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Low concentrations of perfluoroalkyl acids (PFAAs) in municipal drinking water associated with serum PFAA concentrations in Swedish adolescents

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ABSTRACT

While highly contaminated drinking water (DW) is a major source of exposure to perfluoroalkyl acids (PFAAs), the contribution of low-level contaminated DW (i.e. < 10 ng/L of individual PFAAs) to PFAA body burdens has rarely been studied. To address this knowledge gap, we evaluated the association between concentrations of perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorohexane sulfonic acid (PFHxS) and perfluorooctane sulfonic acid (PFOS), and their sum ($\sum_4$PFAAs) in DW and serum in Swedish adolescents using weighted least squares regression. We paired serum PFAA concentrations in adolescents (age 10–21 years, n = 790) from the dietary survey Riksmaten Adolescents 2016–17 (RMA) with mean PFAA concentrations in water samples collected in 2018 from waterworks (n = 45) supplying DW to the participant residential and school addresses. The median concentrations of individual PFAAs in DW were < 1 ng/L. Median concentrations of PFNA and PFHxS in serum were < 1 ng/g, while those of PFOA and PFOS were 1–2 ng/g. Significant positive associations between PFAA concentrations in DW and serum were found for all four PFAAs and $\sum_4$PFAAs, with estimated serum/DW concentration ratios ranging from 210 (PFOA) to 670 (PFHxS), taking exposure from sources other than DW (background) into consideration. The mean concentrations of PFHxS and $\sum_4$PFAA in DW that would likely cause substantially elevated serum concentrations above background variation were estimated to 0.9 ng/L and 2.4 ng/L, respectively. The European Food Safety Authority has determined a health concern concentration of 6.9 ng $\sum_4$PFAAs/mL serum. This level was to a large degree exceeded by RMA participants with DW $\sum_4$PFAA concentrations above the maximum limits implemented in Denmark (2 ng $\sum_4$PFAAs/L) and Sweden (4 ng $\sum_4$PFAAs/L) than by RMA participants with DW concentrations below the maximum limits. In conclusion, PFAA exposure from low-level contaminated DW must be considered in risk assessment for adolescents.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a substantial group of > 4,700 anthropogenic substances (OECD, 2018; US EPA, 2022), some with persistent organic pollutant (POP)-like properties (EU, 2019; EU, 2020). PFAS have excellent surfactant properties, are heat-stable and resistant to chemical and UV-light degradation. They have widely been used in products such as aqueous film forming fire-fighting foams, water- and grease repellent coatings, adhesives, and cosmetics, and in various industrial applications, since the 1940s (ITRC, 2020). This has led to a global pollution where PFAS have been ubiquitously detected in air, sediments, soils, ground- and surface waters, indoor dust and air, and in wild-life and human matrices (Kelly et al., 2009; Ahrens and Bundschuh, 2014; DeLuca et al., 2021). Perfluoroalkyl acids (PFAAs), a subgroup of PFAS, are highly persistent and some have very long half-lives in humans (Xu et al., 2020). These long half-lives, in relation to the suggestive immuntoxic and endocrine disruptive effects (among others) in humans (Fenton et al., 2021), have contributed to growing

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international concern surrounding the entire class of chemicals.

Given their widespread occurrence, human exposure to PFAS is frequently multifaceted, thereby complicating exposure assessments. For the general adult population, diet - in particular fish and shellfish - is considered a significant source of exposure to many of the perfluorocarboxylic acids (PFCAs) and perfluorosulfonic acids (PFSAs) with fluorinated chain-length of ≥ 7 carbons and ≥ 6 carbons, respectively (i.e. long-chain PFAAs) (Sunderland et al., 2019). Drinking water (DW) has also been implicated as an important PFAA exposure source, specifically for populations whose DW is impacted by pollution from point sources (Sunderland et al., 2019; Johanson et al., 2023). Extensive use of PFAS-containing fire-fighting foams, industrial emissions, and use of PFAS-contaminated soil conditioners on agricultural lands have resulted in PFAA concentrations in DW exceeding 100 ng/L of individual PFAA (Emmett et al., 2006; Hölzer et al., 2008; Post et al., 2012; Pitter et al., 2020; Li et al., 2020; Johanson et al., 2023). Thus, serum/plasma concentrations measured in populations living close to PFAA hotspots are highly elevated compared to those living far away from major point sources. A large fraction of the European population has an intake that exceeds the European Food Safety Authority's (EFSA) recently established health-based tolerable weekly intake (TWI) of 4.4 ng/kg body weight per week for the sum of perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorohexanesulfonic acid (PFHxS) and perfluorooctanesulfonic acid (PFOS) ($\sum_4$PFAA) (EFSA, 2020). Meanwhile, few studies have specifically assessed the extent to which low-level contaminated DW (<10 ng/L of single PFAA) contributes to the exceedance of the TWI.

The widespread use of PFAS over the last seven decades has contributed to dispersal beyond major point sources, leading to widespread low-level PFAS contamination in DW (in general, <10 ng/L of individual PFAS) (Zafeiraki et al., 2015; Li et al., 2019; Arinaitwe et al., 2021). Limited research suggests that low-level PFAA contamination of DW contributes to measurable increases in the long-term cumulative exposure of at least some PFAAs (e.g. PFOA, PFNA, PFHxS and PFOS) with long half-lives in the human body. For example, higher PFAA concentrations in serum/plasma were observed in adults and children drinking water with low-level PFAA contamination compared to those drinking water with non-detectable PFAA concentrations (Post et al. 2012; Hu et al., 2019; Gyllenhammar et al., 2019; Glynn et al., 2020). Nevertheless, the contribution of low levels of PFAA in DW to the body burden is difficult to distinguish from contributions from both historical and contemporary exposures. The voluntary industrial and regulatory phase-out of PFOA, PFHxS, PFOS and related substances was initiated in the early 2000s (Buck et al. 2011) and later PFNA as a higher PFOA homologue in 2010–2015 (US EPA, 2023), and it is reasonable to assume that the long-term cumulative exposure to these substances has historically been higher among adults compared to children/adolescents born around the time of phase-out (Nyberg et al., 2018; Miaz et al., 2020; Lin et al., 2021). Low-level exposure from DW may subsequently not contribute equally to long-term cumulative exposure across age groups, with a possible higher relative contribution among children/adolescents than among adults. Johanson et al. (2023) observed significant associations between PFAA concentrations in DW and serum (matched samples) among adults exposed to a wide range of concentrations up to above 1000 ng $\sum$PFAAs/L, but to the best of our knowledge no study has investigated associations in young human populations exposed to low-level PFAS contaminated DW. Such knowledge is of importance in the risk assessment of human exposure to PFAS.

The first aim of our study was to evaluate the associations between low concentrations of PFOA, PFNA, PFHxS, PFOS and $\sum_4$PFAA in DW and serum concentrations of these PFAA in Swedish adolescents, who participated in the nation-wide dietary survey Riksmaten Adolescents 2016–17 (RMA). The associations were also evaluated from a gender-specific perspective. The results of this analysis were used to determine the bioaccumulation potential of the studied PFAAs from DW to serum by estimating the ratios between PFAA concentrations in DW and serum, taking exposure from other sources that are prevalent in the general population (from here on referred to as background exposure) into account. From these results, we also attempted to determine the lowest mean PFAA concentrations in DW that would cause measurable elevated serum PFAA levels above background variation when sampling other adolescents in Sweden. The second aim was to risk assess adolescent PFAA exposure from DW by estimating the proportion of RMA participants exceeding the EFSA safe serum concentration of 6.9 ng $\sum_4$PFAAs/mL. We also compared the percentages of participants exceeding the safe serum concentration at DW concentrations above or below the Danish and Swedish maximum limits of 2 ng$\sum_4$PFAAs/L and 4 ng $\sum_4$PFAAs/L om DW, respectively (SLV, 2022; DK EPA, 2021).

2. Material and methods

2.1. Study population

We utilized a subsample of the nationally representative school-based dietary survey Riksmaten Adolescents 2016–17 (RMA) conducted by the Swedish Food Agency. In-depth descriptions of the study design and population are provided in Moraeus et al. (2018), Lindroos et al. (2019) and Nyström et al. (2022a). Briefly, schools with grades 5, 8 and 11 were invited to participate in RMA between September 2016 and May 2017. Selection of schools was carried out by Statistics Sweden and was based on municipality classification, geographical spread and whether the school was public or charter. Each participant was asked to retrospectively register their food, DW and beverage consumption over two non-consecutive days in the validated web-based system RiksmatenFlexDiet (RFD). Participants also answered questions regarding infrequently consumed food items and socio-economic and lifestyle factors in the web-based RiksmatenFlexQuestionnaire (Moraeus et al., 2018).

