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Behavioral outcomes and exposure to perfluoroalkyl substances among children aged 6–13 years: The TEDDY child study

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ABSTRACT

Background: Although some studies report that exposure to per- and polyfluoroalkyl substances (PFAS) during pregnancy and early life stages of a child could adversely impact neurodevelopment, literature shows mixed evidence.
Objectives: Using an ecological framework for human development, we assessed the association of risk factors for environmental PFAS exposure and childhood PFAS concentrations with behavioral difficulties among school-age children exposed to PFAS from birth, while also controlling for the important influence of the parenting and familial environment.
Methods: The study participants included 331 school-age children (6–13 years) born in a PFAS-contaminated area in the Veneto Region (Italy). We study the associations between environmental risk factors of maternal PFAS exposure (residential time, consumption of tap water, residence in Red zone A or B), and breastfeeding duration with parent assessments of children's behavioral problems (using the Strengths and Difficulties Questionnaire [SDQ]), adjusting for socio-demographic, parenting and familial variables. The direct relationships between serum blood PFAS concentrations and SDQ scores was evaluated in a subset of children ($n = 79$), both with single PFAS and weighted quantile sum (WQS) regressions.
Results: Poisson regression models reported positive associations between high consumption of tap water and externalizing SDQ scores (Incidence Rate Ratio [IRR]: 1.18; 95% confidence interval [CI]: 1.04–1.32) and total difficulty scores (IRR: 1.14; 95% CI: 1.02–1.26). Childhood perfluorooctane sulfonate (PFOS) and perfluorohexane sulfonate (PFHxS) were associated with higher internalizing SDQ scores (4th vs. 1st quartile, PFOS IRR: 1.54, 95% CI: 1.06–2.25), externalizing scores (4th vs. 1st quartile, PFHxS IRR: 1.59, 95% CI: 1.09–2.32), and total difficulty scores (4th vs. 1st quartile, PFOS IRR: 1.37, 95% CI: 1.05–1.71; PFHxS IRR: 1.54, 95% CI: 1.09–1.90). The WQS regressions confirmed the associations reported by single-PFAS analyses.
Conclusions: We observed cross-sectional associations of tap water consumption and childhood PFOS, and PFHxS concentrations with greater behavioral difficulties.

1. Introduction

Per- and poly-fluoroalkyl substances (PFAS) are a class of structurally diverse synthetic organic chemicals that are widely used to synthesize different kinds of products for daily use, such as non-stick cookware and water-repellents (Buck et al., 2011). Because PFAS are chemically stable, resistant to degradation, persistent in terrestrial and aquatic environments, and have a long elimination half-life, they are termed "forever chemicals" (Starnes et al., 2022).

The widespread presence of PFAS globally and their prolonged persistence in the human body (Li et al., 2019) have motivated researchers to study their effects on physical and psychological health. Recent epidemiological studies have shown an association between PFAS concentration and certain rare cancers (Steenland and Winquist, 2021), ulcerative colitis, pregnancy-induced hypertension, hypercholesterolemia, and liver diseases (Steenland et al., 2020). In addition, exposure to PFAS has been associated with preeclampsia (Savitz et al., 2012; Bommarito et al., 2021) and glucose tolerance during pregnancy

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(Preston et al., 2020).

Both in vitro and experimental studies on animals have reported a link between exposure to PFAS and neurotoxic outcomes (Cao and Ng, 2021). A single mice neonatal exposure to perfluorohexane sulfonic acid (PFHxS) has been reported to alter spontaneous behavior and cognitive functioning in adult male and female mice. Such effects are both dose–response-dependent and long-lasting/irreversible (Viberg et al., 2013). Another in vitro experimental study has demonstrated that PFAS affect the development of neuronal cells and cognitive functioning (Slotkin et al., 2008).

The above-mentioned reports emphasize the potential neurotoxic effects of exposure to PFAS, largely on sensitive developmental windows and populations. Children's early stages of life are characterized by a plastic central nervous system that is extremely affected by the environment, including toxic substances. Moreover, because complete development occurs over a long period of time, it provides an extended window of vulnerability (Landrigan et al., 2018). Compared to adults, fetuses and children have a higher susceptibility to environmental pollutants, which is attributed to their greater absorption and slower clearance (Heyer and Meredith, 2017). The literature reports the identification of PFAS in the serum from the maternal cord and newborn blood, suggesting as these chemicals can penetrate the placenta potentially influencing fetal development. They are associated with a reduced body weight and head circumference of newborns (Apelberg et al., 2007). In addition, infants are exposed to these contaminants in the postnatal period through breast milk. Prolonged breastfeeding can decrease the serum concentration of PFAS in mothers (Girardi et al., 2022), simultaneously increasing such concentrations in their infants (Kim et al., 2020). Although certain observational studies have investigated the associations between PFAS exposure and children's psychological development, the findings are mostly mixed and often contradictory. A few researchers have highlighted the negative impact of these substances on attention, executive functions, and behaviors, whereas others have supported their protective effects on development (Rappazzo et al., 2017). Different designs (selection criteria, statistical methods, and domains of interest), target populations, and multiple PFAS concentrations make it challenging to compare findings.

Some cross-sectional studies with school-age children do not suggest adverse associations between PFAS exposure and neurodevelopmental or behavioral problems (Forns et al., 2020; Vuong et al., 2021). However, other studies strongly support a positive association between children's exposures to certain PFAS (primarily perfluorooctane sulfonate [PFOS], PFHxS and perfluorooctanoic acid [PFOA]) and impulsivity (Gump et al., 2011) as well as attention-deficit/hyperactivity disorder (ADHD) (Stein and Savitz, 2011). More recent studies have investigated the effect of exposure to these compounds during pregnancy and early childhood reporting similar consistent effects. Prenatal exposure to PFOS and PFOA exerted a small to moderate effect on neurobehavioral development in children, specifically in terms of hyperactive behavior (Høyer et al., 2015). Furthermore, data obtained on children's behavior with validated scales (i.e., Strengths and Difficulties Questionnaire [SDQ]) using maternal reports have demonstrated an association between prenatal exposure to PFHxS and behavioral problems (Harris et al., 2021). A link between exposure to two PFAS, perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA), and increased hyperactive behaviors (Høyer et al., 2018) has also been reported. Furthermore, positive associations between PFOA, PFNA, and PFDA and total behavioral difficulties have been reported by Oulhote et al. (2016). Additional confirming evidence was provided by Vuong et al. (2021) who reported consistent associations between prenatal exposure to PFOS and PFNA with ADHD-like symptoms and between prenatal PFHxS levels and externalizing and internalizing behavioral difficulties. Such associations were confirmed by studies based on objective data obtained by standardized tests and/or clinical diagnoses. That is, highly exposed 1–7 years old children living in Ronneby (Sweden) had an increased risk of language disorders (Stübner et al., 2023). A positive association between neurodevelopment and PFAS exposure was confirmed by cohort studies among infants and young children (Luo et al., 2022; Zhou et al., 2023). In addition, a recent meta-analysis provided an association between PFAS exposure and diagnosis of ADHD and autism spectrum disorder (ASD) (Yao et al., 2023). However, the epidemiologic literature linking PFAS exposures with neurodevelopmental outcomes is still not sufficiently conclusive, suggesting more research is required (Skogheim et al., 2021).

