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Quantitative relationships of perfluoroalkyl acids in drinking water associated with serum concentrations above background in adults living near contamination hotspots in Sweden

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ABSTRACT

Contaminated drinking water (DW) is a major source of exposure to per- and polyfluoroalkyl substances (PFAS) at locations around PFAS production/use facilities and military airports. This study aimed to investigate quantitative relationships between concentrations in DW and serum of nine perfluoroalkyl acids (PFAAs) in Swedish adult populations living near contamination hotspots. Short-chained (PFPeA, PFHxA, PFHpA, and PFBS) and long-chained PFAAs (PFOA, PFNA, PFDA, PFHxS and PFOS) were measured in DW and serum. We matched DW and serum concentrations for a total of 398 subjects living or working in areas receiving contaminated DW and in one non-contaminated area. Thereafter, linear regression analysis with and without adjustments for co-variates was conducted. This enabled to derive (i) serum concentrations at background exposure (C_B) from sources other than local DW exposure (i.e. food, dust and textiles) at 0 ng/L DW concentration, (ii) population-mean PFAA serum:water ratios (*SWR*) and (iii) PFAA concentrations in DW causing observable elevated serum PFAA concentrations above background variability. Median concentrations of the sum of nine PFAAs ranged between 2.8 and 1790 ng/L in DW and between 7.6 and 96.9 ng/mL in serum. DW concentration was the strongest predictor, resulting in similar unadjusted and adjusted regression coefficients. Mean C_B ranged from <0.1 (PFPeA, PFHpA, PFBS) to 5.1 ng/mL (PFOS). Serum concentrations increased significantly with increasing DW concentrations for all PFAAs except for PFPeA with *SWRs* ranging from <10 (PFHxA, PFHpA and PFBS) to 111 (PFHxS). Observed elevated serum concentrations above background variability were reached at DW concentrations between 24 (PFOA) and 357 ng/L (PFHxA). The unadjusted linear regression predictions agreed well with serum concentrations previously reported in various populations exposed to low and high DW levels of PFOA, PFHxS and PFOS. The quantitative relationships derived herein should be helpful to translate PFAA concentrations in DW to concentrations in serum at the population level.

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1. Introduction

Per- and polyfluoroalkyl substances (PFAS) have been widely used in industrial and consumer applications (e.g. food-contact material, electronic products, textiles, aqueous firefighting-foams (AFFF), cosmetics, production of polymers) since the 1950s (Banzhaf et al., 2017). Perfluoroalkyl acids (PFAAs) form a subgroup of PFAS, which consist of a fully fluorinated carbon chain and a hydrophilic functional group, giving them favorable characteristics such as high chemical stability and surfactant properties. PFAAs are very persistent in the environment, highly mobile in soil and have high water solubility. These properties, combined with extensive use, have resulted in worldwide contamination of drinking water (DW) (Banzhaf et al., 2017). PFAA-contaminated DW has thus become a major exposure source for humans, in addition to background exposure from other sources such as food, dust and textiles (D'Hollander et al., 2010).

There are numerous reports of DW contamination in communities located in close proximity to manufacturing facilities where PFAS have been produced/used, or airports (civilian or military) deploying PFAS-containing AFFFs. Concentrations >100 ng/L of individual PFAAs have been reported from West Virginia, New Jersey, and Minnesota (U. S.), Arnsberg (Germany), Veneto Area (Italy) and Ronneby (Sweden) (Herrick et al., 2017; Hölzer et al., 2008; Landsteiner et al., 2014; Pitter et al., 2020; Post et al., 2013; Xu et al., 2021). In the U.S. for example, increasing number of PFAS hotspots with individual PFAS concentrations >100 ng/L have been identified about the last 10 years (https://www.ewg.org/interactive-maps/pfas_contamination/map/, October 2022). Body burdens of perfluorohexane sulfonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), measured either as serum or plasma concentrations, were elevated more than 100-fold in individuals drinking highly contaminated DW for extended periods compared to individuals drinking non-contaminated DW (Glynn et al., 2020; Nair et al., 2021; Xu et al., 2021). These long-chained PFAAs have emerged as a major health concern due to their high bioaccumulation potential, long elimination half-lives in humans and toxicological profiles (EFSA, 2020; Li et al., 2018; Xu et al., 2020). However, DW exposure to perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonic acids (PFSAs) with perfluoroalkyl chain lengths of <7 and 6 carbon atoms, respectively, is also common (Gyllenhammar et al., 2015; Hölzer et al., 2008; Pitter et al., 2020; Xu et al., 2020). Concentrations of short-chained PFAAs in DW can be as high as or even higher than long-chained PFAAs (Pitter et al., 2020; Xu et al. 2020, 2021). Moreover, short-chained PFAAs are as persistent and even more mobile than long-chained PFAAs (Li et al., 2020), thus might contribute significantly towards total PFAA exposure.

In 2020, the European Food Safety Authority (EFSA) determined a tolerably weekly intake (TWI) of 4.4 ng/kg body weight from food and DW for the sum of PFOA, perfluorononanoic acid (PFNA), PFHxS and PFOS. The TWI was established based on maternal long-term PFAAs exposure before pregnancy, causing decreased antibody response to vaccination in one-year old toddlers as the most critical effect. EFSA (2020) concluded that this TWI also protects against other potential adverse effects in humans, such as lowered birth weight as well as increased serum cholesterol and serum liver enzyme levels (EFSA, 2020). Due to the phase-out and substitution of legacy PFAA production and use, human exposure to e.g. PFOA, PFHxS and PFOS is currently declining in the Swedish general population (Miaz et al., 2020; Nyberg et al., 2018). Nevertheless, PFAA-contamination of important surface and groundwater DW sources will most likely persist for a long time, in the worst case for millennia (Cousins et al., 2016), and sometimes at levels posing potential health risks, unless costly remediation actions are taken. DW producers and risk managers thus have the task to reduce PFAA concentrations in order to provide clean DW, which is also one of the United Nations sustainable development goals (United Nations, 2017). Meanwhile, there is a lack of knowledge about the contribution of DW to total PFAA exposure. Of specific interest is to determine DW concentrations at which elevated population-averaged PFAA concentrations in serum are observable above background variability.

The aim of this study was to establish quantitative relationships between PFAA concentrations in DW and serum. To this end, we used published data from PFAA-contaminated hotspots in four different Swedish communities (Arvidsjaur, Lulnäset, Uppsala and Visby) and in one non-contaminated site (Karlshamn). In total, nine PFAAs were selected that had paired DW-serum concentrations data from at least one of the sites (i.e. perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), PFOA, PFNA, perfluorodecanoic acid (PFDA), perfluorobutanesulfonic acid (PFBS), PFHxS and PFOS). The first objective was to compare DW and serum composition of PFAAs between the four sites. The second objective was to develop unadjusted (i.e. without co-variates) and adjusted (i.e. including co-variates) linear regression models for the relationships between concentrations of the nine PFAAs in DW and serum. This enabled to estimate (i) background concentrations in serum originating from non-DW sources at 0 ng/L DW concentration, (ii) the accumulation potential from DW and (iii) PFAA concentrations in DW that cause observable elevated serum concentrations above background variability. The last objective was to evaluate the predictability of our regression models by comparing predicted and measured PFAA concentrations in serum, departing from measured PFAA concentrations in DW from other hotspots in Europe, U.S. and China from prior studies.

