixed findings with respect to sex differences. Several noted greater problems with behavioral and conduct problems, adaptive functioning, inattention among girls relative to boys [17, 18, 55, 68]. However, other studies saw more pronounced relationships with behavioral problems in boys [66–68] or no clear sex differences [15, 49, 58, 62, 64].

Summary The SDQ and CBCL were frequently used but showed inconsistent relationships with PFAS across studies: some studies linked prenatal and postnatal PFAS exposure to behavior problems like hyperactivity and conduct issues, while others found no consistent patterns. Notably, sex differences were observed, with some studies indicating greater behavioral problems in girls and others in boys.

Attention/ADHD

Prenatal We identified 11 studies that examined prenatal PFAS levels in relation to ADHD-related outcomes (Table 6). Two of these reported adverse associations, 6 null associations, and 3 positive associations, though many studies reported a mix of these across different PFAS. Two studies examined PFAS using complex mixture approaches.

ADHD Diagnosis Four studies found no association [70–73] and one reported inverted U-shaped relationships with PFOS and PFOA [74].

Connor Continuous Performance Test (CPT) Among four studies that administered the CPT, a computerized task measuring sustained and selective attention, two found no associations among 4–5 [26] and 8 year-olds [54]. Another found better performance among 3–4 and 6–12 year olds

Table 6. Summary of studies examining ADHD-related outcomes (red denotes adverse association, green denotes beneficial association, blue denotes mix of adverse and beneficial associations, and no color denotes null association)

Author	Year	Sample size/ Population	Cohort name	Country	Birth years	PFAS exposure assessment	Neurodevelopmental outcome	Age at neuro assessment	Primary findings
Prenatal									
Carrizosa et al	2021	1240	INMA	Spain	2004-2008	Prenatal	Prenatal -Conners' Kiddie Continuous Performance Test (K-CPT) and the Attention Network Test (ANT)	4-5 and 7 years	No association with attentional function.
Forns et al	2020	4,826	12 European birth cohorts	Six countries	1996-2008	Prenatal	ADHD diagnosis	4-11	No consistent evidence of association between PFAS and ADHD.
Liew et al	2015	220 cases, 550 controls	Danish National Birth Cohort	Denmark	1996-2002	Prenatal	ADHD diagnosis	9-15 years	No consistent evidence of association between PFAS and ADHD.
Ode et al	2014	206 cases, 206 controls	Malmö	Sweden	1978-2000	Prenatal	ADHD diagnosis	5-27 years	No consistent evidence of association between PFAS and ADHD.
Reimann et al	2024	99	Flemish Environment and Health Study (FLEHS)	Netherlands	2002-2004	Prenatal	CPT-II	15 years	PFAS mixture modeled with quantile g-comp, was associated with better sustained and selective attention during adolescence, primarily driven by PFHxS.
Skogheim et al	2021	821 cases, 980 controls	MoBA	Norway	2002-2009	Prenatal	ADHD diagnosis	10-17	Quartile 2 of PFOA associated with increased odds of ADHD. PFDA and PFUNDA inversely associated with odds of ADHD. Overall mixture, modeled with quantile g-comp, not associated with ADHD.
Stein et al	2013	320	C8 Health Study	USA	1993-2000	Prenatal	CPT-II	6-12 years	PFOA associated with decreases in symptoms of ADHD
Strom et al	2014	876	Danish Fetal Origins 1988 (DaFO88) Cohort	Denmark	1988-1989	Prenatal	ADHD diagnosis	22-23 years	PFOA and PFOS not associated with ADHD
Vuong et al	2018	218	HOME	USA	2003-2006	Prenatal	CPT-II	8 years	No association with attentional function.
Vuong et al	2021	190	HOME	USA	2003-2006	Prenatal	Diagnostic Interview Schedule for Children-Young Child (DISC-YC)	5 years	PFOS and PFNA were significantly associated with greater DISC-YC symptoms and diagnostic criteria related to hyperactive-impulsive type ADHD. PFNA was associated with increased risk of any-type ADHD.
Postnatal									
Hoffman et al	2010	571	NHANES	USA	1984-1992	Postnatal	ADHD diagnosis	12-15 years	PFOS, PFOA, and PFHxS associated with higher odds of ADHD
Kim et al	2023	521	Environment and Development of Children (EDC) Study	South Korea	2008-2010	Postnatal	ADHD Rating Scale IV (ARS)	8 years	All six PFAS at age 2 exhibited inverted U-shaped curves with ADHD symptoms. No association with age 4 levels. Similar relationship observed with overall PFAS