In the 57 participating schools, 2377 pupils were invited to donate blood samples (Moraeus et al., 2018). For 1098 participants, dietary record and questionnaire answers were available together with serum samples, which were analysed for PFAS (Nyström et al., 2022a). Only participants receiving DW from sampled waterworks both at home and at school (see section 2.2) were included in this study. Consequently, 215 participants were excluded as their residences did not receive DW from a participating waterworks. Moreover, 37 participants were excluded since they were going to school and/or living in areas with a known history of high PFAS contamination of municipal DW, and where remediation of contamination had occurred before blood and DW sampling (Nyström et al., 2022a). Finally, 56 participants were excluded from the analyses due to incomplete dietary or questionnaire data. The final number of participants included in the statistical analyses were 790 (Table 1).

2.2. Sampling and chemical analysis of raw and drinking water

Raw water (RW) and DW were sampled (one sample each) in the spring and autumn of 2018 from waterworks (n = 45) providing DW to the participating schools and homes of the adolescents in RMA (see 2.4 Exposure assessment, 2.4.1 Identification of waterworks). Samples were collected in thoroughly rinsed 1 L high density polypropylene bottles by waterworks staff (grab samples), typically at a tap of the pipe representing ingoing RW and outgoing DW. Samples were stored in darkness at 4 °C until analysed by the Department of Aquatic Sciences and Assessment at the Swedish University of Agricultural Sciences.

A total of 24 different PFAS were analysed in DW and RW samples. The following PFAS were analysed: C_4–C_{14}, C_{16} and C_{18} PFCAs, perfluorobutanoic acid (PFBA), perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), PFOA, PFNA, perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorotridecanoic acid (PFTriDA), perfluorotetradecanoic acid (PFTeDA), perfluorohexadecanoic acid (PFHxDA), perfluorooctadecanoic acid

Table 1
Personal characteristics of the participants in Riksmaten Adolescents 2016–17, Sweden, who were included in the present study. The table shows categorical and continuous covariates included in the statistical analysis.

Categorical covariates	**n = 790 *(%)***	
Gender		
Male	350 *(44)*	
Female	440 *(56)*	
School grade		
5	253 *(32)*	
8	324 *(41)*	
11 (second year upper secondary school)	213 *(27)*	
Birth country (participant/mother)[a]		
Both low and lower-middle income countries	30 *(4)*	
High and upper-middle and low and lower-middle income countries	23 *(3)*	
Upper-middle and upper-middle income countries	29 *(4)*	
High and upper-middle countries	65 *(8)*	
High and high income countries	643 *(81)*	
Maternal education level		
No formal education or primary education	70 *(9)*	
Vocational education or equivalent	116 *(15)*	
3–4 year upper secondary education or equivalent	174 *(22)*	
University education or equivalent	430 *(54)*	
Continuous covariates	**Median (min - max)**	**Mean (SEM)**
Age (years)	14.5 (10.6 – 21.1)	14.5 (0.9)
Habitual seafood consumption (g/day)	21.5 (0 – 101)	23.8 (0.53)
Habitual long-term drinking water consumption (mL/day)	502 (40.6 – 2780)	583 (13.7)

Note: SEM, standard error of the mean.
[a] Categorization is based on the per capita gross national income level in accordance with the World Bank Country Classification of 2018 (World Bank Group 2018; Nyström et al. 2022a).

(PFOcDA)); C_4, C_6, C_8 and C_{10} PFSAs (PFBS, PFHxS, PFOS, PFDS); 6:2, 8:2, 10:2 fluorotelomer sulfonates (FTSA); perfluorooctanesulfoneamide (FOSA); perfluorooctane sulfonamidoacetic acid (FOSAA); methyl and ethylperfluorooctane sulfonamidoacetic acid (MeFOSAA and EtFOSAA, respectively) (Table 2 and Table S1 in Supporting Information (SI)).

The water samples were analysed using a validated method in accordance with Gobelius et al. (2018), with few modifications. Briefly, 500 mL water sample was filtered (1.2 μm glass fiber filter GFF, GE Healthcare Life Sciences, Whatman UK) and then spiked with 100 μL of mass-labelled internal standard (IS) mixture (20 ng mL^{-1} of each IS, n = 16). The samples were extracted by solid phase extraction (SPE) using Oasis WAX cartridges (6 cc, 500 mg, 60 μm, Waters Corporation, USA) which were preconditioned with 4 mL of 0.1 % ammonium hydroxide in methanol solution (1:1 methanol: Millipore water). After loading, the cartridges were buffered with 25 mM ammonium acetate buffer in Millipore water and then dried in a centrifuge (2000 rpm, 3 min). Thereafter, the cartridges were eluted with 6 mL methanol, followed by 6 mL 0.1% ammonium hydroxide solution in methanol. The extracts were then concentrated to 1 mL and analysed using a DIONEX UltiMate 3000 ultraperformance liquid chromatograph (UPLC) system coupled to a triple quadrupole mass spectrometer (MS/MS) (TSQ Quantiva, Thermo Fischer Scientific, Waltham, MA, USA). As a standard procedure, quality control samples included matrix spiked samples (n = 7), duplicate samples (n = 8), and laboratory blanks (n = 12).

For RW/DW samples, the limits of quantification (LOQ) were calculated for individual PFAS based on the average concentration in the blanks (n = 12) plus three times standard deviation of the blanks. If no PFAS were detected in the blank, the lowest quantifiable concentration in the calibration curves were set as the LOQ. Ranges of LOQs and the number of samples ≥ LOQ for each analysed PFAS are given in Tables 2 and S2 in SI. The LOQs for PFOS were slightly higher in some analytical batches. To improve the statistical power in the analyses of associations between PFOS concentrations in serum and DW, PFOS concentrations in DW < LOQ but > LOD were used when reported by the laboratory. From here on, PFAS concentrations in DW > LOQ, and/or > LOD (PFOS) when reported, will be referred to as detected.

Table 2
PFAA concentrations (ng/L) in drinking water (DW) and raw water (RW) samples from waterworks (n = 45)[a] sampled in spring and autumn 2018, used for calculations of mean PFAA concentrations in DW supplied to the schools and residences of the participants.

		Spring		**Autumn**	
PFAS		**Range of LOQ *(n ≥ LOQ)***	**Median[b] (min, max)**	**Range of LOQ *(n ≥ LOQ)***	**Median[b] (min, max)**
PFOA	DW	0.086 – 0.42 *(29)*	0.56 (0.13, 1.9)	0.070 – 0.67 *(10)*	0.74 (0.47, 2.5)
	RW	0.062 – 0.36 *(30)*	0.88 (0.22, 5.1)	0.062 – 0.69 *(17)*	0.77 (0.26, 1.4)
PFNA	DW	0.031 – 0.22 *(20)*	0.23 (0.11, 0.37)	0.066 – 0.19 *(6)*	0.26 (0.21, 0.32)
	RW	0.047–0.14 *(20)*	0.27 (0.16, 0.42)	0.063 – 0.25 *(16)*	0.38 (0.17, 0.48)
PFHxS	DW	0.041 – 0.20 *(17)*	0.46 (0.19, 7.9)	0.057 – 7.5 *(11)*	0.36 (0.14, 5.6)
	RW	0.099 – 0.52 *(22)*	0.53 (0.14, 6.1)	0.053 – 6.3 *(17)*	0.52 (0.075, 1.5)
PFOS	DW	0.31 – 1.9 *(6)*	2.55 (1.1, 4.2)	0.67 – 2.8 *(22)*[c]	0.60 (0.22, 3.0)[c]
	RW	0.04 – 4.2 *(4)*	2.95 (1.6, 5.6)	0.59 – 3.0 *(6)*	1.1 (0.71, 2.1)
Σ_4PFAAs	DW		0.81 (0.13, 14)		0.81 (0.22, 10)
	RW		1.3 (0.14, 11)		1.1 (0.075, 4.0)

Note: LOQ, limit of quantification; min, minimum; max, maximum. Σ_4PFAA include PFOA, PFNA, PFHxS and PFOS.
[a] Due to analytical issues or missed sampling, n = 42 and 39 in DW samples in spring and autumn respectively, and n = 41 and 42 in spring and autumn RW samples respectively.
[b] The median and min/max was only calculated for samples > LOQ.
[c] Values < LOQ and > limit of detection (LOD) are included.