2. Material & methods

2.1. PFAA-contaminated sites and study populations

This study focused on the four monitored sites Arvidsjaur (Xu et al., 2020), Uppsala (Gyllenhammar et al., 2015), Lulnäset (Forsell et al., 2016) and Visby (Isaksson et al., 2020), where the historical use of AFFF during fire-fighting training contributed to PFAS-contamination of DW (Table 1). Blood was sampled in 2018 from employees (N = 26) at Arvidsjaur airport after discovery of PFAS-contaminated DW at the workplace, while the municipal DW was uncontaminated (Xu et al., 2020). In Uppsala, serum samples were collected from first time mothers between 2008 and 2011 (N = 148), before PFAS-contaminated municipal DW was remediated in 2012 (Gyllenhammar et al., 2015). In Lulnäset, near Luleå airport in northern Sweden, the study group was a mix of permanent and seasonal adult residents (N = 14) consuming DW from private wells and a common summer waterworks, with blood sampled in 2018. Finally, the study group from Visby (N = 73), on the Swedish island of Gotland, was also a mix of permanent and seasonal adult residents and consumed DW from private wells, provided blood samples in 2018 (Isaksson et al., 2020). In addition to the four hot spots, we included DW and serum PFAA data from 137 adults in Karlshamn in southern Sweden. As no PFAS-contamination had been discovered in Karlshamn DW, we assumed that these subjects had been exposed only via background sources (Xu et al. 2020, 2021). The total data set consisted of 398 subjects and summary characteristics of the participating subjects at each site are given in Table 1.

Information on the duration of exposure to contaminated DW duration was obtained from participants in Arvidsjaur, Lulnäset and Visby as (i) the self-reported average number of weeks per year of residence (at work in the case of Arvidsjaur), and (ii) the time span between moving to the residence (or start working) and serum sampling (Table 1). The serum-sampling period spanned over ten years between 2008 (Uppsala) and 2018 (Visby). During this period, a decline in background exposure to PFAAs was observed in Sweden (Miaz et al., 2020; Nyberg et al., 2018). Serum sampling was conducted after the discovery of DW-contamination (except in Uppsala) and the lag time from cessation of contaminated DW consumption to serum sampling varied from 11 to 14 days in Arvidsjaur to approximately 60 days in Lulnäset. Bottled water was provided to the airport workers in Arvidsjaur immediately after discovery of the contamination, while Lulnäset

Table 1
Summary characteristics of the participating subjects and exposure at the five Swedish sites.

		Arvidsjaur	Lulnäset	Uppsala	Visby	Karlshamn	Total
Number of subjects	Total	26	14	148	73	137	398
	Women	7 (27%)	7 (50%)	148 (100%)	42 (57%)	76 (56%)	280 (70%)
	Men	19 (73%)	7 (50%)	0 (0%)	31 (43%)	61 (44%)	118 (30%)
Year of serum sampling		2018	2015	2008–2011	2018	2016	2008–2018
Age (years)	Mean	43	67	30	57	41	41
	Range	22–62	36–81	21–40	18–82	18–60	18–82
Body mass index (kg/m^2)	Mean	28	25	24	27	26	25
	Range	23–31	22–30	18–37	18–45	19–38	18–45
	Missing information	12/26 (46%)	0/14 (0%)	3/148 (2%)	2/75 (3%)	2/137 (1%)	17/398 (4%)
Residence type	Permanent	26/26 (100%) [a]	4/14 (29%)	148/148 (100%)	46/73 (63%)	137/137 (100%)	361/398 (91%)
	Seasonal	0/26 (0%)	10/14 (71%)	0/148 (0%)	27/73 (37%)	0/137 (0%)	37/398 (9%)
Parity (at least one child)	Yes	3/7 (43%)	2/7 (29%)	148/148 (100%)	31/42 (74%)	22/76 (29%)	206/280 (73%)
	No	4/7 (57%)	5/7 (71%)	0/148 (0%)	11/42 (26%)	13/76 (17%)	33/280 (12%)
	Missing information	0/7 (0%)	0/7 (0%)	0/148 (0%)	0/42 (0%)	41/76 (54%)	41/280 (15%)
Breastfeeding ≥ three months	Yes	3/7 (43%)	2/7 (29%)	148/148 (100%)	30/42 (71%)	20/76 (26%)	203/280 (72%)
	No	4/7 (57%)	5/7 (71%)	0/148 (0%)	12/42 (29%)	15/76 (20%)	36/280 (13%)
	Missing information	0/7 (0%)	0/7 (0%)	0/148 (0%)	0/42 (0%)	41/76 (54%)	41/280 (15%)
				Exposure characteristics			
Data availability of DW concentration	Measurements	26/26 (100%)	14/14 (100%)	148/148 (100%)	62/73 (85%)	137/137 (100%)	387/398 (97%)
	Missing information	0/26 (0%)	0/14 (0%)	0/148 (0%)	11/73 (15%)	0/137 (0%)	11/398 (3%)
Time spent in residence (weeks per year) [b]	Mean	46	27	46	35	46	43
	Median	46	23	46	46	46	46
	Range	0	7–46	0	2–51	0	2–51
	Missing information	0/26 (0%)	0/14 (0%)	0/148 (0%)	1/73 (1%)	0/137 (0%)	1/398 (<1%)
Residence/employment time until serum sampling (years)	Mean	10.9	38	Not determined	19	Not determined	17
	Median	8.9	49		18		19
	Range	0.5–28	7–71		<0.1–57		<0.1–71
	Missing information	0/26 (0%)	0	148/148 (100%)	20/73 (27%)	137/137 (100%)	305/398 (77%)
Consumption of contaminated DW (glasses per day)	≤7 [c]	8/26 (31%)	7/14 (50%)	0	39/73 (54%)	0	54/398 (14%)
	>7 [c]	17/26 (65%)	7/14 (50%)	0	20/73 (27%)	0	44/398 (11%)
	Missing information	1/26 (4%)	14/14 (100%)	148/148 (100%)	14/75 (19%)	137/137 (100%)	314/398 (79%)
Change in consumption of contaminated DW after discovery of contamination	Reduction	26/26 (100%)	0	0	17/73 (23%)	0	43/398 (11%)
	No change	0	0	148/148 (100%) [e]	39/73 (54%)	137/137 (100%) [d]	324/398 (81%)
	Increase	0	0	0	6/73 (8%)	0	6/398 (1%)
	Missing information	0	14/14	0	11/73 (15%)	0	25/398 (7%)
Lag time between remediation of contaminated DW and serum sampling (days)		11–14	~60	0	Not reported	0	

DW – Drinking water.
[a] In Arvidsjaur. full time employment was regarded as equivalent to permanent residence.
[b] Six weeks of absence from the residence was assumed due to annual vacation (Arvidsjaur. Karlshamn. Uppsala).
[c] Seven glasses of DW per day was the mean for all subjects from Arvidsjaur, Lulnäset and Visby.
[d] In Karlshamn. no contamination of DW was discovered.
[e] In Uppsala, sampling occurred before contamination was discovered.

residents collected clean DW from a provided tank. In Visby, families with contaminated well water were offered refunds on purchased bottled DW in 2016. However, self-reported questionnaires revealed that only 23% of the subjects reduced their consumption of contaminated DW between 2016 and 2018, while 62% did not reduce or even increased their consumption. Thus, the lag time for subjects in Visby was uncertain. We assumed that no change in sources of DW consumption occurred in Karlshamn and Uppsala.