Table 6. (continued)

									mixture modeled by quantile g-comp.
Lenters et al	2019	1199	HUMIS Study	Norway	2002-2009	Postnatal	ADHD diagnosis	~13 years	PFOS associated with increased odds of ADHD in multipollutant models using elastic net penalized logistic regression to account for co-exposure confounding.
Stein & Savitz et al	2011	10,546	C8 Health Study	USA	1987-2001	Postnatal	ADHD diagnosis	5-18 years	Inverted J-shaped association between PFOA and ADHD. PFHxS associated with greater odds of ADHD plus medication.
Stein et al	2013	320	C8 Health Study	USA	1993-2000	Postnatal	CPT-II	6-12 years	PFOA associated with decreases in symptoms of ADHD
Stein et al	2014	321	C8 Health Study	USA	1993-2000	Postnatal	Conner's ADHD Diagnostic and Statistical Manual of Mental Disorders IV Scales (CADS)	3 to 4 years and 6-12 years	No consistent associations with Mother or Teacher CADS
Vuong et al	2018	218	HOME	USA	2003-2006	Postnatal	CPT-II	8 years	No association with attentional function.

with higher PFOA exposure, though the prenatal exposure was extrapolated from childhood serum levels [47]. The fourth found improved performance in relation to prenatal exposure to a mixture of PFAS and organochlorine compounds, mainly driven by prenatal exposure to PFHxS [59].

Diagnostic Interview Schedule for Children–Young Child (DISC-YC) The DISC-YC is a structured diagnostic interview administered to the caregiver. The HOME study found that prenatal exposure to PFOS and PFNA correlated with increased risk of ADHD, including the hyperactive-impulsive subtype at 5 years [68].

Postnatal Among seven studies that examined postnatal PFAS levels in relation to ADHD-related outcomes, four found adverse associations, two null associations, and two positive associations. Two examined PFAS using mixture approaches.

ADHD Diagnosis Two studies found relationships between PFOS exposure and higher odds of ADHD [16, 75] and one found a positive association between PFHxS and medicated ADHD and a non-monotonic association with PFOA [76]. One of these studies, conducted in 12–15 years olds in NHANES, additionally found that PFOA and PFHxS were cross-sectionally associated with ADHD in 12–15 year olds [16].

CPT One study found better performance on the task with higher PFOA among 6–12 year olds [47] while the other found no association in 8 year olds [54].

Other Assessments Two studies used parent and/or teacher-reported rating scales of ADHD-like behaviors. The C8 cohort found no association [18] while the other, in a Korean sample, found inverted U-shaped relationships with levels of 6 PFAS in blood at 2 years but not at 4 years [77].

Sex Differences Evidence of sex differences varied across studies. Four found PFAS exposure was associated with greater ADHD/attention problems in girls [18, 54, 72, 75] and either fewer symptoms or no associations in boys. In Denmark, PFAS were associated with greater ADHD in boys but the number of girls with ADHD was small [70]. Five studies did not find a clear pattern of sex differences [26, 47, 68, 74, 77].

Summary Studies of PFAS and ADHD-related outcomes have yielded equivocal results: some found no associations, while others indicated both improved and worsened performance linked to different PFAS. Postnatal studies similarly showed a range of effects, with some reporting increased ADHD risk and others finding no significant associations. Sex differences were noted, with several studies indicating greater ADHD-related issues in girls, though results varied across studies.