Table 3
Serum PFAA concentrations (ng/g) for the RMA participants (n = 790).

PFAA	LOD *(%>LOD)*	Median (min, max)	Mean (SEM)[a]
PFOA	0.29 *(99.9)*	1.2 (<LOD, 5.3)	1.30 (0.02)
PFNA	0.10 – 0.18 *(95.0)*	0.39 (<LOD, 2.8)	0.43 (0.01)
PFHxS	0.017 – 0.22 *(99.7)*	0.40 (<LOD, 16)	0.62 (0.04)
PFOS	0.031 – 0.26 *(100)*	1.9 (0.28, 15)	2.5 (0.07)
Σ_4PFAAs	–	4.2 (0.71, 33)	4.9 (0.10)

Note: LOD, limit of detection; min, minimum; max, maximum; SEM, standard error of the mean; Σ_4PFAA, sum of (lin-) PFOA, PFNA, (lin-) PFHxS and (lin-) PFOS.

[a] Values < LOD were assigned LOD/$\sqrt{2}$ for calculations of the mean and SEM.

2.3. Sampling and chemical analysis of blood

A detailed description of the blood sampling and chemical analysis is given in both Moraeus et al. (2018) and Nyström et al. (2022a). In brief, non-fasting blood samples were taken during study visits to the participating schools in 2016–2017. Venous blood samples were drawn by trained staff and stored in 10 mL tubes coated with coagulation activators. Once centrifuged, serum was stored at −20 °C onsite and during transport until final storage at −80 °C awaiting analysis (Moraeus et al., 2018).

We previously reported concentrations of 42 different PFAS in serum among the RMA participants (Nyström et al., 2022a). In the present study, only linear (lin-) PFOA, PFNA, lin-PFHxS and lin-PFOS were included in the statistical analyses as these PFAA (Table 3) i) were detected at enough frequency in both serum (≥95%) (Nyström et al., 2022a) and DW (≥10%) (Table 2) in order to be included in the statistical analysis and ii) were included in the EFSA risk assessment (EFSA, 2020). From here on, lin-PFOA, lin-PFHxS and lin-PFOS will be referred to as PFOA, PFHxS and PFOS, unless otherwise stated.

The analytical method, including quality control, and measured serum PFAS concentrations have previously been accounted for in Nyström et al. (2022a). In brief, serum samples were fortified with 0.5 ng of individual isotopically-labelled internal standards and thereafter extracted twice with 4 mL of acetonitrile in an ultrasonic bath. The extracts were combined and concentrated to 1 mL under a stream of nitrogen, and then purified with graphitized carbon and acetic acid. A portion of the final extract was suplanted with 4 mM aqueous ammonium acetate and 0.5 ng of individual volumetric standards, prior storage at −20 °C. Instrumental analysis was performed using a Waters Acquity ultra performance liquid chromatograph (UPLC) equipped with a C18 column and coupled to a Waters Xevo TQS triple quadrupole mass spectrometer. The mass spectrometer was operated in negative electrospray ionization, multiple reaction monitoring (MRM) mode. Quantification was based on isotope dilution. Quality control included analysis of blanks, spiked samples, and NIST Standard Reference Material 1957 (see Nyström et al., 2022a for details). If a signal occurred in the method blanks within a batch, the reporting limit was based on the limit of quantification (LOQ, mean blank + 3x standard deviation), otherwise, the reporting limit was set as the limit of detection (LOD, concentration at a signal-to-noise ratio of 3).

2.4. Exposure assessment

2.4.1. Identification of waterworks

The waterworks producing DW for the participating schools were identified based on the postal codes of the schools. A questionnaire was sent to the identified waterworks to verify that they were indeed supplying DW to the participating schools. Since we only wanted to include participants receiving DW from identified waterworks both at school and at home, each participant's home address postal code was matched to the waterworks DW distribution areas. Postal codes within the waterworks distribution areas were retrieved from the DW producers. In the event DW producers could only provide local names of the areas receiving their DW, this information was matched with the postal code of the participants using the online postal service PostNord (PostNord, 2022).

2.4.2. Calculations of mean PFAA concentrations in DW

As explained in section 2.3., only PFOA, PFNA, PFHxS and PFOS were included in the analyses of associations between PFAA concentrations in serum and DW. To increase the n-values of DW PFAA concentrations, we investigated if both RW and DW data could be utilized in the calculation of the averaged PFAA concentration in DW (ng/mL), since it has been reported that standard DW treatment techniques such as disinfection, granular/micro-/ultra-filtration and alum coagulation are largely ineffective in removing PFAS (Appleman et al., 2014). Thus, a two-sided paired *t*-test was carried out investigating whether PFOA, PFNA, PFHxS and PFOS concentrations significantly differed between DW and RW samples or not. This analysis was carried out for spring and autumn samples separately. Although statistically significant differences between RW and DW were found in certain cases, the differences were not consistently in the same direction in the spring and autumn (Table S2 in SI). Therefore, both RW and DW PFAA concentrations were used to calculate an arithmetic averaged DW PFAA concentration (Table 4).

Inter-analytical batch variation in PFAA LOQs in the DW and RW samples made it necessary to use multiple ways to compute a mean DW PFAA concentration, exemplified by three scenarios provided in Table S3 in SI. Firstly, in the case of all samples from a waterworks having concentrations ≥ LOQ, the concentration was calculated as a mean of PFAA concentrations in all spring and autumn RW and DW samples (example 1, Table S3 in SI). Secondly, if at least one sample from a waterworks had a PFAA concentration ≥ LOQ, the concentrations < LOQ were set at LOQ/2 (example 2, Table S3 in SI) before calculation the mean concentration. If the LOQ of one or more samples was higher than the lowest actual detected concentration, then these data were excluded from the calculation of mean DW concentrations (example 2, Table S3 in SI). Lastly, if concentrations in all samples from the waterworks were < LOQ, only the lowest LOQ/2 was used to estimate the mean DW concentration (example 3, Table S3 in SI).

In addition, in the event that more than one waterworks provided DW to a school or home, a weighted mean DW concentration of PFAA was calculated using the reported distribution proportion of each waterworks to the DW and the individual DW concentration for the waterworks. If no such information could be retrieved, the waterworks were assumed to contribute equally to the final mean DW PFAA concentration.

2.4.3. PFAA concentrations in serum

In some analytical batches concentrations < LOQ but ≥ LOD were reported, these data were used as reported (Bergstrand and Karlsson, 2009; RSC, 2001; Nyström et al., 2022a). If concentrations were < LOD they were set to LOD/$\sqrt{2}$. In analytical batches with only LOQ reported, concentrations < LOQ were replaced with LOQ/$\sqrt{2}$.

Table 4
Calculated median and arithmetic mean PFAA concentrations in drinking water from the participating waterworks (n = 45) using both raw and drinking water samples from spring and autumn 2018.

PFAA (ng/L)	Median (min - max)	Mean (SEM)
PFOA	0.45 (0.03 – 1.7)	0.54 (0.01)
PFNA	0.15 (0.03 – 0.32)	0.16 (<0.01)
PFHxS	0.30 (0.03 – 2.5)	0.47 (0.02)
PFOS	0.63 (0.24 – 3.3)	0.92 (0.03)
Σ_4PFAAs	1.5 (0.39 – 6.3)	2.1 (0.06)

Note: Min, minimum; max, maximum; SEM, standard error of the mean; Σ_4PFAA, sum of PFOA, PFNA, PFHxS and (lin-) PFOS.

2.4.4. Estimation of long-term drinking water consumption

The daily habitual (long-term) DW consumption was derived from the RMA dietary registration in the RFD by the Multiple Source Method (MSM, Version 1.0.1) (Harttig et al., 2011; Haubrock et al., 2011), and included direct tap water consumption and consumption of beverages made with tap water registered by the participants during two independent days (24-hour recall registration) (Table 1). The MSM is based on shrinkage models, a method that has been recommended when estimating long-term DW intake (Cuvelier and Bartell, 2021). The beverages made from tap water included tea, coffee and fruit/berry syrups/concentrates diluted with tap water (in Swedish: "saft").