2.2. Sampling of drinking water and PFAA analysis

We assigned DW concentrations to each subject (Table 2). Airport workers in Arvidsjaur consumed DW from a common source supplied by the employer, which was sampled three times between August and September 2018. We used the results from the last DW sample, taken 8–11 days before serum sampling (Xu et al., 2020). Subjects living in Karlshamn received DW from the municipal waterworks and DW was sampled twice (Xu et al., 2020). Regarding Uppsala, Gyllenhammar et al. (2015) reconstructed the historic distribution of PFAS-contaminated municipal DW from 1996 onwards, based on DW samples taken between 2012 and 2014. Four districts were characterized by different PFAA concentrations in the DW. Therefore, each subject was assigned PFAA concentrations in DW determined in the districts where they lived at the time of serum sampling. Subjects living in Lulnäset answered questionnaires regarding their relative use of DW from their own private well and a common municipal summer waterworks. The questionnaire data on DW use were combined with PFAA concentration data for each well to calculate weighted arithmetic mean PFAA concentrations in DW for each subject. In Visby, between one and 16 DW samples were collected from 34 private wells between 2011 and 2018. We averaged PFAA concentrations per private well and assigned a private well to each subject according to the subject's residential address (SI Fig. 3).

PFAAs in DW were measured by two commercial laboratories, SYNLAB and ALS Scandinavia, as described in the Supplement Information (SI). Both are accredited by SWEDAC according to SS-EN ISO/IEC 17025. PFAAs were analyzed by liquid chromatography-tandem mass spectrometry (LC/MS/MS) after solid-liquid extraction (F 42) (DIN 38407–42). Limits of detection (LOD) are given for each site in SI Table 2. DW concentrations below the LOD were substituted by LOD/$\sqrt{2}$ for all statistics. Obviously, values below the limit of quantification (LOQ) are more uncertain than values above the LOQ. However, inclusion of values down to the LOD increases the sample size and strengthens the statistical analyses, particularly at low concentrations.

Table 2
Characteristics of drinking water sources, sampling and concentrations [ng/L] of PFAA at the five Swedish sites.

	Arvidsjaur[a]	Lulnäset[b]	Uppsala[c]	Visby[d]	Karlshamn[a]
Contamination discovery	2018	2015	2012	2016	No contamination
Sampling time	September 3, 2018	August 1, 2018	July 4, 2012–Feb 11, 2014	April 21, 2011–January 18, 2019	January 15, 2020
DW source	1 common waterworks - groundwater	32 private wells and one common summer waterworks - both groundwater	District 1 - private wells or municipal water from the local waterworks. District 2 - common waterworks from Gränby District 3 & 4 common waterwarks from Bäcklösa & Gränby all 4 Distrcts -groundwater	34 private wells - groundwater	1 common waterworks - surface water
total number of analyzed DW samples	3	1 sample from each well	District 1 (outside Uppsala): 2 samples District 2 (no contamination): 2 samples District 3 (10% contamination): 105 samples District 4 (60% contamination): 105 samples	1 to 16 samples over time per private well	2
Number of subjects receiving sampled drinking water	100% from airport water supply: 26	100% from private wells: 4.100% from common waterworks: 7. mix consumption 3	District 1–27 District 2–60 District 3–15 District 4 - 48	100% from private wells: 64 no imeasurements: 11	100% from municipal waterworks: 144
Laboratory			**Commercial accredited laboratory**		
Reference	Xu et al. (2020)	Forsell et al., (2016)	Glynn et al., (2012). Gyllenhammar et al., (2015)	Isaksson et al. (2020)	Xu et al. (2021)
LOD handling	LOD/$\sqrt{2}$	LOD/$\sqrt{2}$	LOD/$\sqrt{2}$	LOD/$\sqrt{2}$	LOD/$\sqrt{2}$
PFAAs in drinking water [ng/L] – Median [Arithmetic mean; Range; Detection frequency]					
PFPeA	180 [100%]	Not determined	Not determined	13.1 [28.2; <0.3–96.5; 70%]	<0.6 [0%]
PFHxA	330 [100%]	Not determined	<0.3 [2.2; <0.3–6.3; 41%]	11.0 [28.6; <0.3–100.0; 70%]	<0.3 [0%]
PFHpA	97 [100%]	54.0 [47.8; 23.6–55; 100%]	<0.3 [1.5 < 0.3–4.2; 41%]	4.9 [10.8; <0.3–40.0; 70%]	<0.3 [0%]
Linear PFOA	210 [100%]	55.3 [48.9; 23.7–59; 100%]	0.2 [1.7; 0.2–4.7; 100%]	4.8 [9.8; <0.3–38.5; 71%]	<0.3 [0%]
PFNA	<0.6 [0%]	7.1 [6.7; <3.9–7.1; 0%]	Not determined	0.3 [0.5; <0.3–2.2; 59%]	<0.6 [0%]
PFDA	<0.6 [0%]	7.1 [6.7; <3.9–7.1; 0%]	Not determined	0.3 [0.3; <0.3–0.5; 22%]	<0.6 [0%]
PFBS	200 [100%]	Not determined	<0.3 [2.8; <0.3–8.0; 41%]	5.0 [7.8; <0.3–18.0; 81%]	<0.3 [0%]
Linear PFHxS	710 [100%]	682 [574.1; 81.9–714.0; 100%]	0.9 [16.0; 0.3–46.3; 100%]	27.2 [49.5; <0.3–190.81%]	<0.3 [0%]
Linear PFOS	62 [100%]	434 [367.4; 32.0–515.0; 100%]	0.8 [9.4; 0.1–26.8; 100%]	47.7 [69.4; <0.3–355.0; 84%]	<0.2 [0%]
Sum of PFAA median concentrations	1790	1240	<2.8	114	<3.5
Sum of PFOA. PFNA. PFHxS and PFOS median concentrations	983	1178	1.9	80	<1.4

LOD – limit of detection. DW – drinking water.
[a] Multiple water samplings were performed in Arvidsjaur and Karlshamn. For Arvidsjaur. concentrations are listed from the last time point. For Karlshamn. PFAAs in DW were below LOD in both samples.
[b] Measured water samples from private wells and common waterworks were averaged according to self-assessed annual consumptions from subjects.
[c] Concentrations from the contaminated wells producing drinking water distributing to the four different districts are listed as a summary (see Gyllenhammar et al., 2015 for district specific DW concentrations).
[d] Multiple water samplings were performed between 2011 and 2019. Listed are time-averaged PFAA concentrations based on anonymous address data.