The present study focuses on the emotional and behavioral functioning of school-age children and their mothers living in a severely PFAS contaminated area (called "Red zone") of the Veneto Region (Northern Italy). Large-scale presence of PFAS in the groundwater was reported in 2013 and was attributed to a factory active since the late 1960s. Hence, residents were inadvertently exposed for decades to PFAS through contaminated tap water, resulting in high PFAS concentrations, mostly PFOA, in their blood (Pitter et al., 2020).

We collected data from a pilot study, known as the TEDDY-Child (Tracing the Environmental Determinants of the Development of Your Child), conducted at the University of Padua, and aimed at assessing the effects of PFAS exposure on children's emotional and behavioral functioning. We adopted a bio-psycho-social perspective and considered in our model the role played by environmental, individual, and biological factors, in affecting the development and behavior of children (Lehman et al., 2017). Developmental psychologists and health practitioners report that children's functioning and development are largely influenced by the continuous interactions between their individual characteristics and the socio-emotional and physical environment in which they are growing up (Borrell-Carrió et al., 2004; Ferguson et al., 2013). Socio-emotional characteristics of children's environment have been frequently underestimated and overlooked by studies assessing the effect of pollutants on their development. This is highly surprising considering their important function in directing developmental trajectories toward typical or atypical paths (Scrimin et al., 2018). According to Bronfenbrenner's "socioecological" framework (Bronfenbrenner, 1979), factors related to the family environment, and parental support and availability strongly impact a child's development. These factors interact with each other as risks or protective factors, increasing a child's vulnerability or resilience. Their effects are defined as the products of beneficial exchanges between the child and the environment (Masten and Cicchetti, 2016). For example, parental stress is frequently associated with dysfunctional parenting practices and a child's behavioral difficulties (Morgan et al., 2005), whereas a low level of maternal education is considered a risk factor and linked to low psychological, social, and emotional skills for coping with pregnancy and subsequent child-rearing practices (Wakschlag and Hans, 2000). Therefore, our investigation while aiming at investigating the effects of PFAS exposure considering proxy variables derived from maternal exposure and childhood PFAS measurements on child functioning, also controlled for familial and environmental confounders.

Based on these findings, we addressed two integrated research questions (RQs) in this study:

- RQ 1: Which physical maternal environmental factors and child characteristics predict the serum blood PFAS levels among school-age children?
- RQ 2: To what extent do physical maternal environmental factors related to PFAS exposure (or the current PFAS exposure) while controlling for other parenting and familial factors influence the presence of internalizing or externalizing behavioral difficulties in school-age children?

The theoretical simplified network of relationships for each RQ between outcome and other influencing variables is presented in Fig. 1 using a directed acyclic graph (DAG). We explored each research question among a subpopulation of school-age children living in a territory affected by severe PFAS contamination.

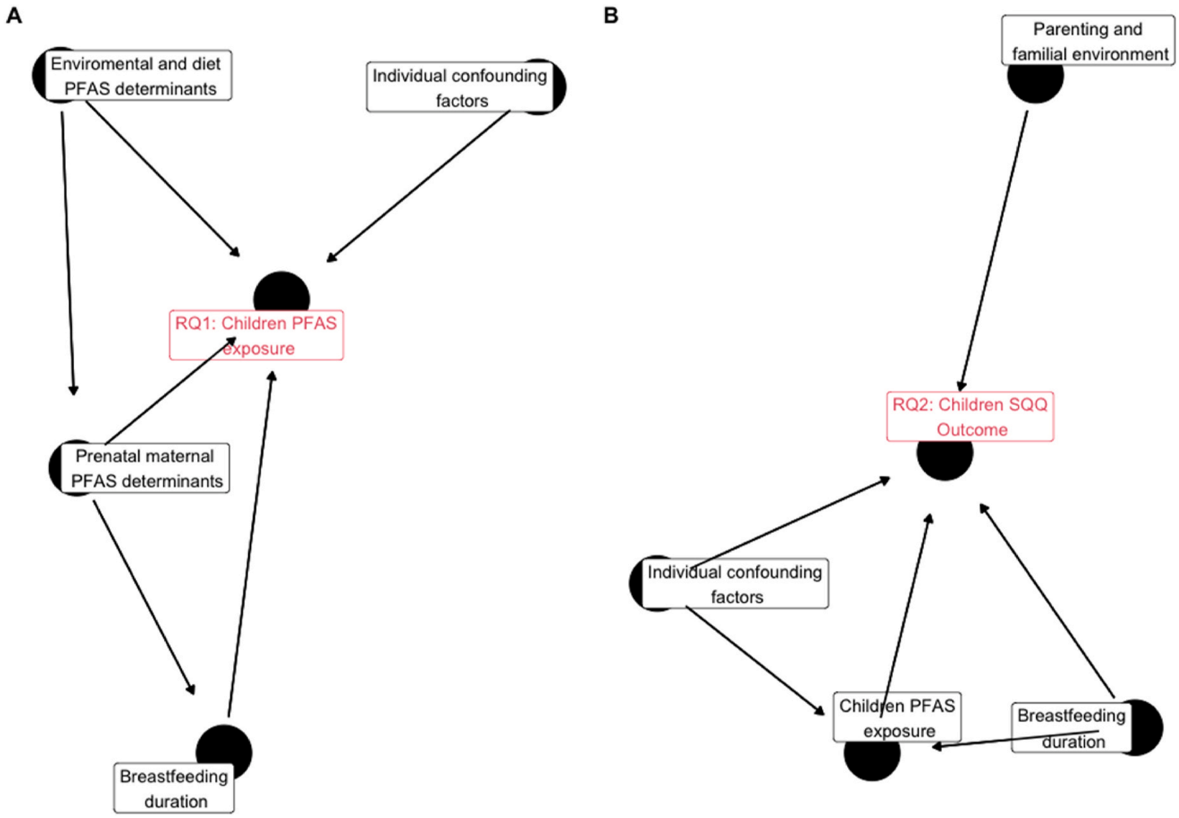

Fig. 1. DAG representation for determining the potential causal route between groups of analyzed variables for research questions 1 (A) and 2 (B).