2.5. Statistical analysis

The statistical analyses were executed in R (version 4.0.4; R Development Core Team), except for the two-sided paired *t*-test which was performed in Excel; version 2016. All analyses used a statistical significance level of $p \leq 0.05$. We determined DW and serum PFAA concentration relationships using both univariate and multivariate linear regression analyses. In the univariate analysis, the calculated mean PFAA concentrations in DW (independent variable) were matched and modeled against participants' serum PFAA concentrations (dependent variable). This association was investigated for PFOA, PFNA, PFHxS and PFOS individually, as well as for the sum of these four ($\sum_4$PFAAs) since EFAS's TWI is based on these homologues (EFSA, 2020). In our previous studies (Nyström et al., 2022a; Nyström et al., 2022b), age (years), gender (male/female), maternal education level, habitual seafood consumption (g/day) and birth country (joint covariate including both maternal and participant birth country) were significant determinants of serum PFAA concentrations among the RMA participants (Table 1). These determinants were included in the multivariate regression models, as additional independent variables. Since the normality assumption of the residual errors when fitting the data using an ordinary least squares regression was not met, weighted linear regression was performed as described in Johanson et al. (2023). Weights for serum PFAA concentrations were defined by the inverse absolute residuals obtained in the ordinary least squares regression. Such weights allow extreme values to influence the regression fit to a lesser extent than in the ordinary least square analysis without the need of transforming the dependent data variable. Transformation makes interpretation of the results difficult as back-transformation to its original scale is needed.

The intercept of the regression line was interpreted as the mean background serum concentration (ng/g; we assume a 1:1 ratio between blood volume and weight as 1 mL serum equals 1.06 g serum), originating from other exposure sources than local DW such as food, air/dust and other unidentifiable sources (Johanson et al., 2023). The coefficient of the association between PFAA concentrations in DW and serum (i.e., the slope of the regression line) was defined as the serum:water ratio (SWR) (Bartell, 2017). In order to generalize this association to other demographically comparable adolescents in Sweden, we estimated the minimum PFAA concentration in DW that ought to cause a measurable increase in PFAA concentrations in serum due to DW exposure (DWES). This was achieved by determining the DW PFAA concentration at which the regression line, representing the fitted population-averaged PFAA concentration in serum, reaches the upper 68% and 95% prediction interval at the background serum concentration ($DWES_{68}$ and $DWES_{95}$). By using the prediction intervals, we were able to account for the variation in estimated background PFAA concentrations and consequently make predictions for other/new observations of PFAA concentrations in serum from adolescents in Sweden (Johanson et al., 2023). These estimates was only derived for those PFAA were the fitted regression line reached the 68% and 95% prediction intervals within the range of DW PFAA concentrations studied as extrapolation outside the DW concentration range was considered too uncertain. Furthermore, we derived the fitted population-averaged PFAA serum concentration at each of the upper prediction interval limits, i.e., the mean serum concentration corresponding to $DWES_{68}$ and $DWES_{95}$.

As gender-based differences in serum PFAA concentrations have previously been reported among adolescents in RMA (Nyström et al., 2022a), a multivariate weighted linear regression analysis was performed with an interaction term between PFAA concentrations in serum and gender. Moreover, we evaluated whether long-term DW consumption influenced the associations between concentrations of PFAA in DW and in serum, and if concentrations of PFAA in serum were associated with DW consumption. This was carried out by adding the long-term DW consumption covariate to the existing multivariate regression analysis as an additional independent variable.

2.6. Risk assessment of PFAA exposure from drinking water

The $\sum_4$PFAA concentration among the RMA participants were compared with the serum concentration attained after life-time average intake of $\sum_4$PFAA (35 years) at the TWI level among females (6.9 ng Σ_4PFAAs/mL serum) (EFSA, 2020). We used a χ^2-test of independence to compare the proportions of individuals exceeding 6.9 ng/mL at Σ_4PFAA concentrations in DW below or above established maximum limits in Denmark (2 ng $\sum_4$PFAAs/L) (DK EPA, 2021) and Sweden (4 ng $\sum_4$PFAAs/L) (SLV, 2022).

3. Results and discussion

3.1. PFAS in drinking and raw water

Our analyses of associations between PFAS concentrations in serum and DW only covered PFOA, PFNA, PFHxS and PFOS (Table 3), since the other PFAS measured in DW (Table S1, Supporting Information) were rarely detected in serum (Nyström et al., 2022). Nevertheless, we aimed to present data on a large number of PFAS in municipal DW that have otherwise rarely been published. FOSA and PFOA were the most abundantly detected PFAS among the spring DW samples (detection frequency 67% and 69%, respectively), followed by PFNA and PFHxS (detection frequency > 40%; Table 2 and S1 in SI). Among the autumn DW samples, 6:2 FTSA was the most frequently detected (64%), followed by PFOS (56%), FOSA (46%), PFHxS (28%) and PFOA (26%) (Table 2 and S1 in SI). PFCA with carbon chains longer than PFNA were rarely observed in both RW and DW (Table S1 in SI). A similar pattern was observed for the FTSAs, with almost no samples having 8:2 or 10:2 FTSA concentrations ≥ LOQ (Table S1 in SI). A lower mobility in soil/ground water for the PFAS with longer chain lengths could at least partially contribute to these observations (Baduel et al., 2017; Nguyen et al., 2020; Cai et al., 2022). The relatively frequent detection of 6:2 FTSA and FOSA in Swedish municipal DW (Table S1 in SI) is in line with a survey of surface/groundwater in Sweden (Gobelius et al., 2018), and with DW samples from the Great Lakes/St. Lawrence River in Canada (Kaboré et al., 2018).

The highest median concentration for the sum of all PFAS were found in spring DW samples, with a concentration of 2 ng/L (Table 2 and S1 in SI). The median sum of PFOA, PFNA, PFHxS and PFOS in DW was < 1 ng/L for both spring and autumn, though with a maximum of 14 ng/L in a waterworks sampled in spring (Table 2). The highest individual PFAS concentrations in DW were observed for PFBA (22 ng/L), followed by PFPeA (18 ng/L), 6:2 FTSA (17 ng/L) and PFHxS (~8 ng/L) (Table 2 and S1 in SI). These concentrations are within the range of previous studies (Gellrich et al., 2013; Zafeiraki et al., 2015; Park et al., 2018; Gobelius et al., 2018; Li et al., 2022a). Comparisons of PFAS concentrations and composition in DW between studies are complicated as LOQ may vary between studies and, perhaps more important, different studies have not necessarily measured the same PFAS. Moreover, depending on the distance between the DW and contamination source, along with the nature of the contamination, the occurrence of different PFAS in DW may vary considerably (Gyllenhammar et al., 2015; Gobelius et al., 2018; Zhang et al., 2019; Nickerson et al., 2021). Yet, legacy PFAAs, such as PFOA,

PFNA, PFHxS and PFOS, have frequently been found globally in both ground- and surface water, as well as in finished DW, even in areas with unknown presence of highly contaminated point sources (Kaboré et al., 2018; Ao et al., 2019; Arinaitwe et al., 2021; Sims et al., 2021). Contrastingly, FOSA was not observed in DW samples from Spain, Brazil and France (Schwanz et al., 2016), but has been quantified in about 4% of DW samples in Germany (Gellrich et al., 2013), in around a third of samples from Uganda (Arinaitwe et al., 2021) and detected in 53% in DW samples from Canada (Kaboré et al., 2018).

3.2. PFAAs in serum

As reported in Nyström et al. (2022a), (lin-) PFOA, PFNA, (lin-) PFHxS, and (lin-) PFOS were detected in ≥ 95% serum samples (Table 3). In contrast, other PFAS (e.g. short-chain PFAA and polyfluoroalkyl substances) were detected in only a few serum samples (Nyström et al. 2022a), even though some of the PFAS were detected at relatively high concentrations in single samples from certain waterworks and/or with high frequency in DW/RW (Table 3).

PFOS showed the highest median concentration in serum followed by PFOA, both at > 1 ng/g serum (Table 3). PFNA and PFHxS occurred at median concentrations < 1 ng/g serum (Table 3). The median concentration of $\sum_4$PFAAs was 2.2-fold higher than that of PFOS. The concentration ranges of PFHxS and PFOS in serum spanned over two orders of magnitude, while those of PFNA and PFOA spanned over one order of magnitude (Table 3). The measured concentrations were within the range of those previously reported for adolescent populations in South Korea, Taiwan, Norway and Denmark (Ji et al., 2012; Guang-Hui et al, 2013; Averina et al., 2018; Thomsen et al., 2021).