2.3. Blood sampling and PFAA analysis

In Uppsala, maternal venous blood samples were taken three weeks after delivery (Glynn et al., 2012; Gyllenhammar et al., 2015), using 10 mL Vacutainer® or Vacuette® serum tubes. Following centrifugation, samples were stored at −20 °C until analysis. In Arvidsjaur, Karlshamn, Lulnäset and Visby, approximately 5 mL venous blood was sampled in Vacutainer® serum tubes. After centrifugation, the serum samples were frozen at −20 °C and transported to the final site of storage using cold chain logistics where the samples were stored at −80 °C (Forsell et al., 2016; Isaksson et al., 2020; Xu et al., 2020).

PFAAs in serum were measured by three different analytical methods (Table 3) with different LODs (SI Table 4). Gyllenhammar et al. (2015) previously described analytical method 1 used for the Uppsala site. Xu et al. (2021) reported method 2 used for Lulnäset and all samples from Karlshamn (137/137 samples) sites. Xu et al. (2020) provided a detailed description of method 3 used for Visby, a subsample including around 40% of all samples from Karlshamn (59/137 samples), and Arvidsjaur sites. Concentrations below LOD in serum samples from Karlshamn, Lulnäset and Uppsala subjects analyzed by method 1 and 2 were assigned LOD/$\sqrt{2}$. Concentrations in the 59 serum samples from Karlshamn, and the samples from Arvidsjaur and Visby analyzed by method 3 were reported by the laboratory even when signals were below the LOD of the analytical method but above the baseline of the blank. These data were used as reported by the laboratory. Notably, such values are less accurate than values ≥ LOD, but are used to improve the statistical power of the statistical analyses instead of using substituted data such as LOD/$\sqrt{2}$. This approach is generally considered to result in less statistical bias (Bergstrand and Karlsson, 2009).

2.4. PFAA selection

In total, 11 PFCAs and 7 PFSAs were analyzed in DW and serum samples from all five sites. We selected three PFCAs (i.e. linear forms of PFHxA, PFHpA and PFOA) and three PFSAs (i.e. linear forms of PFBS and PFHxS as well as linear and total (linear and branched) PFOS), for

which paired DW-serum concentrations were available for subjects from at least three of the five sites. We additionally included PFPeA in the analysis as DW concentrations (measured only in Visby) ranged by two orders of magnitude. Additionally, we included PFNA and PFDA for which DW concentrations were below LOD or not analyzed in four of the five sites but were quantified in serum in over 86% of the subjects in all five sites (Table 3). The selected PFAAs possess a broad range of physicochemical characteristics (SI Table 1).

2.5. PFAA patterns in drinking water and serum

We investigated how PFAA patterns in DW and serum samples differed between the study populations. Correlations between log-transformed PFAA concentrations in serum were also analyzed by Pearson correlation. To determine the relative contribution of individual PFAAs to the total concentrations, we used molar concentrations instead of mass concentrations. The relative contribution of individual PFAAs was calculated using the ratio between the concentrations of the arithmetic mean of each PFAA and the total arithmetic mean of all PFAAs.

2.6. Regression models

Regression modeling was used to estimate the relationship between concentration in DW (C_{DW}, ng/mL) and serum (C_s, ng/mL) for each PFAA without co-variates (unadjusted model, eq. (1)).

$$C_S = C_B + SWR \times C_{DW} + \varepsilon \quad (1)$$

A linear relationship between DW and serum concentrations was assumed with the slope corresponding to the serum:water ratio (*SWR*, unit-less). The intercept C_B corresponds to the background serum concentration at 0 ng/L DW concentrations of PFAAs, representing exposure via sources other than the local DW source, e.g. food, cosmetics and dust. The term $\mathcal{E}$ represents the residual error between measured individual serum concentrations and estimated population mean.

In a second step, we expanded the unadjusted model by including co-variates (X_i) representing factors reported to be associated with serum concentrations (eq. (2)).

$$C_S = C_B + SWR \times C_{DW} + \beta_i \times X_i + \varepsilon \quad (2)$$

Five co-variates were introduced, namely age, BMI, gender (male/female with male as reference), residence form (permanent/temporary with permanent as reference) and year of serum sampling.

Table 3
Characteristics of serum sampling and PFAA concentrations [ng/mL] in serum from the subjects from the five Swedish sites.

	Arvidsjaur	Lulnäset	Uppsala	Visby	Karlshamn
Sampling Time	September 11, 2018–September 14, 2018	October 26, 2015–October 27, 2015	January 25, 2008–November 27, 2011	September 07, 2018–October 05, 2018	May 03, 2016–October 25, 2016
Number of analyzed samples	26	14	148	73	137
Laboratory	Occupational and Environmental Medicine. Lund University. Sweden	Occupational and Environmental Medicine. Lund University. Sweden	Environmental Science and Analytical Chemistry. Stockholm University. Sweden	Occupational and Environmental Medicine. Lund University. Sweden	Occupational and Environmental Medicine. Lund University. Sweden
Chemical analysis	Method 3	Method 2	Method 1	Method 3	Method 2 & Method 3[a,b c]
Reference of chemical analysis description	Xu et al. (2020)	Xu et al. (2021)	Gyllenhammar et al. (2015)	Xu et al. (2020)	Xu et al., (2020) & (2021)
LOD handling	manually quantified below LODs	LOD/$\sqrt{2}$	LOD/$\sqrt{2}$	Manually quantified below LOD	LOD/$\sqrt{2}$ (Method 2) and manually quantified below LODs (Method 3)
	PFAAs in serum [ng/mL] – Median [Arithmetic mean; Range. Detection frequency]				
PFPeA	Not determined	Not determined	Not determined	0.02 [0.03; 0.01–0.07; 0%]	Not determined
PFHxA	0.38 [0.43; 0.16–1.06; 100%]	Not determined	<0.3 [0%]	0.09 [0.11; 0.02–0.42; 68%]	<0.07 [0%] [c]
PFHpA	0.45 [0.66; 0.07–2.23; 100%]	0.30 [0.50; <0.1–2.20.86%]	0.04 [0.06; <0.04–0.30.55%]	0.05 [0.07; 0.02–1.05; 47%]	<0.05 [0%][c]
Linear PFOA	9.05 [10.86.2.95–30.93; 100%]	3.50 [4.41; 0.30–10.90; 100%]	1.48 [1.61; 0.20–13.05.100%]	1.71 [2.02; 0.33–13.88; 98%]	1.61 [1.82; 0.26–4.91; 100%] [b,c]
PFNA	0.89 [1.02; 0.38–1.98; 100%]	1.25 [1.44; 0.10–4.30.100%]	0.46 [0.52; 0.06–2.18.100%]	0.71 [0.89; 0.15–4.07.100%]	0.65 [0.69; 0.22–1.45.100%] [c]
PFDA	0.36 [0.38; 0.16–0.76; 100%]	0.40 [0.47; <0.10–1.20; 86%]	0.25 [0.28; <0.05–1.14.94%]	0.29 [0.38; 0.06–1.48.99%]	0.27 [0.30; 0.11–0.75.100%] [c]
PFBS	0.33 [0.42; <0.05–1.34; 96%]	<0.05 [0%]	0.03 [0.05; <0.01–0.80.81%]	0.02 [0.03; <0.01–0.07.4%]	<0.03 [0%] [c]
Linear PFHxS	75.97 [105.56; 17.43–401.50; 100%]	41.75 [44.67; 3.80–192.00; 100%]	3.52 [5.03; 0.29–32.72; 100%]	3.23 [8.12; 0.35–60.42; 100%]	0.60 [0.61; <0.05–1.13.98%] [b,c]
Linear PFOS	9.51 [11.04; 5.42–27.77; 100%]	18.58 [17.50; 2.95–49.24; 100%] [a]	4.38 [4.66; 0.21–12.09; 100%]	5.70 [7.95; 1.22–34.88; 100%]	4.33 [5.15; 0.30–43.74; 100%] [a,b,c]
Sum of PFAA median concentrations	96.94	65.83	10.46	11.82	7.63
Sum of PFOA. PFNA. PFHxS and PFOS median concentrations	95.42	61.98	9.84	11.35	7.19

LOD – Limit of detection.