2. Methods

2.1. Study population

Data were collected as part of the TEDDY-Child study conducted between March 2021 and June 2021 using a series of online surveys. The TEDDY-Child study investigated the effects of PFAS on the development of children in the Veneto Region (Italy). For further details, please refer to Girardi et al. (2022). In the present study, a subset of the original study dataset has been considered. The sub-set comprised children aged between 6 and 13 years and who were resident in the Red zone at the time of birth (Pitter et al., 2020). The recruitment was voluntary, and all participants provided informed consent. The study was approved by the Ethics Committee of the Department of Developmental Psychology and Socialization of the University of Padova, Italy (protocol ID 4051).

A total of 359 child–mother dyads met the inclusion criteria (residence in the Red zone and aged 6–13 years old). However, the sample size was reduced to 331 dyads to meet further selection criteria (see Table S1). In line with previous studies (Gump et al., 2011; Quaak et al., 2016; Lien et al., 2016), we excluded from the analysis adopted children, those with genetic diseases or with a certified disability, children with ASD, or with diagnosed preeclampsia during pregnancy. In addition, we did not include children with mothers born outside Europe; we kept only mothers who had lived in the Red zone for at least 1 year since birth to reduce the possible selection bias.

2.2. Children's blood PFAS measures

In January 2017, a free population-based screening program was offered by the regional health services to the residents of the Red zone. PFAS were quantified using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) (Prominence UFLC XR 20 [Shimadzu] coupled to an API 4000TM LC-MS/MS System [Sciex]) that included PFOS, PFOA, PFHxS, perfluorononanoic acid (PFNA), perfluoroheptanoic acid (PFHpA), perfluorobutanesulfonic acid (PFBS), perfluorohexanoic acid (PFHxA), perfluorobutanoic acid (PFBA), perfluoropentanoic acid (PFPeA), perfluorodecanoic acid (PFDeA), perfluoroundecanoic acid (PFUnA), and perfluorododecanoic acid (PFDoA). Additional information on the analytical method is published elsewhere (Pitter et al., 2020). Out of 331, we collected serum PFAS concentration from 79 children. The blood analysis was performed from 2018 to 2020. Three types of PFAS, namely PFOA, PFOS, and PFHxS, were considered for the subsequent analysis. Two measurements of PFHxS and one of PFOS were below the limit of quantification (LOQ) and were equal to 0.5 ng/ml, and a value of $0.5/\sqrt{2}$ was imputed. Childhood PFOA, PFOS, and PFHxS concentrations reported a skewed distribution, in particular for PFOS concentration (Figure S1). The correlation between PFHxS and PFOA was very high (Pearson correlation = 0.811).

2.3. Children's emotional and behavioral problems

Children's emotional and behavioral problems were measured using the Strengths and Difficulties Questionnaire (SDQ)-parent report (Goodman, 1997). The SDQ is a 25-item questionnaire that is used to measure children's hyperactivity, conduct problems, emotional problems, problems with peers, and prosocial behavior scored on a 3-point scale. A total difficulty score can be generated by the sum of scores from all the scales except the prosocial scale. Goodman, Lamping, and Ploubidis (Goodman et al., 2010) reported that theoretically and empirically, the SDQ's emotional and peer subscales can be combined into an 'internalizing' subscale, and the behavioral and hyperactivity subscales into an 'externalizing' subscale. Because we were interested in studying both internalizing and externalizing domains, we included both scales. In addition, we included an individual total difficulty score, which was computed as the sum of the other two. The summary of the reported SDQ scores is shown in Table 1.

The scoring values showed a skewed distribution (Figure S2) and were in line with those of a healthy children population (Tobia and Marzocchi, 2017). The externalizing and internalizing domains showed a medium correlation (Figure S2).

2.4. Socio-emotional environment

Socio-emotional environment was characterized by parental stress and sensitivity toward the child, parenting practices, and parental perceived social support. Three scales were used to assess the general socio-emotional environment experienced within the family.

Parenting Stress Index-Short Form (PSI-SF), one of the most widely used instruments to assess parenting stress in clinical and non-clinical families, was used to evaluate parenting stress. The mothers were asked to complete this questionnaire (Abidin, 1995), which includes 36 items. It is rated on a 5-point scale and distributed across three subscales, namely, parental stress, parent–child dysfunctional interactions, and the extent to which the parent considers the child to be "difficult." A final overall score is obtained by the sum of the three subscales. The PSI-SF has been validated on the Italian population with high reliability and construct validity. We used the total stress raw score as an indicator of the mother's overall experience of parenting stress.

The Alabama Parenting Questionnaire (APQ)-parent version (Frick, 1991) was used to study parenting practices. It is a 5-point Likert-type scale (1 = never to 5 = always) and consists of 35 items that assess five parenting constructs, namely, parental involvement, positive parenting, poor monitoring and supervision, inconsistent discipline, and parental use of corporal punishment. Because we were interested in investigating the emotional parent–child relation, we focused on inconsistent discipline and corporal punishment subscales. The APQ has been translated into Italian and has good psychometric properties.

Parental perceived social support was measured using the Multidimensional Scale of Perceived Social Support (MSPSS). Higher scores were indicative of higher perceived rates of social support. The scale has good psychometric characteristics, with adequate internal and test–retest reliability, strong factorial validity, and moderate construct validity (Zimet et al., 1988).

2.5. Descriptive statistical analysis

Variables are summarized in tables and figures (frequency for categorical variables, median and interquartile range [IQR] for continuous variables). Wilcoxon test was applied to compare the distribution of continuous variables by binary categorization of the total SDQ difficulty score according to the median value (7 points). The relationship between categorical variables was checked using chi-squared tests.