Even though FOSA, a known PFOS precursor (Benskin et al., 2009), was frequently detected in DW (Table S1 in SI), it was only detected in a few of the RMA serum samples at a maximum concentration of 0.1 ng lin-FOSA/g serum (Nyström et al. 2022a). In pooled serum samples from Swedish first-time mothers, FOSA declined from > 0.05 ng/g serum in 1997 to < 0.01 ng/g serum in 2006–2012 (Gebbink et al., 2015). It has been suggested that FOSA, unlike many of the long-chained PFAA with a high binding affinity for albumin in serum and plasma, favorably binds to red blood cells (Hanssen et al., 2013; Poothong et al., 2017). Among Norwegian adults sampled in 2013–2014, the median FOSA concentration in serum was 0.03 ng/mL (range: <0.002–0.05), and in whole

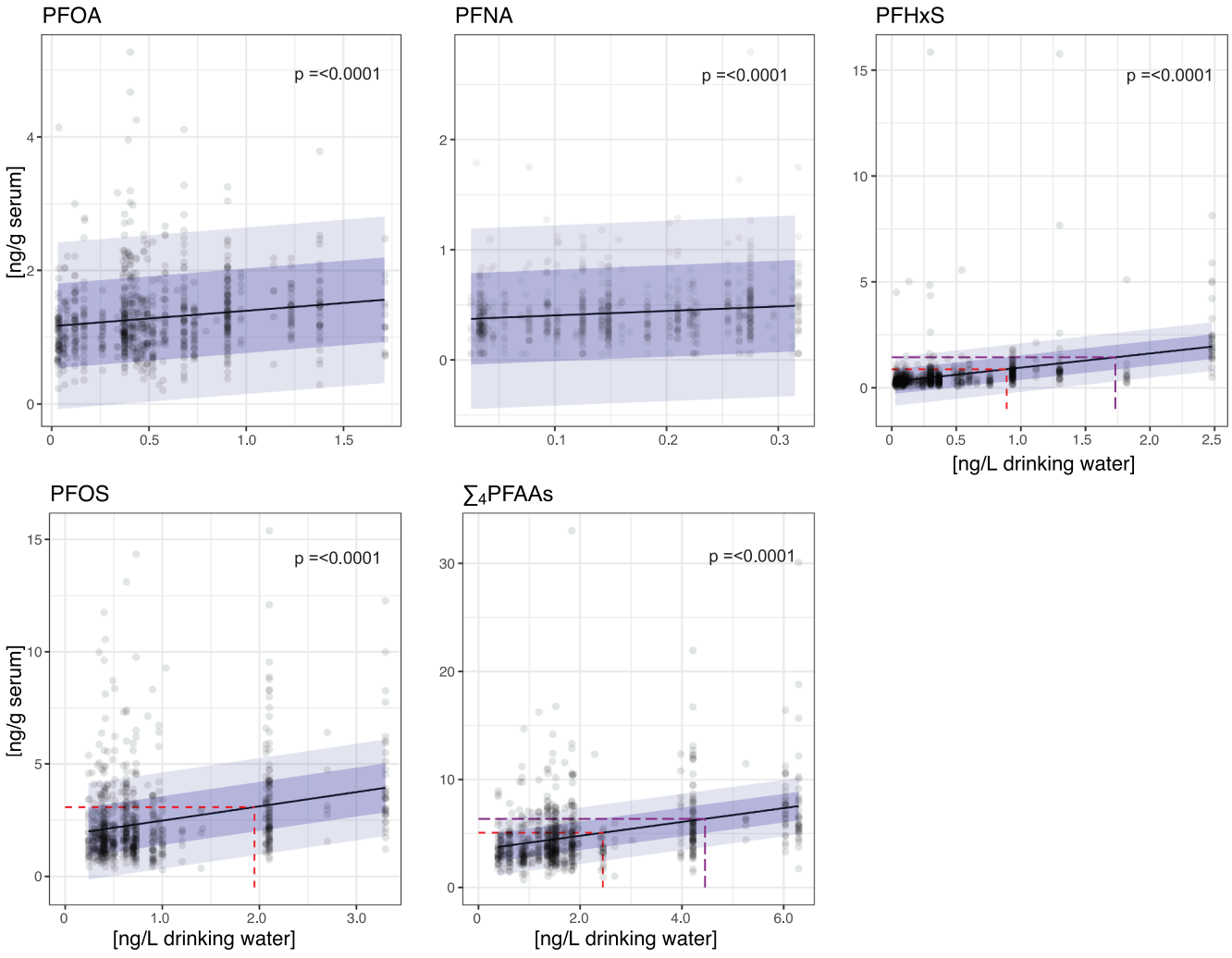

Fig. 1. Univariate weighted linear regression analysis of associations between DW and serum PFAA concentrations (n = 790). The solid black line represents the regression line and the light blue and light grey band represents the 68% and 95% prediction interval (PI), respectively. The horizontal red and purple dashed lines represent the estimated mean serum concentrations at the upper 68% and 95% PI limit of the background PFAA concentration (intercept). The vertical red ($DWES_{68}$) and purple ($DWES_{95}$) line represents the PFAA concentration in DW corresponding to the mean regression line PFAA concentration in serum at the upper PI limit of background PFAA concentration in serum (PI 68% $DWES_{68}$, 95% $DWES_{95}$). Grey circles are individual PFAA concentrations in serum. $DWES_{68}$ and $DWES_{95}$ could not be determined for PFOA, PFNA and PFOS ($DWES_{95}$) since we did not extrapolate DWES outside the ranges of DW concentrations observed. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

blood 0.14 ng/mL (0.05–2.35) (Poothong et al., 2017). In RMA, FOSA concentrations in general were not detectable in serum, making it impossible to evaluate the contribution of FOSA in DW to adolescent FOSA body burdens. Since FOSA with current analytical methods seems to be more easily detected in whole blood than in serum, whole blood needs to be considered as an analytical matrix in future studies with the aim to understand whether DW is an important exposure source for this PFOS precursor. Another possibility is to markedly decrease the detection limits of FOSA in serum so that the detection frequency increases in future studies.

3.3. Regression analyses

3.3.1. Associations between PFAA concentrations in drinking water and serum

Concentrations of PFOA, PFNA, PFHxS, PFOS and $\sum_4$PFAAs in DW displayed a significant positive association with concentrations in serum, in both the univariate (Fig. 1, Table 5) and multivariate weighted regression analyses (Table 5). The mean estimated SWR values ranged between 230–670 and 210 – 630 in the univariate and multivariate analyses, respectively, showing that the SWR values of the univariate models were not markedly different from those estimated by multivariate regression analyses (Table 5). The ordinary least squares regression analysis yielded similar results but with high parameter uncertainty (results not shown). The highest SWR was obtained for PFHxS, followed by $\sum_4$PFAA and PFOS (Fig. 1, Table 5), whereas the lowest was estimated for PFOA.

There are however important limitations to consider when interpreting the SWR. First and foremost, PFAA concentrations in DW were measured in the waterworks, instead of at the tap in the schools and homes of the participants. This was due to limited resources but also due to the fact that sampling at participants' residency was impossible as only participants postal codes and not addresses were at our disposal. Therefore, estimated mean PFAA concentrations in the DW represented the area of residence/school more than concentrations of each participańts home and school. Secondly, water samples were collected 1–2 years after the blood-sampling period, which could influence the exposure assessment and consequently the SWR. For example, if the exposure from DW would be higher at the time of blood sampling than during the time of water sampling, the estimated exposure from DW would have been underestimated, resulting in an underestimation of the SWR, and vice versa. However, as the average PFAA half-lives in humans are > 1 year (Xu et al., 2020; Li et al., 2022b), the concentrations in serum is in fact a result of long-term PFAA exposure for several years, with water being one exposure source. We were however not able to evaluate the long-term exposure of PFAAs from DW, as DW/RW was sampled once in spring and once in autumn in 2018. Lastly, no information was available on how long participants had resided in the area in which the participating waterworks supplied DW. Albeit these uncertainties in DW PFAA exposure assessment, our results show that the measured PFOA, PFNA, PFHxS, PFOS and $\sum_4$PFAA concentrations in DW were representative enough as estimates of long-term PFAA exposure from DW to result in significant positive associations between serum and DW PFAA concentrations.