[a] Serum concentrations of total PFOS from 14 samples from Lulnäset and 78 samples from Karlshamn measured using method 2 were translated to linear PFOS using correlation between method 2 and method 3 (SI Fig. 2).

[b] Linear PFOA. linear PFHxS and total PFOS were analyzed in 137 serum samples from Karlshamn with method 2 and a randomly selected subset of serum samples (59/137) was reanalyzed using method 3. See correlation between PFOA. PFHxS and PFOS serum concentrations measured by method 2 and method 3 in Supplement information (SI Fig. 1).

[c] PFHxA. PFHpA. linear PFOA. PFNA. PFDA. PFBS. linear PFHxS and linear PFOS were measured in 59 of the total 137 serum samples using method 3.

Confidence and prediction intervals of the regression line were determined for both unadjusted and adjusted models (eqs. (1) and (2)). The prediction interval allowed us to derive PFAA concentrations in DW (*DWES*) that caused observable elevated PFAA concentrations in serum above background variability. Observable elevated concentrations in serum above background variability were defined to be equal or higher than the upper prediction interval level of C_B. The upper 68% (one standard deviation) and 95% (two standard deviations) prediction interval levels were denoted as $DWES_{68}$ and $DWES_{95}$, respectively.

Three separate analyses were conducted by adding co-variates to the adjusted regression model. First, the influence of DW exposure duration on serum concentrations was studied using information from Arvidsjaur, Lulnäset and Visby. Second, DW consumption was added as a categorical variable, i.e. lower (reference), equal to or higher than the average DW consumption of water of seven glasses per day, derived by available data from Arvidsjaur, Lulnäset and Visby. The daily DW consumption in Arvidsjaur was reported as plain water only, while that in Lulnäset and Visby subjects included plain water, water used for home-made lemonade and hot beverages. Third, we explored the impact of a lag time between contamination cessation and serum sampling based on reported changes in consumption after contamination discovery from Visby subjects by adding DW consumption change as a categorical variable (reduced (reference), not changed or increased).

Gender-specific regression coefficients were estimated by gender-stratified regression analyses. In addition, we evaluated the impact of menstruation on the female regression model by excluding females older than 50 years (Xu et al., 2021). We further added parity (having at least one child) as categorical co-variate as this factor is known to influence PFAA concentrations in serum (Mondal et al., 2014).

All statistical analyses were performed in R (version 4.1.1) and the significance level was set to $p \leq 0.05$. We used untransformed concentrations in all regression models. To avoid heteroscedasticity and to reach normally distributed residuals, we performed the regression analyses using the inverse of the absolute residual error ($1/|r|$) as a weighting procedure. We also performed linear regression analyses using the iteratively reweighted least squares (IRLS) method (R package robustreg, version 01–11). The IRLS method weights the impact of each observation and may statistically identify and exclude outliers from the linear regression analysis. The goodness-of-fit was evaluated by the residual error and the coefficient of determination. Confidence and prediction intervals were computed using the lm function from the stats package (version 4.1.1) and ggpredict from the ggeffects package (version 1.1.1), respectively. The variance inflation factor (VIF) was determined for each analysis to quantify high multi-collinearity between explanatory co-variates with VIF>10 as cut-off value.

2.7. Sensitivity analysis

Multiple sensitivity analyses were performed to examine the robustness of the associations between DW and serum concentrations for both unadjusted and adjusted regression models. To this end, we evaluated the effect of excluding different site subgroups from the analysis. The possible influence of over-representation of women in the study population was analyzed by excluding Uppsala population of young women, which in many cases were exposed to very low DW concentrations. The two sites with the highest PFAA concentrations in DW (Arvidsjaur and Lulnäset alone and together) were excluded to evaluate whether the associations between DW and serum concentrations remained stable for subgroups exposed to lower PFAA concentrations via DW or not. The Karlshamn site was excluded in order to evaluate the impact of all PFAA concentrations in DW below LOD on the regression analyses. Visby was excluded to investigate how the uncertainty caused by unknown individual lag times after cessation of contaminated DW intake influenced the results.

2.8. Predictability of serum concentrations

We tested how well the unadjusted regression models predict literature-reported biomonitoring data for populations exposed to a variety of known PFAA concentrations in DW. We identified eight studies that documented both DW and serum concentrations for PFOA, PFHxS and PFOS. Table 15 in the SI summarizes exposure characteristics of all studies. We predicted PFOA, PFHxS and PFOS serum concentrations (population-mean ± 95% prediction interval) based on reported DW concentrations and compared the predicted population-means with reported population-averaged serum concentrations. In addition, we compared our predictions with predicted serum concentrations of PFOA, PFHxS and PFOS at steady-state based on the "serum PFAS calculator for adults" published by Lu and Bartell (2020), a computational tool using central tendency measures of daily DW consumption, DW concentrations, elimination half-life and volume of distribution as predictors for individual serum concentrations.

3. Results & discussion

3.1. PFAAs in drinking water

Table 2 lists descriptive characteristics of PFAAs in DW for the respective sites. The observed PFAA concentrations in DW are in the range of previously reported concentrations near PFAA hotspots contaminated either due to AFFF usage as in Sweden (Xu et al., 2021) or due to industrial discharge as in Italy (Pitter et al., 2020) and the mid-Ohio Valley, U.S. (Frisbee et al., 2009). PFOA, PFHxS and PFOS were the main PFAAs, as also previously reported (Li et al., 2018; Pitter et al., 2020; Xu et al. 2020, 2021), and contributed on average between 47% (Arvidsjaur) and 93% (Lulnäset) to total PFAA (Fig. 1, SI Table 5). PFHxS was the most dominant PFAA at all contaminated sites (Fig. 1, SI Table 5). Despite this, the PFAA composition varied markedly between contaminated sites, with PFOS contributing ≥20% to total PFAA concentrations in Lulnäset, Uppsala and Visby, but <5% in Arvidsjaur. Average PFHpA and PFOA contributions were close to or less than 10% at all contaminated sites. PFNA and PFDA proportions ranged between 0.02% and 2% that were biased by LODs differing between sites. The short-chained PFAAs, i.e. PFPeA, PFHxA and PFBS, contributed between 9% and 21%. These patterns are in line with previous publications showing that short-chained PFAAs have comparable and sometimes even higher DW concentrations than legacy PFAAs (Pitter et al., 2020; Xu et al., 2021). The different PFAA patterns at the four sites may be due to site-specific differences in the hydrologic position of wells in relation to the pollution sources, geochemistry, and land use (McMahon et al., 2022), as well as composition of PFAS-containing AFFFs (Herzke et al., 2012).