The relationships between research questions, influencing factors, and outcomes are shown using the DAG presented in Fig. 1. We applied the following statistical approaches to answer the proposed RQs:

1) RQ 1: We used a linear regression model to conduct an explorative analysis aimed at identifying factors influencing a childhood level of log-PFOA, log-PFOS, and log-PFHxS. We considered a log transformation of the PFAS concentrations because of their skewed marginal distribution. Next, we included four pre-defined environmental maternal determinants (residence [Red zone A or B], binary tap water consumption [10-point Likert scale; 1–5: low, 6–10: high], residential time [≤10 years or >10 years], and breastfeeding duration (no, 1–6 months, 7–12 months, >12 months), and other children predictors, such as age at blood analysis in continuous form and gender (male, female). Residence and residential time were evaluated at the year of childbirth; we inquired about maternal tap water consumption habits prior to local understanding concerning the existence of PFAS contamination. The results are reported as regression coefficients and relative 95% Confidence Intervals (CIs).
2) RQ 2: Considering the externalizing, internalizing, and total SDQ difficulty scores as dependent variables, three different Poisson regression models were used for the study population (n = 331). For multiple children belonging to the same family (about 1.2 children per mother), we estimated coefficient standard errors (clustered standard errors) using a robust method based on hierarchical data. The four pre-defined environmental determinants of maternal exposure, i.e., residence [Red zone A or B], binary tap water consumption (10-point Likert scale; 1–5: low, 6–10: high), residential time [≤10 years or >10 years], and breastfeeding duration [no, 1–6 months, 7–12 months, >12 months]) were used as proxy variables of environmental PFAS exposure. The regression models included a series of confounders potentially correlated to prenatal PFAS exposure, that is the presence of siblings [no, 1, 2+] and mother's age at birth [≤25, 25–35, >35 years], while controlling for covariates to keep into account mainly the cross-sectional nature of the study (children's age [≤8, 8–11, >11] and gender, mother's education level [middle school or lower, high school, university degree or higher], mother's smoking status [no, yes, and ex-smoker], marital status [in a relationship/married, single/widowed], the mother's occupational status [housewife/unemployed, part-time defined as less than 30 h/week, or full-time defined as 30 or more h/week], and the confirmed diagnosis of child learning disorders [no, yes]). Next, based on an ecological framework (Bronfenbrenner, 1979) we included adjustment covariates on children's socio-emotional family environment, that is: the occurrence of postpartum depression, parental perceived social support (i.e., MSPSS score), parenting stress scores, and parenting practices subscales for disciplinary inconsistency and corporal punishment (APQ scales). Among the subset of children with PFAS measures (n = 79), the marginal effects of the serum blood PFOA, PFOS, and PFHS concentrations on SDQ scores (externalizing, internalizing, and total SDQ difficulty scores) was assessed by a Poisson regression model considering as predictor each PFAS concentration categorized into quartiles to account for non-linear relationships. Because of the limited sample size, we adjusted the regressions for a reduced and aggregated set of confounders (breastfeeding [yes, no], gender [male, female], mother's educational level [high school or lower, degree or higher], mother's occupational status [housewife/unemployed, at work], parenting stress score, total APQ score, mother's smoking status [former/yes, no], and learning disorders [no, yes]). The results of the estimated Poisson regression models are reported using Incidence Rate Ratios (IRRs), by an exponential transformation of regression coefficients, with relative 95% CIs. In addition, to investigate associations between the mixture of the three most represented PFAS (PFOA, PFOS, and PFHxS) and behavioral outcome, we applied a Weighted Quantile Sum (WQS) regression model (Carrico et al., 2015) by creating a weighted linear index of correlated predictors according to their strength of association with the outcome of interest. Results were reported by the adjusted IRR associated with the WQS index and its relative 95% CI, reporting the estimated weights. As adjustment, we included the same set of covariates used for single-PFAS analysis. WQS index was created by means of the three considered

Table 1
Summary statistics of SDQ scores of the children included in the study.

Scales and subscales	SDQ score, N = 331[a]
Conduct problems score	0 - [0 (1) 2] - 7
Hyperactivity score	0 - [1 (2) 4] - 10
Externalizing score	0 - [2 (4) 6] - 15
Emotional problems score	0 - [1 (1) 3] - 9
Peer problems score	0 - [0 (1) 2] - 9
Internalizing score	0 - [1 (2) 4] - 16
Total difficulties score	0 - [4 (7) 10] - 30

[a] Minimum - [25% (Median) 75%] - Maximum.

PFAS categorized into quartiles. Due to the limited sample size, we employed the same dataset to perform training and validation, estimating empirical weights for each PFAS over 1000 bootstrapped samples.

All analyses were performed using the R software version 4.1 and Poisson clustered models using the R package miceadds, while for WQS regression we employed the R package gWQS.

3. Results

The majority of children were between 8 and 11 years old, with a slightly male predominance (53%). Only 14% of them were only children. An overall high level of mothers' education (8.8% had a middle-school degree; Table 2) was reported with a low percentage of homemakers or unemployed (14%) or part-time employees (28%). Most of mothers were long-term residents in the Red zone (81% had been staying there for more than 10 years at childbirth). The consumption of tap water was low (1–5 points: 68%), whereas the reported breastfeeding duration was mainly between 7 and 12 months (30%), and more than 12 months (29%). Males reported higher SDQ values than females ($p < 0.001$), whereas children with learning disorders exhibited more difficulties in terms of SDQ scores ($p < 0.001$). Considering the variables related to the maternal lifestyle and familial context, parenting stress and APQ scores were positively correlated with total SDQ difficulty scores (all $p < 0.001$), whereas the presence of perceived social support exerted an opposite and protective effect ($p = 0.013$).

As reported in Table S2, children who had undergone a blood serum PFAS analysis were broadly and equally distributed among gender with a median age of 11 years, a limited age span (IQR = 10–12 years), and a median lag time of 2 years between blood collection and response to the questionnaire. Other characteristics indicated a limited number of children with learning disorders (n = 9, 11%).

The serum blood PFAS concentrations were influenced by tap water consumption (Table S3, PFOA [$p = 0.011$], PFOS [$p = 0.003$], and PFHxS [$p = 0.03$]), whereas PFOA and PFHxS concentrations were higher among children who were breastfed ($p < 0.001$, and $p = 0.002$, respectively). No statistically significant effects were observed for breastfeeding duration and PFOS concentrations. Results of multiple regression models on log-PFAS concentration are shown in Table 3: a positive correlation was recorded with tap water consumption (high vs. low) on the log-PFOA and log-PFOS concentration ($p = 0.020$ and $p = 0.045$, respectively), whereas the increase due to the habit to drink tap water was borderline for log-PFHxS ($p = 0.062$). Breastfeeding duration strongly influenced the concentration of log-PFOA and log-PFHxS, with the highest increases for those with a breastfeeding duration of at least 7 months.