Autism and Other Developmental Disabilities

Prenatal We identified seven studies that examined prenatal PFAS levels in relation to autism-related outcomes (Table 7). Four of these reported adverse associations, 2 null associations, and 4 positive associations, though some

Table 7. Summary of studies examining autism-related outcomes and other developmental disorders (red denotes adverse association, green denotes beneficial association, blue denotes mix of adverse and beneficial associations, and no color denotes null association)

Author	Year	Sample size/ Population	Cohort name	Country	Birth years	PFAS exposure assessment	Neurodevelopmental outcome	Age at neuro assessment	Primary findings
Prenatal									
Ames et al	2023	1429	NIH ECHO	USA	1991-2018	Prenatal	Social Responsiveness Scale and ASD diagnosis	2.5-17 years	Individual PFAS, nor their mixture, not associated with SRS scores although suggestive association with PFNA and greater autistic traits. PFAS not associated with SRS in mixture models using Bayesian Shared Means and Bayesian Weighted Sums.
Braun et al	2014	175	HOME	USA	2003-2006	Prenatal	Social Responsiveness Scale	4-5 years	PFOA associated with fewer autistic behaviors, in semi-Bayesian hierarchical regression mixture model model.
Liew et al	2015	990	Danish National Birth Cohort	Denmark	1996-2002	Prenatal	ASD diagnosis	9-15 years	No consistent evidence of association between PFAS and ASD.
Liew et al	2014	156 cases, 550 controls	Danish National Birth Cohort	Denmark	1996-2002	Prenatal	Cerebral palsy diagnosis	8-14 years	PFOS and PFOA associated with higher risk of CP in boys but not girls.
Lyall et al	2018	553 cases, 433 controls	Early Marker for Autism (EMA)	USA	2000-2003	Prenatal	ASD and ID diagnosis	4.5-9 years	Most PFAS not associated with ASD or ID, though significant inverse associations were found for PFOA and PFOS
Oh et al	2021	173	MARBLES	USA	2009-2015	Prenatal	ASD diagnosis	3 years	PFOA and PFNA associated with increased risk of ASD. PFHxS associated with lower risk. Primary PC from PFAS PCA also associated with increased risk of ASD.
Shin et al	2020	453	CHARGE	USA	2004-2013	Prenatal	ASD diagnosis	4 years	PFHxS and PFOS marginally associated with increased odds of ASD
Skogheim et al	2021	400 cases, 980 controls	MoBA	Norway	2002-2009	Prenatal	ASD diagnosis	10-17	Quartile 1 of PFOA associated with increased odds of ASD. PFDA, PFUNDA, and PFOS inversely associated with odds of ADHD. Overall, carboxylate, and sulfonate mixtures, modeled with quantile g-comp, were inversely associated with ASD.
Postnatal									
Oh et al	2022a	551	CHARGE	USA	2004-2013	Postnatal	ASD diagnosis	2-5 years	PFOA associated with greater ASD and DD, PFHpA associated with greater ASD. PFUNDA associated with lower odds of ASD. WQS index associated with greater ASD (PFHpA, PFPeA, and PFOA were main contributors).

studies reported a mix of these across different PFAS. Four studies examined PFAS using complex mixture approaches. One study focused on cerebral palsy (CP) and only reported results from sex-stratified analyses [78].

Autism Diagnosis In the US-based Early Markers for Autism study ($n=553$ cases, 433 controls), PFAS were not associated with increased odds of diagnosis, though inverse associations were noted for PFOA and PFOS [79]. The two other largest studies come from Scandinavian registry cohorts. In the Norwegian Mother, Father and Child Cohort Study ($n=400$ cases, 980 controls), PFOA showed an inverted U-shape relationship with autism spectrum disorder (ASD) diagnosis while other PFAS analytes and mixtures of carboxylate and sulfonate PFAS mixtures showed an inverse relationship [74]. Findings in the Danish National Birth Cohort ($n=220$ cases, 550 controls), in contrast, were null [70]. Two smaller studies in California, the first in an autism case-control sample and the second, enriched for familial autism risk, also presented mixed findings with respect to diagnosis. Shin et al. (2020) [80] found that PFHxS and PFOS were associated with increased odds of ASD. In contrast, Oh et al. (2021) [81], studying younger siblings of autistic individuals, reported that PFOA and PFNA, were linked to higher odds of ASD, while PFHxS was associated with lower odds. Lastly, PFAS were not associated with diagnosis in the NIH ECHO cohort, though there were few autism cases in this general population sample.

Social Responsiveness Scale (SRS) The SRS is a survey instrument completed by the caregiver that measures mild to severe problems in social communication and repetitive and restrictive behaviors associated with autism. The largest study ($n=1224$) to examine PFAS in relation to the SRS, in the NIH Environmental influences on Child Health Outcomes (ECHO) cohort, reported a small increase in autistic traits associated with PFNA but not other PFAS in a pooled sample of children across early- and mid-childhood [82]. This finding conflicts with a smaller US study in 4–5 years olds which reported fewer autistic traits associated with PFOA exposure in a multipollutant mixture model [83].