Median DW concentrations from Arvidsjaur and in some DW wells in Lulnäset with the sum of PFAAs reaching 1790 ng/L and 1240 ng/L exceeded by far the maximum limit of 500 ng/L total PFAS set by the revised drinking water directive aimed to be implemented by 2023 (Directive (EU), 2020/2184). In addition, the recommended Swedish action limit, defined as 90 ng/L for the total concentration of eleven PFAS (perfluorobutanoic acid, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFBS, PFHxS, PFOS and 6:2 fluorotelomer sulfonate) in 2014, was exceeded in Arvidsjaur, in some DW wells in Lulnäset and Visby, as well as in one of the four Uppsala districts. Uppsala district 4 had highest PFAA levels with the total concentrations of six of the eleven PFAAs being 96 ng/L (Gyllenhammar et al., 2015). In Visby, 54% of the subjects consumed DW that exceeded 90 ng/L sum of PFAAs. Thus, our study adds to the disconcerting fact that DW from private wells and municipal DW production wells may be severely contaminated by PFAAs from firefighting training sites.

Importantly, the concentrations of PFNA and PFDA in DW are generally much lower compared to the other long-chained PFAAs and were (except in Visby) either not analyzed or below LOD (Table 2). Furthermore, differences in LOD between study sites may have biased the regression analyses, as many values were assigned $LOD/\sqrt{2}$. Thus,

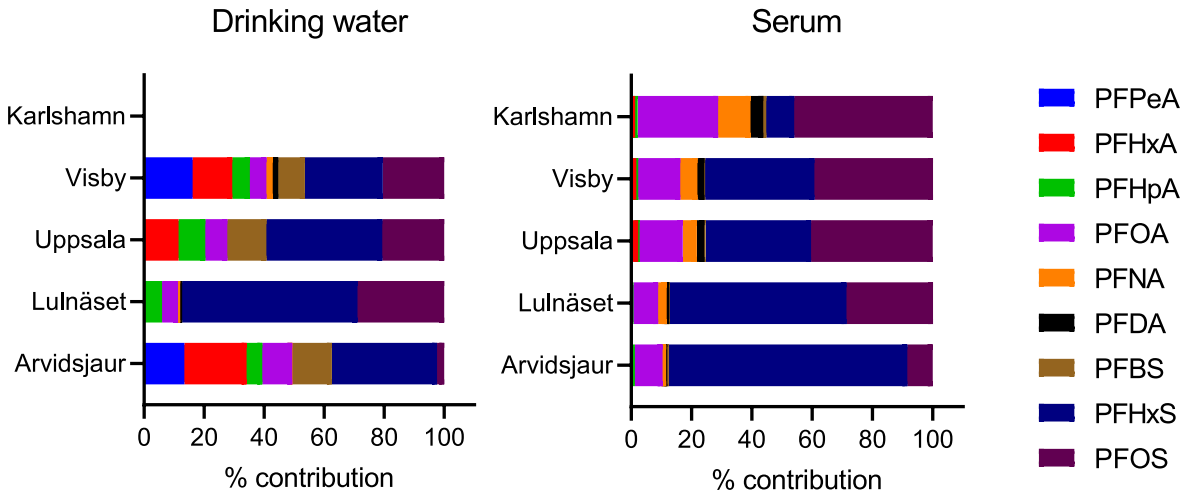

Fig. 1. Relative contribution of individual PFAAs to the total concentration [based on molar concentration] of nine PFAAs in drinking water and serum samples from four PFAA hotspots in Sweden with different levels of drinking water contamination. PFAA composition in drinking water from Karlshamn was excluded as background levels were below LOD. Relative composition of each PFAA was tabulated as ratio of the arithmetic mean in all samples to the total arithmetic mean of all PFAAs.

the C_B and *SWR* estimates for PFNA and PFDA (Table 4, SI Tables 7–14) are highly uncertain. More sensitive analytical methods with lower LODs need to be developed to derive better C_B and *SWR* estimates for PFNA and PFDA.

As in our study, reports on PFAA composition and concentration in DW are generally based on a single spot sample or a few samples with information on temporal trends, hampering the understanding of variability of PFAAs in DW over time. In Uppsala, the concentrations of PFHxA, PFBS, PFHxS and PFOS in DW production wells varied approximately three-fold during a period of 1.5 years (Gyllenhammar et al., 2015, SI Table 3). Repeatedly sampled DW from wells in Visby showed highly variable concentrations of individual PFAA over time (SI Fig. 3). In addition, DW concentrations varied depending on the location of private wells as seen in Lulnäset (Forsell et al., 2016) and Visby (SI Fig. 3). Thus, single spot sampling of DW may add substantial uncertainty to PFAA exposure assessment. Most recent DW measured concentrations of short-chained PFAAs and time-averaged DW concentrations of long-chained PFAAs may be most relevant measures for interpreting influence on serum concentrations.

3.2. Analytical methods for PFAAs in serum

Analytical method comparisons were conducted to evaluate reproducibility of quantified serum concentrations of PFOA, PFNA, PFHxS and PFOS. For batches of 20 serum samples, serum concentrations determined by method 1 were highly correlated with those determined by method 2 for linear PFHxS and total PFOS ($R^2 > 0.97$, $N = 20$), but less so when excluding the highest measured PFHxS and PFOS concentrations ($R^2 < 0.55$, $N = 19$) (SI Fig. 1). Moderate correlations were found for PFOA ($R^2 = 0.8$) and PFNA ($R^2 = 0.4$) (SI Fig. 1). For 59 randomly selected serum samples from Karlshamn (59/137), concentrations of the linear PFOA, linear PFHxS and total PFOS determined by method 2 were compared to the concentrations of the linear forms of PFOA, PFHxS and PFOS determined by method 3, showing high correlations for PFOA and PFOS ($R^2 > 0.9$), but less for PFHxS ($R^2 = 0.5$) (SI Fig. 2). In addition, no statistically significant differences were observed between PFAA serum concentrations determined using method 1 versus method 2 and method 2 versus method 3 (two-sided paired *t*-test, $p > 0.05$) except for PFHxS (two-sided paired *t*-test, $p < 0.05$). Thus, we translated total PFOS determined by method 2 in serum for Karlshamn (85/137) and Lulnäset subjects to linear PFOS using the slope from the simple linear regressions (SI Fig. 2). Regarding PFHxS, we used only the measured PFHxS concentrations in 59 of the total 137 serum samples from Karlshamn based on method 3 for all statistics.