While investigating the factors contributing to environmental PFAS exposure (Table 4), we found that children who frequently consumed tap water was associated with increased frequency of externalizing and total SDQ scores (IRR: 1.18, 95% CI: 1.05–1.31 and IRR: 1.14, 95% CI: 1.02–1.26, respectively). Children with residential time longer than 10 years were associated with a modest and statistically borderline increase in SDQ difficulty scores (IRR: 1.12, 95% CI: 1.00–1.24, $p = 0.065$). The breastfeeding duration exerted a protective effect only on the SDQ internalizing score. The residence didn't influence the SDQ score. Among other covariates, the male gender was associated with increased SDQ scores with respect to that female for all domains (internalizing, externalizing, and overall). The full-time employment versus no work/housewife and the former smoking status (vs. no smoking) of mothers was associated with an increased externalizing and total SDQ scores. Parenting stress and APQ scores were strongly and positively associated with externalizing and total SDQ difficulty scores. We observed a 40% increase in all SDQ scores in children with learning disorders.

Regression results among children with blood serum PFAS measurements (n = 79) were reported in Table 5 and revealed that PFOA concentrations did not influence the SDQ scores, except for a protective effect reported for the third quartile (vs. first quartile) for the internalizing score (IRR: 0.63, 95% CI 0.41–0.96). With respect to the first quartile, the second and fourth quartiles of serum PFOS were associated with a statistically significant increase in internalizing SDQ scores with an IRR of 1.61 (95% CI: 1.07–2.44) and 1.54 (95% CI: 1.06–2.25), respectively. The last quartile of PFHxS concentration (vs. the first quartile) reported higher values of externalizing SDQ scores (IRR: 1.59 [95% CI: 1.09–2.32]). Upon comparing the first and fourth quartiles, a positive association between total difficulty scores with PFOS and

Table 2
Main characteristics of the children included in the study.

Characteristics	Overall, N = 331[a]	Total SDQ difficulties		P-value[b]
		[0,7], N = 188[a]	(7,36], N = 143[a]	
Age [Years]	10 (8, 11)	10 (8, 11)	9 (8, 11)	0.17
Gender [Males]	177 (53%)	84 (45%)	93 (65%)	<0.001
Number of Sibilings				0.85
No	47 (14%)	25 (13%)	22 (15%)	
1	185 (56%)	107 (57%)	78 (55%)	
2+	99 (30%)	56 (30%)	43 (30%)	
Tap water consumption				0.14
Low [1–5]	224 (68%)	134 (71%)	90 (63%)	
High [6–10]	107 (32%)	54 (29%)	53 (37%)	
Residence				0.39
Red zone A	186 (56%)	110 (59%)	76 (53%)	
Red zone B	145 (44%)	78 (41%)	67 (47%)	
Residential time				0.52
≤ 10 years	62 (19%)	38 (20%)	24 (17%)	
> 10 years	269 (81%)	150 (80%)	119 (83%)	
Breastfeeding duration				0.80
No	49 (15%)	25 (13%)	24 (17%)	
1–6 months	88 (27%)	49 (26%)	39 (27%)	
7–12 months	99 (30%)	58 (31%)	41 (29%)	
>12 months	95 (29%)	56 (30%)	39 (27%)	
Maternal education level				0.52
Middle school or lower	29 (8.8%)	14 (7.4%)	15 (10%)	
High school	190 (57%)	107 (57%)	83 (58%)	
Degree or higher	112 (34%)	67 (36%)	45 (31%)	
Mother's age at birth				0.70
≤25 years	17 (5.1%)	8 (4.3%)	9 (6.3%)	
25–35 years	219 (66%)	126 (67%)	93 (65%)	
>35 years	95 (29%)	54 (29%)	41 (29%)	
Mother's occupational status				0.64
Housewife/ Unemployed	47 (14%)	25 (13%)	22 (15%)	
Part time	94 (28%)	57 (30%)	37 (26%)	
Full time	190 (57%)	106 (56%)	84 (59%)	
Marital Status				0.31
In a relationship/ Married	298 (90%)	166 (88%)	132 (92%)	
Single/Widowed	33 (10.0%)	22 (12%)	11 (7.7%)	
Mother's smoking status				0.066
No	235 (71%)	143 (76%)	92 (64%)	
Yes	36 (11%)	17 (9.0%)	19 (13%)	
Former smoker	60 (18%)	28 (15%)	32 (22%)	
Learning disorders [Yes]	33 (10.0%)	8 (4.3%)	25 (17%)	<0.001
Parenting stress score	61 (53, 70)	56 (50, 63)	68 (60, 76)	<0.001
Mother's depression [Yes]	38 (11%)	18 (9.6%)	20 (14%)	0.28
MPSS score	5.33 (4.33, 6.33)	5.50 (4.48, 6.44)	5.25 (3.75, 6.00)	0.013
APQ - Discipl. Incons.	14 (11, 16)	13 (10, 15)	15 (12, 17)	<0.001
APQ - Corp. Punish.	6 (5, 7)	5 (5, 6)	6 (5, 8)	<0.001

[a] Median (IQR) or Frequency (%).

[b] Pearson's Chi-squared test; Wilcoxon rank sum test.

Table 3
Coefficients estimated by the multivariate linear regression model on the log PFAS concentration (log-PFOA, log-PFOS, and log-PFHxS) with respect to the reference category[a].

Predictors	Log-PFOA			Log-PFOS			Log-PFHxS		
	β	95% CI	P-value	β	95% CI	P-value	β	95% CI	P-value
(Intercept)	1.74	0.33–3.14	0.016	1.48	0.03–2.92	0.045	−0.90	−2.39 – 0.59	0.233
Tap water consumption [High]	0.35	0.06–0.64	0.020	0.34	0.04–0.64	0.025	0.29	−0.02 – 0.60	0.062
Residence [Red zone B]	−0.14	−0.44 – 0.15	0.346	−0.08	−0.39 – 0.22	0.580	−0.02	−0.34 – 0.29	0.876
Breastfeeding [1–6 months]	0.34	−0.09 – 0.76	0.119	0.02	−0.42 – 0.45	0.943	0.24	−0.22 – 0.69	0.300
Breastfeeding [7–12 months]	0.75	0.34–1.16	<0.001	0.10	−0.32 – 0.52	0.629	0.57	0.14–1.01	0.011
Breastfeeding [>12 months]	0.71	0.26–1.16	0.002	0.02	−0.44 – 0.48	0.923	0.45	−0.03 – 0.92	0.065
Residential time [>10 years]	0.33	−0.04 – 0.71	0.083	−0.15	−0.53 – 0.24	0.450	0.24	−0.16 – 0.64	0.230
Gender [Male]	0.24	−0.03 – 0.50	0.077	0.06	−0.22 – 0.33	0.683	0.17	−0.11 – 0.45	0.228
Age at blood analysis [+1 year]	0.07	−0.08 – 0.22	0.369	−0.06	−0.22 – 0.09	0.416	0.11	−0.05 – 0.27	0.178
Observations	79			79			79		
R^2/R^2adjusted	0.359/0.286			0.123/0.023			0.223/0.134		

[a] Tap water consumption [Low], Residence [Red zone A], Breastfeeding [No], Residential time [≤10 years], Gender [Female].