Postnatal To-date, only one study has examined postnatal exposures with respect to autism (Table 7). This case-control study found that, cross-sectionally, PFOA was associated with a higher likelihood of autism and developmental delay. PFHpA was additionally associated with higher odds of ASD and PFUNDA with lower odds. WQS further supported increased odds of autism driven mostly by PFOA, PFHpA, and PFPeA [55].

Sex Differences Patterns of sex differences have been inconsistent across these studies. Several studies have found that

prenatal exposure to PFOS and PFOA is associated with increased autism-related outcomes in boys [70, 80, 83]. In contrast, three studies have linked either PFOS and PFHxS exposure to ASD or PFDA to DD among girls [55, 74, 82]. Additionally, two studies have found no clear sex differences in these outcomes [79, 81]. However, a Danish study found PFOA and PFOS to be strongly associated with likelihood of CP in boys but not girls [78].

Summary The evidence to-date has been inconsistent and does not support a clear link between early life PFAS exposure and autism. However, studies of postnatal PFAS exposures are limited.

Discussion

Summary of the Literature

In the last five years, 35 studies have been published on the topic of early life PFAS exposure and neurodevelopment. Taken together with 23 earlier studies, this literature continues to depict a mixed portrait of whether prenatal and childhood PFAS exposure negatively affect different domains of neurodevelopment. Multiple rigorous studies suggest that PFAS may reduce cognitive, motor, and language development in infancy and early childhood, worsen executive functioning in mid-childhood, and increase problem behaviors such as hyperactivity and inattention in mid-childhood and adolescence. Less consistent evidence has been observed for autism and cognition in mid-childhood. Restricting to the largest studies (1000+ participants), PFAS exposure has been linked to subtle delays in cognitive, motor, and language development in infancy and difficulties with executive function, cognition, motor skills, behavioral problems, ADHD, and autism in childhood [15, 24, 26, 29, 37, 50, 57, 58, 61, 74–76]. However, these findings must be considered in light of other studies that show conflicting evidence, including large studies that have reported null findings with respect to these neuropsychological domains [15, 35, 44, 45, 52, 56, 72, 82] or protective findings [26, 58], making it difficult to draw firm conclusions about the developmental neurotoxicity of PFAS in humans. Motor function in mid-childhood and neurodevelopmental endpoints during adolescence have received the least attention (Fig. 1).

Some studies observe clear sex differences in these associations, including cognitive decrements in males [43] and increased risk of ADHD and hyperactivity among girls [17, 65, 72] in association with PFAS exposure. However, many studies either did not examine sex differences or found no differences. Smaller studies (<300 individuals) were likely underpowered to reliably estimate differences by child sex. As both ADHD and ASD are more commonly diagnosed

in boys, the case-control studies of these conditions were especially prone to small samples of girls.

Most studies have focused on long chain, legacy PFAS such as PFOA and PFOS. Replacement, short chain PFAS have received less study, often because they tend to have lower concentrations that do not meet the detection criteria to be included in the main analyses. However, several recent studies are finding evidence that these varieties may also be linked to neurodevelopmental problems [25, 33] and that they may cross the placenta with greater efficiency than legacy PFAS [84]. Furthermore, most studies examined PFAS in the context of low, background-level exposure (Fig. 2). While the estimated neurodevelopmental effects were often subtle, small shifts in the population distribution of neuropsychological functioning can make a large impact on the tails of the distribution [85, 86].

The inconsistencies in the evidence—spanning different cohorts, study designs, neurodevelopmental domains, and countries—should be evaluated in light of several methodological considerations. First, exposure levels and the composition of PFAS exposures vary across cohorts, due to differing birth years, geographies, and the rise of replacement PFAS since the PFOA/PFOS phase-out (Fig. 2). Concentrations of PFOS, PFOA, and PFHxS have declined in North American and European populations, showing the success of efforts to discontinue production of these chemicals. However, they remain elevated in Asia. Other legacy PFAS such as PFNA have increased over time, with highest levels in Asian cohorts.