3.3. PFAAs in serum

Significant correlations were observed between serum concentrations of most of the studied PFAAs (SI Fig. 4), probably because DW was a significant PFAA exposure source for almost all PFAAs. The relative PFAA composition in serum differed considerably from that of the corresponding DW samples (Fig. 1, SI Table 6). Generally, PFOA, PFNA, PFHxS and PFOS serum concentrations contributed to at least 94% of the total PFAA concentration in serum at all sites (SI Table 6). The contribution of PFHxS to total PFAA in serum increased with both increasing total PFAA contamination level in DW, except for the Arvidsjaur site, and with increasing total PFAA serum concentrations (Fig. 1). In contrast, the contributions of PFOA and PFOS to total PFAA in serum decreased with increasing total PFAA contamination level in DW. The contributions of short-chained PFAAs to total PFAA in serum were minor (<2%), which stands in contrast to a marked contribution in DW (Fig. 1). Taken together, these results strongly suggest that short-chained PFAAs have a lower degree of bioaccumulation, which is in line with the shorter half-lives compared to the long-chained PFAAs (Xu et al., 2020, SI Table 16, SI Fig. 8). An additional factor taken into consideration are lower measured serum concentrations of short-chained PFAAs that may result from higher volumes of distribution compared with those for the long-chained PFAAs. However, volume of distributions only span a factor of two between the different PFAAs (SI Table 16), suggesting a small impact of volume of distribution on the body burden and the estimation of bioaccumulation, compared to that of differences in half-lives which span by several orders of magnitude.

Table 3 lists descriptive characteristics of PFAAs in serum for the respective sites. The subjects from Arvidsjaur had the highest median concentrations of any single PFAA in serum, followed by adults living in Lulnäset, Visby and Uppsala. The highest median concentration overall was observed for PFHxS in Arvidsjaur and Lulnäset (>40 ng/mL). Subjects from Arvidsjaur, Lulnäset, Uppsala and Visby had 127-, 70-, 6-, and 5-fold higher median concentrations of PFHxS, respectively, than the reference group from Karlshamn. The concentrations of PFOS in serum were <20 ng/mL and subjects in Lulnäset had the highest median concentration, being 4-fold higher than in subjects from Karlshamn. The concentrations of PFOA were highest in Arvidsjaur, being 6-fold higher than in Karlshamn. Similar to previous studies, our results clearly show elevated concentrations of long-chained PFAAs in serum from subjects exposed to PFAA-contaminated DW in AFFF hotspot areas (Barton et al.,

2020; Hölzer et al., 2008; Landsteiner et al., 2014; Pitter et al., 2020; Xu et al., 2021). For instance, Barton et al. (2020) showed that subjects living near an air force base in Colorado with PFHxS-contaminated DW had a 12-fold higher median PFHxS concentration (14.8 ng/mL) than the U.S. average. Hölzer et al. (2008) identified up to 8-fold higher PFOA concentrations in subjects consuming PFOA-contaminated tap water compared with subjects drinking non-contaminated DW. Ronneby residents, who lived in a municipality in southern Sweden and consumed highly contaminated DW with a sum of PFAAs >10,000 ng/L, had 135-, 35- and 4-fold higher geometric means of PFHxS, PFOS and PFOA in serum, respectively, than the reference group from Karlshamn (Xu et al., 2021).

The Arvidsjaur and Lulnäset data show that high exposures to the short-chained PFAAs (PFPeA, PFHxA, PFHpA and PFBS) from DW cause observable elevated serum concentrations above background variability, the medians being >2-fold higher than in subjects from Karlshamn, even though they are not regarded as highly bioaccumulative in the regulatory context (Brendel et al., 2018). The increase may be due to daily regular PFAA exposure via DW, the single component of the diet that is consumed in large quantities several times per day on a long-term basis by almost all individuals in the Swedish population, where consumption of bottled water is low (Säve-Söderbergh et al., 2018). Serum concentrations of PFHpA and PFBS were also elevated above background variability in adult populations exposed via highly contaminated DW (Hölzer et al., 2008; Xu et al., 2021). Among the workers from Arvidsjaur airport, serum concentrations of PFHpA and PFBS significantly decreased after consumption of contaminated DW had stopped, with half-lives less than 4 months (Xu et al., 2020). This further illustrates that consumption of contaminated DW is a major exposure source for short-chained PFAAs.

The median concentrations of the long-chained PFAAs PFNA and PFDA in serum were <1.2 ng/mL, indicating no distinct DW-related pattern (Table 3). These PFAAs were predominately present in DW at concentrations below LOD (Table 2). This suggests that PFNA and PFDA are not major components in DW contaminated from AFFF sites in Sweden. Similarly, serum concentrations of PFNA and PFDA measured in highly exposed subjects from Ronneby were in the range of the reference group (Xu et al., 2021). In contrast, Yu et al. (2021) reported an elevated median PFNA concentration of 3 ng/mL in serum from subjects living in New Jersey, where DW was highly contaminated with PFNA up to 150 ng/L by a manufacturing facility. For PFDA, high DW concentrations have not been reported so far, to the best of our knowledge. However, PFDA serum levels in Chinese women drinking bottled water were significantly lower than among those drinking tap water (Zhou et al., 2019).

3.4. Relationship between drinking water and serum

The present study for the first time uses concentrations of nine PFAAs measured in DW and serum from four different hotspots in Sweden, allowing for determination of quantitative associations between the two measures (Fig. 2, SI Fig. 5, Table 4).

3.4.1. Unadjusted regression analysis

DW concentrations explained >70% of the serum concentration variance for PFHxA, PFHpA, PFOA, PFBS and PFHxS and >60% for PFOS (Table 4, Fig. 2). The C_B estimates, representing only exposures via sources other than the local DW source, e.g. food, cosmetics, and dust, were highly significant for all PFAAs (Table 4). PFOS had the highest C_B followed by PFHxS and PFOA with mean values > 1.7 ng/mL. Our C_B estimations for PFOA and PFOS (1.7 and 5.2 ng/mL, respectively) were similar to reported geometric means of background serum levels for the U.S. (1.5 and 4.5 ng/mL, respectively, CDC (2018)) and European populations (1.9 and 7.7 ng/mL, respectively, EFSA (2020)) as well as estimates conducted by Bartell (2017) and Zhang et al. (2019). However, the C_B estimation for PFHxS (2.3 ng/mL) was higher than 1.1 ng/mL and 0.7 ng/mL reported by CDC (2018) and EFSA (2020), respectively. In Sweden, a 2010–11 population-based survey of PFAA in adults reported similar median concentrations of PFNA, PFDA and PFHxS in serum (Bjermo et al., 2013) to our estimates. However, the estimated C_B of PFOA and PFOS in the present study were lower than median concentrations of 2.3 ng PFOA/mL and 11 ng PFOS/mL reported by Bjermo et al. (2013). The lower values in the present study can most probably be explained by a combination of both decreasing background PFOA and PFOS exposure in Sweden (Miaz et al., 2020) and our more recent sampling study compared to the 2010-11 study. Thus, temporal trends of background PFAA exposure have to be considered in comparisons of PFAA concentrations in serum between studies.