PFHxS resulted in statistical significance (PFOS IRR: 1.37 [95% CI: 1.05–1.71]; PFHxS IRR: 1.43 [95% CI: 1.09–1.90]).

Results from the WQS regression analysis confirmed the single PFAS analysis (Table 5). A 1-point increase in the WQS index was associated with an IRR equal to 1.17 (95% CI: 1.03–1.33) for internalizing SDQ scores mainly attributed to PFHxS (estimated weight 84%). The association of the WQS index with externalizing SDQ scores was not statistically significant, while a positive association resulted between the WQS index and total SDQ scores (IRR:1.13; 95% CI: 1.03–1.24) with an equal contribution of PFOS and PFHxS (44% and 55%, respectively).

4. Discussion

The present study is the first in Italy to consider the effects of PFAS exposure on school-age children's behavioral problems and to investigate the complex relationship between child behavioral outcomes and exposure to perfluoroalkyl substances. It simultaneously controls for the role of other demographic and family factors in influencing child functioning. Data were collected in 2021 as part of an observational pilot study on a small sample of school-age children (n = 331) who grew up in a PFAS-contaminated region (Red zone). We selected school-age children as the target population to limit the impact of pubertal and hormonal changes on neurodevelopment, which are typical during the preadolescent and adolescent periods (Høyer et al., 2015, 2018; Vuong et al., 2021; Harris et al., 2021).

Our data corroborated previous studies, demonstrating that specific factors such as the consumption of tap water, the residential time, and breastfeeding duration were strongly associated with PFAS blood concentrations in the local population (Pitter et al., 2020). Considering the subset of children with blood PFAS measurements, we confirmed an association between the previously reported well-recognized environmental risk factors (Pitter et al., 2020; Girardi et al., 2022) and PFAS exposure. We then examined the association between these environmental risk factors related to PFAS exposure and children's behavioral problems as reported by their parents, and indexed by the SDQ questionnaire scores (externalizing, internalizing, and total difficulties). The results revealed a positive association between the total SDQ scores and the consumption of tap water. Moreover, externalizing problems such as hyperactivity and aggressive behaviors increased in children who consumed tap water more frequently. Among children with blood measures (n = 79), 4th quartile concentrations of PFOS and PFHxS were associated with an increase in reported internalizing and externalizing behaviors, respectively, compared to the 1st quartile group. Augmented scores in total SDQ difficulties were associated with higher values of PFOS and PFHxS, adjusting for a set of relevant confounders. The mixture analysis confirmed associations with PFOS and PFHxS found in the single-PFAS analysis.

In response to the first RQ, consumption of contaminated tap water represented one of the major sources of PFAS exposure (Pitter et al., 2020). In addition, we confirmed how breastfeeding, although a major elimination route of PFOA and PFHxS for mothers, was a direct source of exposure for newborns (Mondal et al., 2014; Kim et al., 2020; Girardi et al., 2022).

In relation to the second RQ, the reported results support the findings of high-quality studies (Høyer et al., 2018; Oulhote et al., 2016; Lenters et al., 2019) that demonstrated a potential negative impact of these pollutants on development and specifically on the regulation domain (in terms of attentional and behavioral regulation), especially when exposure occurs during early developmental stages (prenatal and in early childhood) (Høyer et al., 2015; Oulhote et al., 2016; Lien et al., 2016; Vuong et al., 2021). Interestingly, this association seems to be stronger in relation with emotional and behavioral domains as studies linking PFAS exposure with outcomes on child cognitive domains has been rarely reported (Oh et al., 2022), and mostly showed an inconsistent pattern of associations (Harris et al., 2018; Vuong et al., 2019; Skogheim et al., 2020; Carrizosa et al., 2021).

Overall, these results corroborate those of previous existing studies on the effects of PFAS blood serum concentration on children's behavioral problems. Several reports have elucidated the biological mechanisms underlying how early life exposure to PFAS could influence neurodevelopment. In vitro models showed how neuronal differentiation is influenced by PFAS concentrations (Slotkin et al., 2008) because it can activate the peroxisome proliferator-activated receptor alpha (PPAR-α), a nuclear receptor influencing cell growth and metabolism (Lenters et al., 2019). Toxicological studies in mice with neonatal exposure to PFOA, PFOS, and PFHxS displayed disrupted spontaneous behavior in adulthood and irregular nicotinic response (Viberg et al., 2013) with altered levels of neuroproteins implicated in brain development in the hippocampus and cerebral cortex (Johansson et al., 2009). In addition, a significant accumulation of PFAS in specific areas of the human brain has been reported to affect the functioning of dopaminergic neurons (Di Nisio et al., 2022).

One of the major strengths of our study is the control for a set of variables related to family and social-environmental factors that are known to have a significant impact on children's development. While our analysis aimed to evaluate the effects of PFAS exposure on behavioral outcomes among school-age children, the inclusion of these covariates helped to bring an important source of variability, commonly unexplained by most previous epidemiological studies, which accounted only for parental educational level and/or socio-economic status (Oulhote et al., 2016; Høyer et al., 2018; Vuong et al., 2019). We adopted a developmental approach and considered the important role played by parents. Parents are the most relevant and proximal system: while overseeing the growing child (e.g., feeding, protection, etc.), they are also responsible for nurturing him/her by providing emotional support and care (Sameroff, 2010). Interestingly, most of the studies examining

Table 4
IRR estimated by the multivariate Poisson clustered regression model on the SDQ score for externalizing score, internalizing score, and total difficulties with respect to the reference category[a]. In bold p-values below 5%.