Second, the timing of the exposure assessment is also consequential. While many PFAS have a long half-life, blood concentrations do change across pregnancy. Changes in plasma volume and changes in placental permeability can contribute to fluctuations in a pregnant person's PFAS levels across the trimesters of pregnancy [87], which can lead to misclassification if the timing of blood collection varies across the sample. While most studies focused on prenatal exposures, a handful of studies considered postnatal exposures, measuring PFAS in breastmilk and child blood (Fig. 1). As the brain continues to undergo changes throughout childhood, with infancy and puberty representing potential periods of heightened sensitivity, postnatal exposures to PFAS are critical to consider. Due to smaller body sizes and more hand to mouth behaviors, children tend to have higher exposures to PFAS, depending on the specific PFAS and the local history of PFAS production and use [88]. However, blood samples can be challenging to collect from infants and children compared to the ease of collecting study blood samples from mothers during routine prenatal visits.

Third, the choice and timing of the neurodevelopmental assessment can also influence the stability of findings. For example, a recent meta-analysis found no systematic pattern between PFAS exposure and child language and

communication development. However, most studies have focused on general developmental assessments, underscoring the need for better outcome classification using instruments specifically designed for assessing language development or diagnosis of language disorders [89]. Additionally, while behaviors in infancy often persist to later childhood [90], some phenotypes may be less reliably measured in infants and young children, who may show less variability in their behaviors than older children. For example, skills of executive function may be more apparent and stable after age 5 [91]. Other phenotypes, such as ADHD and internalizing behaviors, may not emerge until school-age or later. In fact, most studies in this review focused on early childhood with tapering of studies after age 8 (Fig. 1), which could play into inconsistencies across results. Furthermore, direct assessments have been utilized less than survey instruments. Although informant responses are easier to collect and are unlikely influenced by knowledge of the exposure, they may not capture the full extent of a child's behavior as they age, making them less reliable than direct, objective assessments.

Lastly, several studies reported unexpected associations between PFAS and improved neurodevelopmental outcomes, which may have been due to confounding by exposure sources and other factors. Several of these studies used small samples (<200 participants), limiting the scope of their adjustment sets and potentially yielding less reliable estimates of association.

Gaps in the Literature

The picture of how early life PFAS exposure affects neurodevelopment remains complex and in need of further clarification. As children in these cohorts continue to age and exposures to both legacy and alternative forms of these chemicals persist, there are a number of knowledge gaps and new directions for future research to consider. First, few studies have examined how the combination of prenatal and postnatal PFAS exposures may jointly and cumulatively affect child neurodevelopment across multiple critical stages of brain growth and maturation. Further, the risk profiles of vulnerable or potentially more susceptible subgroups have not been fully examined, in part due to the limited sample size of extant studies and the over-representation of participants from higher socioeconomic backgrounds. However, several studies highlight that factors such as length of exclusive breastfeeding, educational enrichment of the home environment, parity, maternal education, and maternal and child diet (e.g., fish and nut intake) may mitigate against neurotoxic chemical exposures [35, 38, 43, 49, 72]. In addition to environmental risk factors, we know very little about how genetics or other factors of biological susceptibility may modify a person's metabolism or response to PFAS exposures.

Given that PFAS exposures tend to be highly correlated and may act on similar biological pathways, studies have increasingly implemented complex mixture methods to isolate the effects of specific compounds, identify the most toxic contributors in the mixture, or explore interactions and cumulative effects. However, given the complexity of mixtures, these approaches often require larger sample sizes to produce reliable estimates. More work is needed to not only understand how joint exposures to PFAS shape health, but also how PFAS may interact with other classes of chemicals, as has been explored with mercury and other persistent pollutants [25, 59]. With most previous studies focusing on legacy PFAS, there is great opportunity to expand research on replacement PFAS. These newer types, such as PFBS and GenX, tend to be less persistent than legacy PFAS but have been shown to have endocrine-disrupting and neurotoxic potential in experimental studies [92].

Lastly, our review highlights that later childhood neuropsychological functioning has received comparably less attention than the early childhood period. Given the ubiquity of PFAS exposures worldwide and the ongoing and significant brain changes children experience as they grow, the potential lingering influence of early life exposure to PFAS warrants additional study. Specifically, preliminary evidence suggests that domains of motor coordination and child social and behavioral functioning in adolescence merit continued attention with potential to extend these studies to neuropsychological health into adulthood.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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