In addition to these uncertainties, it could be speculated that some waterworks had initiated actions to limit PFAA contamination of DW between the blood and water sampling periods. However, in 2014 the Swedish Food Agency issued an action limit of 90 ng/L of $\sum_{11}$PFAS for DW in Sweden, including PFOA, PFNA, PFHxS and PFOS (SLV, 2021). This action limit was in effect in 2018 when the water sampling in the waterworks occurred. None of the waterworks in the current study had, to the best of our knowledge, PFAS concentrations above the action limit when it was introduced in 2014. Telephone and e-mail contact with the waterworks during the planning of the study did not indicate that actions to limit PFAS concentration in the DW had been taken between the time period of blood sampling 2016–17 and water sampling in 2018. However, 37 participants were excluded from the study since they were going to school and/or living in areas with a known history of high PFAS contamination of municipal DW, and where remediation of contamination had occurred before blood and DW sampling (Nyström et al., 2022a).

Previous studies also suffer from some of the limitations presented above, making estimates of SWRs and comparisons of results between studies uncertain. With this in mind, SWRs have previously been determined for PFOA (Emmett et al., 2006; Hoffman et al., 2011; Zhang et al., 2019), and recently also for PFNA, PFHxS and PFOS (Zhu and Bartell, 2020; Xu et al., 2020; Johanson et al., 2023). Our SWR estimate for PFOA of about 200 (Table 5) is similar to those presented in other studies. Zhang and colleagues (2019) estimated a SWR of 231 by simple regression analysis of matched serum and DW PFOA concentrations for the general Chinese population consuming DW at a median concentration of 9.9 ng PFOA/L. Using adjusted robust regression, Hoffman et al. (2011) estimated the SWR of PFOA to be roughly 142 in the C8 cohort who had been exposed to PFOA in their DW at median concentrations of 200 ng/L. Furthermore, a SWR of 105 was reported for PFOA in residents only consuming DW (median PFOA 3550 ng/L) from the public

Table 5
Output from the univariate (uni) and multivariate (multi) weighted linear regression analyses of associations between PFAA concentrations in drinking water (DW, ng/L) and serum (ng/g) in participants from Riksmaten Adolescents (n = 790).

PFAA		Adj R^2	Serum background concentration[a] (SE)(ng/g)	SWR[b] Mean (SE)	p-value SWR	DWES[c] (ng/L)		Serum concentration at DWES[d]	
						68%	95%	68%	95%
PFOA	Uni	0.22	1.2 (0.011)	230 (15)	<0.0001	NA	NA	–	–
	Multi	0.45	1.0 (0.066)	210 (15)	<0.0001	NA	NA	–	–
PFNA	Uni	0.19	0.36 (0.004)	410 (30)	<0.0001	NA	NA	–	–
	Multi	0.52	0.13 (0.023)	360 (33)	<0.0001	NA	NA	–	–
PFHxS	Uni	0.78	0.28 (0.004)	670 (13)	<0.0001	0.9	1.7	0.9	1.4
	Multi	0.77	0.51 (0.052)	630 (16)	<0.0001	1.2	2.4	1.0	1.8
PFOS	Uni	0.30	1.8 (0.03)	630 (34)	<0.0001	2.0	NA	3.1	–
	Multi	0.61	0.36 (0.19)	620 (26)	<0.0001	1.9	NA	2.3	–
Σ_4PFAA	Uni	0.69	3.5 (0.026)	640 (15)	<0.0001	2.4	4.5	5.1	6.4
	Multi	0.63	1.8 (0.27)	600 (23)	<0.0001	2.3	4.2	4.0	5.1

Note: Adj, adjusted; SE, standard error; SWR, serum:water ratio; NA, not applicable since DWES could not be determined within the range of the measured PFAA concentrations in DW; -, not derived as DWES was not determined.
The multivariate analysis was adjusted for age, gender, participant/maternal birth country, habitual seafood consumption and maternal education level.
[a] The regression intercept is interpreted as the serum background concentration that represents exposure from non-DW sources only.
[b] The SWR represents the slope (coefficient) of the regression line of the association between PFAA concentrations in serum and DW.
[c] DWES is the estimated mean PFAA DW concentration (ng/L) that corresponds to the upper 68% and 95% prediction interval limit of PFAA concentrations in serum at the regression line intercept (background concentrations).
[d] The serum PFAA concentration (ng/g) corresponding to the upper 68% and 95% prediction interval limit of background PFAA concentrations at the DWES.

water systems of Little Hocking, U.S., located near a fluoropolymer manufacturing facility (Emmett et al., 2006). Zhu and Bartell (2020), reported a SWR of 114 for PFOA, but no information was given about the DW PFOA concentration range that this SWR was representative for and how the SWR was modelled. More recently reported SWRs for PFOA, PFNA, PFHxS and PFOS in Swedish adults, exposed to a range of $\sum_4$PFAA concentrations in DW between non-detectable to > 1000 ng/L (Johanson et al., 2023), were approximately ten-fold lower than those reported herein. Moreover, among 26 airport workers in northern Sweden, Xu et al. (2020) estimated median serum/DW concentrations ratios of 30, 107 and 153 for PFOA, PFHxS and lin-PFOS, respectively, which also were considerably lower than in RMA. The reported DW concentrations were 300 ng PFOA/L, 710 ng PFHxS/L and 62 ng lin-PFOS/L (Xu et al., 2020). Although the SWRs in the present study were derived using weighted linear regression analysis as in Johanson et al. (2023), our results are not comprehensive enough to explain the higher SWRs among adolescents than adults in Sweden. It is plausible that the differences in study design, to some degree, can explain the difference in association. For example, the study of Swedish adults had considerably wider PFAA concentration ranges in DW than what was observed in the present study (Johanson et al., 2023; Xu et al., 2020). The RMA adolescents is also a more homogenous group compared to the adults included in Johanson et al. (2023), which consisted of multiple study groups from around Sweden with a large variation in age (18 to ca 80 years of age). Adults, unlike adolescents, have also accumulated PFAA from a multitude of exposure sources for a longer period of time, which also leads to greater variability in PFAA body-burdens.

Intriguingly, the highest SWR outside of Sweden were reported by Zhang et al. (2019) for PFOA, where the population, similarly to the RMA participants, had been exposed to comparatively low PFOA concentrations in DW (9.9 ± 1.8 ng/L, mean and standard deviation). Contrastingly, lower SWRs for PFOA has been reported for the populations exposed from DW with considerably higher PFOA contamination, ranging between 1500 and 7200 ng/L (Emmett et al., 2006), <6 ng/L to 13300 ng/L (Hoffman et al., 2011) and < 0.3 ng/L to 210 ng/L (Johanson et al., 2023). Therefore, it may be speculated that DW PFAAs bioaccumulate to a higher degree in human sera at lower DW PFAA concentrations than at higher concentrations. This hypothesis has previously been proposed by Post et al. (2009), who compared the SWR of PFOA in Little Hocking at 105 (Emmett et al., 2006) with SWR at 185 for a population drinking less PFOA-contaminated DW in Village of Pomeroy, U.S. (average levels in DW of 65 ng/L).

A few studies have suggested that PFAA half-lives are shorter at high PFAA exposures from DW than at low exposures, hypothetically being explained by a multi-compartment mechanism (Seals et al. 2011; Li et al., 2022b). Longer half-lives at low DW PFAA exposures, and consequently a higher relative bioaccumulation of PFAA from DW, may thus hypothetically explain the higher SWR at low PFAA concentrations in DW than at high concentrations. One possible mechanisms is saturable bioaccumulation processes, leading to a lower bioaccumulation from DW with high PFAA concentrations. In support of this hypothesis, toxicokinetic studies of PFAS in monkeys and rats showed that renal reabsorption of PFOA and PFOS is restricted at higher exposure doses leading to a higher excretion (Andersen et al., 2006).

In the univariate regression analyses of PFHxS and PFOS, we derived the mean concentration of PFAA in DW that likely would cause substantially elevated serum PFAA concentrations above background variation when sampling other adolescents in Sweden not participating in RMA (Fig. 1, Table 5). $DWES_{68}$, based on the 68% upper prediction interval for background PFAA concentrations in serum, were estimated to be 0.9 ng PFHxS/L, 2.0 ng PFOS/L and 2.4 ng $\sum_4$PFAA/L. For both PFHxS and $\sum_4$PFAAs, the $DWES_{95}$ was ~ 1.9-fold higher than $DWES_{68}$ (Table 5). $DWES_{68\text{-}95}$ could not be determined for neither PFOA nor PFNA due to a too narrow range of concentrations in DW in relation to the regression fit. If other human biomonitoring studies on adolescent populations, with similar demographical and background PFAA exposure patterns as RMA, detect average PFHxS, PFOS and $\sum_4$PFAA concentrations at or above these elevated levels in sera, the possibility of PFAA contamination of the DW should be investigated. Taken together, the results show that significantly elevated PFHxS, PFOS and $\sum_4$PFAAs concentrations in serum above typical variation in background-exposed adolescents may be expected at DW concentrations far <10 ng/L. The estimated DWES of PFOA, PFHxS and PFOS were considerably higher among the Swedish adults ($DWES_{68}$ > 20 ng/L) (Johanson et al., 2023) than in RMA ($DWES_{68}$ < 5 ng/L). Taking into account uncertainties in comparing results from different studies, the higher $DWES_{68}$ among the adults may be due to higher background, and/or larger variability in, serum PFAA concentrations. In line with this hypothesis, children/adolescents (4–12 years old), living in an area with PFAA-contaminated DW, had significantly elevated concentrations of PFOA and PFOS in serum whereas their mothers had not (Gyllenhammar et al., 2015; Gyllenhammar et al., 2019).