Predictors	Externalizing score	Internalizing score	Total difficulties
	IRR [95% CI]	IRR [95% CI]	IRR [95% CI]
Tap water consumption [High]	**1.18 [1.04 – 1.32]**	1.08 [0.91 – 1.25]	**1.14 [1.02 – 1.26]**
Residence [Red zone B]	1.05 [0.91 – 1.19]	1.04 [0.87 – 1.22]	1.05 [0.93 – 1.17]
Residential time [>10 years]	1.13 [0.96 – 1.29]	1.11 [0.93 – 1.29]	1.12 [1.00 – 1.24]
Breastfeeding [1–6 months]	0.97 [0.74 – 1.20]	**0.74 [0.49 – 0.98]**	0.86 [0.67 – 1.05]
Breastfeeding [7–12 months]	1.12 [0.91 – 1.34]	**0.69 [0.46 – 0.93]**	0.90 [0.73 – 1.08]
Breastfeeding [>12 months]	1.12 [0.89 – 1.35]	**0.73 [0.52 – 0.95]**	0.93 [0.75 – 1.11]
Age class (8–11]	0.96 [0.82 – 1.11]	1.16 [0.98 – 1.35]	1.04 [0.91 – 1.16]
Age class (11–13]	0.84 [0.66 – 1.02]	**1.36 [1.15 – 1.57]**	1.04 [0.90 – 1.18]
Gender [Male]	**1.36 [1.22 – 1.49]**	**1.23 [1.07 – 1.40]**	**1.30 [1.19 – 1.41]**
Number of Sibilings [1]	0.82 [0.63 – 1.01]	0.95 [0.71 – 1.18]	0.88 [0.73 – 1.03]
Number of Sibilings [2+]	0.94 [0.72 – 1.16]	1.06 [0.79 – 1.34]	1.00 [0.81 – 1.18]
Mother's education [degree or higher]	0.95 [0.81 – 1.10]	1.10 [0.93 – 1.27]	1.01 [0.89 – 1.13]
Mother's education [middle or lower]	1.17 [0.95 – 1.38]	1.15 [0.89 – 1.42]	1.17 [0.98 – 1.36]
Mother's age at birth [25–35 years]	1.08 [0.79 – 1.37]	0.75 [0.37 – 1.14]	0.90 [0.60 – 1.19]
Mother's age at birth [>35 years]	1.13 [0.82 – 1.44]	0.70 [0.30 – 1.09]	0.89 [0.59 – 1.19]
Mother's occupation [Part-time]	1.18 [0.96 – 1.39]	0.91 [0.65 – 1.17]	1.06 [0.88 – 1.24]
Mother's occupation [Full-time]	**1.27 [1.08 – 1.46]**	1.16 [0.92 – 1.40]	**1.23 [1.06 – 1.39]**
Marital Status [Single/Widowed]	**0.72 [0.49 – 0.95]**	0.86 [0.51 – 1.20]	0.78 [0.53 – 1.03]
Parental stress [+1 point]	**1.02 [1.01 – 1.02]**	**1.02 [1.01 – 1.02]**	**1.02 [1.01 – 1.02]**
Mother's depression [Yes]	1.03 [0.82 – 1.24]	1.16 [0.94 – 1.39]	1.08 [0.91 – 1.25]
MPSS score [+1 point]	**1.05 [1.00 – 1.09]**	1.00 [0.94 – 1.05]	1.03 [0.99 – 1.06]
APQ - Discipl. Incons. [+1 point]	**1.04 [1.02 – 1.06]**	**1.02 [1.00 – 1.04]**	**1.03 [1.01 – 1.05]**
APQ - Corp. Punish. [+1 point]	**1.05 [1.02 – 1.08]**	1.01 [0.97 – 1.05]	**1.03 [1.00 – 1.06]**
Mother's smoking status [Yes]	1.14 [0.95 – 1.33]	1.02 [0.74 – 1.31]	1.07 [0.91 – 1.24]
Mother's smoking status [Former]	**1.33 [1.17 – 1.49]**	**1.21 [1.00 – 1.42]**	**1.27 [1.12 – 1.42]**
Learning disorders [Yes]	**1.37 [1.17 – 1.57]**	**1.41 [1.18 – 1.63]**	**1.38 [1.21 – 1.54]**

[a] Tap water consumption [Low], Residence [Red zone A], Residential time [≤10 years], Breastfeeding [No], Age class [6–8], Gender [Female], Number of Siblings [0] Mother's education [high school], Mother's age at birth [≤25 years], Mother's age at birth [>35 years], Mother's occupation [Housewife/Unemployed], Marital Status [In a relationship/Married], Mother's depression [No], Mother's smoking status [No], Learning disorders [No].

Table 5
Adjusted[a] IRR and relative 95% CI estimated by the multivariate Poisson regression model on the SDQ score for externalizing score, internalizing score, and total difficulties by the single-PFAS (quartiles of PFOA, PFOS, and PFHxS concentration) and WQS regression models. In bold p-values below 5%.

Single PFAS regression	SDQ					
	Externalizing score		Internalizing score		Total difficulties	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
PFOA 1st quartile [3.5–21 ng/ml]	1.00	–	1.00	–	1.00	–
PFOA 2nd quartile (21–28 ng/ml]	1.13	0.78–1.64	0.67	0.44–1.01	0.89	0.68–1.17
PFOA 3rd quartile (28–41.3 ng/ml]	1.03	0.70–1.51	**0.63**	**0.41–0.96**	0.82	0.62–1.09
PFOA 4th quartile (41.3–101 ng/ml]	1.11	0.75–1.64	0.99	0.66–1.48	1.05	0.79–1.39
PFOS 1st quartile [0.35–1.9 ng/ml]	1.00	–	1.00	–	1.00	–
PFOS 2nd quartile (1.9–2.5 ng/ml]	0.86	0.58–1.27	**1.61**	**1.07–2.44**	1.16	0.87–1.53
PFOS 3rd quartile (2.5–3.1 ng/ml]	0.94	0.66–1.33	1.43	0.96–2.13	1.14	0.88–1.47
PFOS 4th quartile (3.1–17.8 ng/ml]	1.25	0.90–1.73	**1.54**	**1.06–2.25**	**1.37**	**1.05–1.71**
PFHxS 1st quartile [0.35–1.7 ng/ml]	1.00	–	1.00	–	1.00	–
PFHxS 2nd quartile (1.7–2.3 ng/ml]	1.14	0.78–1.67	1.41	0.96–2.08	1.27	0.97–1.66
PFHxS 3rd quartile (2.3–3.55 ng/ml]	1.34	0.90–1.99	0.89	0.57–1.40	1.12	0.84–1.51
PFHxS 4th quartile (3.55–7.5 ng/ml]	**1.59**	**1.09–2.32**	1.27	0.84–1.93	**1.43**	**1.09–1.90**
WQS regression						
WQS index +1 point	**1.17**	**1.03–1.33**	1.04	0.99–1.10	**1.13**	**1.03–1.24**
Estimated weights						
PFOA	0.00	–	0.14	–	0.01	–
PFOS	0.16	–	0.70	–	0.44	–
PFHxS	0.84	–	0.16	–	0.55	–

[a] Adjusted for the following covariates: Breastfeeding [Yes, No], Gender [Male, Female], Mother's educational level [High school or lower, Degree or higher], Mother's occupational status [Housewife/Unemployed, At work], Parenting stress score, Total APQ score, Mother's smoking status [Former/Yes, No], and Learning disorders [No, Yes].

the effects of PFAS on child functioning, while relying on parental reports on child development, do not consider parental emotional state in terms of parental stress and beliefs in parenting practices. This is quite surprising given that developmental psychology literature reports how maternal sensitivity, emotional care, and parenting practices strongly influence the developing child both in terms of behavior and functioning. Moreover, parental stress has been reported to be associated with dysfunctional parenting practices, which, in turn, are often connected to the child's behavioral difficulties (Morgan et al., 2005). A parent who is aware of having been exposed to potentially damaging pollutants might be particularly distressed by his/her parental responsibility and might report on his/her child functioning and development in a biased way (either over or underestimating specific behavioral or emotional difficulties). As such, controlling for parental stress and parental practices becomes of paramount importance in order to understand the weight of PFAS exposure on child functioning. In line with this, our findings showed the expected role of parenting stress as an important predictor of a child's functioning. Yet, most importantly, despite the role played by parental emotional state, the significant negative effect of exposure to PFAS was confirmed. Specifically, frequent tap water consumption was associated with increased externalizing behavioral problems and greater SDQ total difficulty scores. Similarly, the effect of longer residential time was linked to an increase in the reported emotional and behavioral problems (i.e., total SDQ score). Conversely, a protective effect of breastfeeding duration was reported only on the internalizing sub-scale, with no effect on the total difficulty scale. These results appear to be contrary to those obtained from studies reporting the overall protective effect of breastfeeding for behavioral problems among all domains (Heikkilä et al., 2011). However, we could not analyze the potential interaction between breastfeeding duration and prenatal PFAS exposure.

These findings are particularly interesting as they elucidate how exposure to water pollutants significantly impacts school-age children's behavioral and regulatory functioning while controlling for important family factors. In addition, we accounted for other possible confounding factors related to maternal lifestyle characteristics, such as type of employment, education, and smoking status, which have been reported to influence the externalizing and total SDQ scores. The literature reports that a full-time occupation could be a risk factor because it is related to frequent separations from the family. Instead, other researchers highlight its positive impact on child development and associate it with greater parental satisfaction (Heinrich, 2014). To increase transparency, datasets and statistical analyses are accessible via a public repository.

Our study had certain limitations. First, the recruitment was voluntary and due to the COVID-19 pandemic was held online, leading to a strong selection bias and an underrepresentation of foreign mothers (who were excluded from the analysis) and mothers with a low education level. The literature reports that families are frequently exposed to the effects of environmental pollution in a different way: disadvantaged communities have less access to health information and healthcare, resulting in lower health promotion interventions, lowering risk prevention, less healthy eating habits and lifestyles, and more adverse conditions that increase the susceptibility to exposure (Buekers et al., 2018; Evans and Kantrowitz, 2002). Furthermore, the online procedure could not guarantee the presence of a controlled and uniform setting for all subjects. With respect to the research design, we could not establish a causal link between exposure to PFAS and reported developmental difficulties. In particular, we could not rule out the differential role of a mother's PFAS exposure, since this latter could affect childhood behavioral outcomes directly, or indirectly by affecting maternal behavior (Banwell et al., 2021; Merrill et al., 2022). In addition, our observational study cannot be employed to measure the effect due to interactions between time-related variables, e. g. the interaction between breastfeeding duration and prenatal maternal PFAS level. Furthermore, a comparison of our results with those of other studies is affected by different research designs (selection criteria, statistical methods, and developmental domains considered), specific PFAS concentrations to which the populations were exposed, and different timings of exposure. In addition, it is challenging to estimate the individual contribution of each PFAS since the presence of multiple quartile comparisons based on three different regression models; the WQS regression permitted to partially deal with this limitation by estimating both the total contribution and the weight of each PFAS. However, considering the limited sample size, the training and the validation step were performed on the same dataset leading to potential overfitting. Further, the lack of longitudinal outcome assessments does not allow us to determine how these pollutants affect the developmental trajectories in multiple domains.

5. Conclusions

The findings from the present study add to the growing literature on PFAS and their effects on child development, while also considering relevant covariates that are not commonly examined in epidemiological studies. Based on our findings, we conclude that population screening should be conducted to monitor the exposure level of mothers and newborns, and they should be advised to avoid potential sources of contamination. Although breastfeeding is a significant source of post-natal exposure, it may affect the child. To understand the role of PFAS exposure, longitudinal studies are required to monitor the concentrations of the entire panel of pollutants measuring attentional and executive functions, and cognitive processes using quantitative and standardized psychometric tests to obtain objective direct measures and developmental trajectories. Altogether, we believe that future studies adopting a bio-psycho-social model of human development are warranted. Child development is affected by multiple levels that go from societal to molecular (Borrell-Carrió et al., 2004). Often epidemiological studies investigating the effects of pollution on children's functioning fail to include important environmental factors, such as the family socio-emotional environment. These factors play an important role in shaping the child's brain and psychological functioning, hence it is paramount to include them as potential protective factors when attempting to understand the role of pollutants on development. Such research designs can help to understand in a more holistic way the risk of being espoused to specific environmental toxic substances such as PFAS.

Author contributions

Conceptualization: PG, AL, and SS; methodology and formal analysis: PG; validation: PG, AL, and SS; investigation: PG, LM, and SS; funding acquisition: PG, AL, and SS; data curation: AL and LM; writing—original draft preparation: PG, AL, and SS; writing—review and editing: PG, AL, LM, and SS; supervision: PG and SS. All authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets generated during the current study and R script used to obtain the reported results are publicly available through the OSF repository [https://osf.io/hqvba].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.116049.

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