Previously, dietary exposure was suggested as the major exposure route for PFOA and PFOS among adults in Sweden, while the predominant route for PFHxS appeared to be DW (Vestergren et al., 2012). Similar findings have been reported outside of Sweden, where dietary exposure was considered the primary exposure route for PFOS in the general U.S population, with DW only contributing with roughly 20% (Egeghy and Lorber, 2011). However, a theoretical intake calculation of PFAA in a study of Swedish schoolchildren suggested that the intake of PFHxS from DW is two times higher than the estimated average intake from food, assuming a DW concentration of PFHxS at 2 ng/L (Glynn et al., 2020). This is also reflected in the present study where the variation in PFHxS concentration in DW were estimated to explain 78% of the variation in the PFHxS concentration in serum (adjusted R^2) (Table 5); a figure which did not change after including covariates in the regression model (Table 5). The degree of explanation was considerably lower for PFOA and PFOS, with adjusted R^2 values of 22% and 30%, respectively, in the univariate analyses, and 45% and 61%, respectively, in the multivariate analyses (Table 5). These R^2 values indicate that other determinants than concentrations in DW explain a significant part of the variation in PFOA and PFOS concentrations in serum among the RMA participants. Although the relative contribution of DW PFAA exposure to the total PFAA exposure was not investigated in the present study, the R2 values make us speculate that exposure via DW contributed more to the total PFHxS than the total exposure of PFOA, PFNA and PFOS. This speculation needs to be further evaluated in future studies.

The interpretation of the SWR and DWES results for $\sum_4$PFAA (Table 5) is difficult given that RMA participants from many areas of Sweden most likely were exposed to different $\sum_4$PFAA compositions from DW. Nevertheless, the univariate SWR and $DWES_{68\text{-}95}$ of $\sum_4$PFAA, estimated at 640 and ~ 2–4 ng $\sum_4$PFAA/L DW, respectively (Table 5), provide further evidence that low-level PFAA contamination of DW with these EFSA priority-listed PFAA indeed contribute significantly to Swedish adolescent PFAA body burdens. The Swedish Food Agency has recently issued a national maximum limit for $\sum_4$PFAA in DW of 4 ng/L (SLV, 2022), while in Denmark it is set to 2 ng $\sum_4$PFAA/L (DK EPA, 2021). A large-scale screening of PFAA in Swedish DW reported that 14 municipal waterworks had $\sum_{11}$PFAS concentrations higher than 10 ng/L, and almost all of these reported waterworks had at least one DW sample with a $\sum_4$PFAA concentration just below or above 4 ng/L (SLV, 2021). These 14 waterworks distribute DW to over 2 million people in Sweden (SLV, 2021), showing that actions to remediate PFAA in DW, even at low-level contamination, is important to ensure that DW is safe for consumption. Furthermore, lowering of PFAA concentrations in DW to levels below the maximum limits will in the long-run contribute to lower total cumulative PFAA exposures in a large fraction of the population served by the 14 waterworks.

3.3.2. *Influence of reported drinking water consumption in RMA on SWR*

Controlling for long-term DW consumption (Table 1) in the multiple regression analyses did not notably change the SWR for any of the PFAA

analysed (Table 5, Table S4 in SI). Albeit being significant for most of the PFAA, the associations between long-term DW consumption and serum PFAA concentrations were weak (Table S4 in SI). The observed weak negative relationships for PFOA and PFHxS could be due to residual confounding. An important uncertainty with the estimated long-term DW consumption data is that water consumption was self-registered retrospectively in RiksmatenFlexDiet (Lindroos et al., 2019). Furthermore, long-term DW consumption was only comprised of direct consumption of tap water and consumption of beverages made from tap water, e.g. tea, coffee and fruit/berry syrups/concentrate diluted with tap water. Consequently, information about consumption of tap water in cooked food, e.g. sauces, soups and stews, was lacking. An underestimation of long-term DW consumption was indicated by the relatively low average of around 0.6 L/day in RMA (Table 1), a consumption that is considerably lower than the average self-reported direct consumption of cold tap water among Swedish adults of ~ 1 L per day, and ~ 1.9 L per day for cold and heated tap water (Säve-Söderbergh et al., 2018).

To the best of our knowledge, only a few previous studies have investigated the influence of DW consumption on the relationships between PFAA concentrations in DW and serum/plasma, with varied results. PFNA, PFHxS and PFOS concentrations in plasma increased with 13–18% among German children (aged 8–10 years) with a self-reported long-term consumption of > 0.7 L DW per day compared to those consuming < 0.7 L per day (Wilhelm et al., 2015). The concentrations in DW were however slightly higher in the German study compared to RMA, with average levels ranging between 1.3 and 43 ng PFOS/L, <LOQ – 37 ng PFOA/L and ~ 3 ng PFHxS/L (Wilhelm et al., 2015). In the previous study of Swedish adults, concentrations of PFBS and PFHxS in serum were significantly higher among participants reporting consuming on average > 1.4 L/day (7 glasses per day) during the year before blood sampling than among those consuming < 1.4 L/day (Johanson et al., 2023). As in RMA, long-term, self-reported, DW consumption among adults and adolescents in the highly contaminated Veneto Region in Italy contributed only marginally to the variation in PFOA, PFHxS and PFOS concentrations in serum (Pitter et al., 2020).

3.3.3. *Influence of gender on SWR*

The interaction between gender and PFAA concentrations in DW was statistically significant for all PFAAs ($p < 0.002$ for all PFAA and $\sum_4$PFAAs, Table S5 in SI). Serum PFAA concentrations increased more steeply per unit increase in PFAA concentrations in DW for males than females (Fig. 2, Table S5 in SI). As also observed in RMA (Nyström et al., 2022a), males tend to have higher PFAA body-burdens than females (Jain, 2018; Kang et al., 2018; Pitter et al., 2020). Males did on average report a slightly less DW consumption compared to females, i.e. 0.56 L/day (range 0.04 – 2.6 L/day) compared to 0.61 L/day (range 0.05 – 2.8 L/day), respectively. These self-reported DW consumption data are

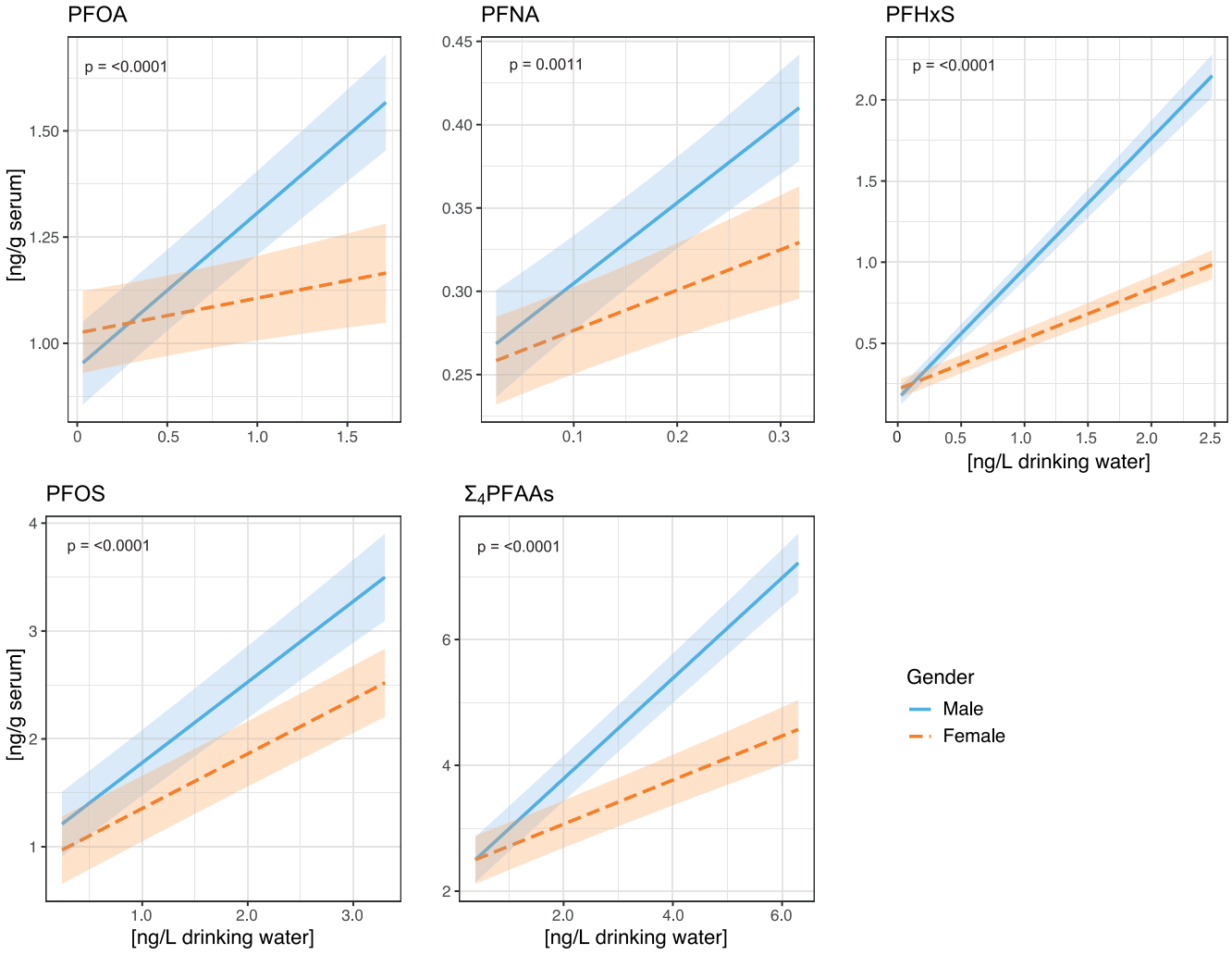

Fig. 2. Gender differences (males n = 350, females n = 440) in the relationship between PFAA in drinking water and serum for the RMA participants (n = 790). Dashed and filled lines show the regression lines for respective gender, shaded areas display the 95% confidence intervals. Associations were adjusted for age, maternal/participant birth country, maternal education level and habitual seafood consumption using weighed linear regression.

uncertain and most likely underestimates, nevertheless they suggest that gender differences in DW consumption were too small to explain the gender differences in the associations between PFAA in DW and serum. This conclusion is further supported by our results showing that the estimated long-term DW consumption of the participants did not appear to substantially influence the PFAA serum concentrations (Table S5 in SI). We hypothesize that the gender difference in the associations of PFAA concentrations in DW and serum may be due to sex differences in the toxicokinetics of PFAAs. Menstruation bleeding has been suggested as a significant excretion route among females (Ding et al., 2020; Park et al., 2019); results that were also to some extent supported in our previous RMA study (Nyström et al., 2022a). However, previous toxicokinetic modelling attempts have suggested that elimination through menstruation cannot entirely explain the gender differences in PFAA concentrations in serum (Wong et al., 2014; Wu et al., 2015; Lorber et al., 2015). Interestingly, a study of PFAA concentrations in urine of adults from China reported that the renal clearance of PFOA, PFNA, PFHxS and PFOS was higher in young females than in men and older females (Zhang et al., 2013). In a study of a Swedish population with high PFAA exposure from drinking water, it was suggested that an estrogenic induction of the renal clearance could contribute to faster elimination (shorter half-lives) of PFOA, PFHxS and PFOS from serum in females than males in the age group 15–50 years (Li et al., 2022b). These sex differences were not observed in younger and older age groups (Li et al., 2022b). More research is needed on possible gender-related differences of PFAA toxicokinetics, including the impact of menstruation and hormonal changes, especially at the onset of puberty.

3.4. Risk assessment of PFAA exposure from drinking water

In the present study, 16% of the participants (n = 790) had $\sum_4$PFAA concentrations in serum > 6.9 ng $\sum_4$PFAA/mL serum, which is the highest estimated serum concentration not connected to health concerns by EFSA (EFSA, 2020). Roughly 19% of the participants were exposed to DW with estimated mean $\sum_4$PFAA concentrations ≥ 4 ng $\sum_4$PFAA/L (Swedish maximum limit), while around 25% were exposed to levels exceeding ≥ 2 ng $\sum_4$PFAA/L (Danish maximum limit). Although only two grab samples (spring and fall) were taken from each participating waterworks, our results suggests that some of the participating waterworks had $\sum_4$PFAA concentrations that were not complying with the Swedish maximum limit that will be enforced in 2026 (Table 2) (SLV, 2022). As a result of the positive relation between serum and DW PFAAs concentrations, 34% of the participants exposed to mean DW concentrations of ≥ 4 ng $\sum_4$PFAA/L had serum levels exceeding 6.9 ng $\sum_4$PFAA/mL serum, while 11% exceeded this level at < 4 ng $\sum_4$PFAA/L in DW. This difference was statistically significant (χ^2-test of independence; $\chi^2 = 48.0$ at one degree of freedom, p-value < 0.0001). Using the slightly more restrictive Danish maximum limit (2 ng/L) (DK EPA, 2021), the corresponding percentages were 30 and 11%, respectively ($\chi^2 = 48.0$ at one degree of freedom, p-value < 0.0001). Taken together, the results show that a higher proportion of the RMA adolescents had $\sum_4$PFAA concentrations in serum above 6.9 ng/mL if the concentrations of $\sum_4$PFAA in DW exceeded the Swedish and Danish maximum limits than when not.

Some RMA participants exposed to very low DW PFAA concentrations (Table 4) still exceeded the 6.9 ng $\sum_4$PFAA/mL serum level (Fig. 1). In these cases, exposure sources other than the local DW most likely contributed to a large fraction of the long-term PFAA exposure. Even at DW PFAA concentrations above the DW PFAA maximum limits exposures from other sources than DW most likely contributed significantly to the exceedances of the 6.9 ng $\sum_4$PFAA/mL serum level. Consequently, efforts are needed to further decrease PFAA exposure, not only from DW but also from other significant sources to ensure that both present and future generations are not exposed to PFAAs at levels of health concern.

4. Conclusion

Drinking water is an indispensable component of the healthy human diet. The present study shows that low-level contaminated DW of the EFSA priority listed PFAAs of health concern, i.e. PFOA, PFNA, PFHxS and PFOS, is a significant exposure source for Swedish adolescents. Furthermore, our results indicate that bioaccumulation of PFAAs from DW in serum appears to be higher at low PFAA contamination levels in DW than at high contamination levels, and that bioaccumulation is higher among males than females. These results need to be further validated and investigated in future studies. Even though other exposure sources contribute to the total adolescent body burden of PFAAs, we show that significantly elevated mean serum PFAA concentrations above background among populations of Swedish adolescents most likely can be attributable to DW exposure at levels ~ 4 ng $\sum_4$PFAAs/L and higher. RMA adolescents having DW with concentrations above the maximum limits implemented in Sweden and Denmark (4 and 2 ng $\sum_4$PFAAs/L) were more likely to have serum PFAA levels exceeding the safe serum concentration estimated by EFSA than participants with DW concentrations below the DW maximum limits. Therefore, it is of considerable importance to reduce $\sum_4$PFAA concentrations in DW to levels below the maximum limits to ensure that DW does not pose a health concern to humans in the future.

CRediT authorship contribution statement

Jennifer Nyström-Kandola: Conceptualization, Methodology, Data curation, Formal analysis, Visualization, Writing – original draft. **Lutz Ahrens:** Investigation, Resources, Data curation, Writing – review & editing. **Anders Glynn:** Funding acquisition, Methodology, Conceptualization, Supervision, Writing – review & editing. **Gunnar Johanson:** Conceptualization, Methodology, Writing – review & editing. **Jonathan P. Benskin:** Investigation, Resources, Data curation, Writing – review & editing. **Irina Gyllenhammar:** Conceptualization, Resources, Data curation, Writing – review & editing. **Sanna Lignell:** Conceptualization, Resources, Data curation, Writing – review & editing. **Carolina Vogs:** Conceptualization, Methodology, Supervision, Writing – review & editing.

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 authors do not have permission to share data.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108166.

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