Associations between PFAA concentrations in DW and serum were significant for all PFAAs except for PFPeA (Table 4, Fig. 2). *SWR* estimates for PFOA, PFNA, PFHxS and PFOS were >30, demonstrating high bioaccumulation from DW. *SWR* for short-chained PFAAs ranged from <1 (PFHxA) to about 6 (PFHpA) (Table 4), being much lower than those of the long-chained PFAAs. *SWR* estimates for the PFCAs increased with carbon chain length up to PFNA (SI Fig. 6). Again, *SWR* estimates for PFNA and PFDA have to be interpreted with high caution due to the usage of LOD substitutes for the non-detectable DW concentrations in four of the five study sites. No clear relation to carbon chain-length was observed among the PFSAs. The *SWR* value for PFHxS was highest followed by PFOS and PFBS, likely due to the lengthy serum half-life of PFHxS (EFSA, 2020). Overall, the serum half-lives correlated well with the *SWR* values (R^2 = 0.57), potentially explaining the differences in *SWR* between PFCAs and PFSAs of the same chain length (SI Fig. 8).

SWR estimates have mainly been reported for PFOA. These estimates ranged between 30 and 231 (Emmett et al., 2006; Hoffman et al., 2011; McDonough et al., 2021; Post et al., 2009; Post, 2021; Xu et al., 2020; Zhang et al., 2019). Thus, Xu et al. (2020) calculated a *SWR* of 30 using concentrations of PFOA in DW and serum in airport workers from Arvidsjaur, i.e. 30% lower than our estimate of 43 (Table 4). In contrast, Hoffman et al. (2011) reported a 2.6-fold higher *SWR* (114) than our estimate, using measured serum concentrations in individuals drinking contaminated DW from private wells with concentrations ranging from 200 to 800 ng/L in Ohio and West Virginia, U.S. The highest *SWR* estimate of 231 (5.4-fold higher than our) was reported by Zhang et al. (2019), based on DW and serum sampled from 13 cities in China.

Comparisons between studies are complicated by inter-study differences in procedure for estimating *SWR* values. Thus, *SWR* values have been estimated using either central tendency measures of clearance factors and daily DW consumption (Bartell, 2017; Lu and Bartell, 2020; Hoffman et al., 2011; Hu et al., 2019), calculating the ratio between concentrations in serum and DW (Xu et al., 2020), or applying regression analysis (the present study). Additionally, the higher PFOA *SWR* estimates reported previously may result from higher DW consumption from beverages and cooking and consumption of locally PFOA-contaminated foods (Hoffman et al., 2011). Notably, the average daily DW intake consisting of pure DW, DW used for beverages and for food preparation is higher in Sweden (0.026 L/kg/day for a 70 kg person) than in U.S. (0.016 L/kg/day) (Lu and Bartell, 2020; Säve-Söderbergh et al., 2018), suggesting possible differences of total daily DW consumption between study areas. Information on exposure duration together with harmonized questionnaires about DW consumption including information on daily intake of pure DW as well as DW usage for other beverages and food preparation might reduce uncertainty when comparing *SWR* values between studies. Another possibility is that *SWR* values may be lower for populations exposed to highly contaminated DW, as indicated by the 30% lower *SWR* value reported by Xu et al. (2020) as compared to our *SWR* values. Whether there is a concentration-dependent bioaccumulation from DW or not need to be explored in future studies. Indications are given by Seals et al. (2011) and Li et al. (2022), who suggested that PFAA elimination processes are time-dependent with faster elimination at highest PFAA serum concentrations at the beginning of exposure cessation. So far, such time-depended half-lives have only been observed in

Table 4
Estimated regression coefficients (mean and standard error (SE)) for nine PFAAs by unadjusted and adjusted weighted linear regression. Weighting was carried out using the absolute value of the residual. The background serum concentration (C_B) represents the regression intercept and the serum:water ratio (*SWR)* represents the regression line slope describing the change in PFAA concentration in serum [ng/mL] per unit change of PFAA concentration in drinking water (C_{DW} in ng/mL). For the adjusted model, the tabulated background serum concentrations, i.e. assuming no exposure via local DW water, are given for male subjects living in a permanent housing. Statistical significance is given by *p ≤ 0.05. **p ≤ 0.01 and ***p ≤ 0.001.

PFAA	Model	C_B [ng/mL]			*SWR* [-]			Age			Gender			BMI			Residence type			Sampling time			DF [2]	Adj.R^2 [2]	Residuals SE [2]
		Mean	SE	p	Mean	SE	p	Mean	SE	p	Mean	SE	p	Mean	SE	p	Mean	SE	p	Mean	SE	p			
PFPeA	unadjusted	0.03	<0.01	***	−0.02	0.03																	60	−0.01	0.09
	adjusted	0.82	0.46		−0.02	0.03		<0.0001	<0.0001		0.0004	0.0016		0.0002	0.0002		0.003	0.002		−0.0752	0.0435		55	0.05	0.10
PFHxA	unadjusted	0.16	<0.01	***	0.77	0.01	***																295	0.90	0.29
	adjusted	0.18	0.01	***	1.08	0.04	***	0.0013	0.0001	***	0.0005	0.0042		0.0010	0.0003	**	0.012	0.007		−0.0209	0.0005	***	275	0.93	0.19
PFHpA	unadjusted	0.04	<0.01	***	5.81	0.17	***																378	0.75	0.26
	adjusted	0.07	0.01	***	9.01	0.20	***	0.0002	0.0001	*	0.0044	0.0026		−0.0012	0.0002	***	−0.155	0.006	***	−0.0009	0.0004	*	356	0.87	0.25
PFOA	unadjusted	1.67	0.02	***	43.23	0.86	***																386	0.87	1.03
	adjusted	1.82	0.18	***	58.15	0.90	***	0.0163	0.0020	***	−0.5396	0.0678	***	−0.0073	0.0067		−1.074	0.095	***	−0.0331	0.0081	***	364	0.93	0.97
PFNA	unadjusted	0.78	0.02	***	78.43	12.77	***																159	0.19	0.65
	adjusted	0.33	0.20		38.31	13.42	**	0.0099	0.0014	***	−0.0786	0.0318	*	0.0058	0.0041		0.098	0.070		−0.0119	0.0230		142	0.54	0.65
PFDA	unadjusted	0.34	0.01	***	13.89	7.03	*																159	0.03	0.41
	adjusted	0.19	0.07	**	5.00	6.54		0.0036	0.0004	***	0.0163	0.0141		−0.0016	0.0014		0.020	0.033		0.0013	0.0077		142	0.55	0.41
PFBS	unadjusted	0.03	<0.01	***	1.82	0.05	***																364	0.76	0.19
	adjusted	0.06	<0.01	***	2.54	0.09	***	−0.0037	<0.0001	***	−0.0010	0.0010		−0.0004	0.0001	**	−0.017	0.005	***	−0.0010	0.0003	***	342	0.73	0.17
PFHxS	unadjusted	2.27	0.18	***	111.08	3.70	***																306	0.74	3.10
	adjusted	1.70	3.01		145.19	5.21	***	0.0457	0.0311		−7.8678	1.4378	***	0.2450	0.0867	**	−28.302	1.536	***	0.0229	0.0786		286	0.78	3.19
PFOS	unadjusted	5.15	0.06	***	33.77	1.31	***																382	0.63	1.72
	adjusted	4.17	0.55	***	28.59	2.03	***	0.1310	0.0070	***	−2.8629	0.1970	***	−0.0260	0.0190		−2.725	0.608	***	−0.2093	0.0201	***	360	0.76	1.63

[1] Co-variates used in the adjusted weighted linear regression include age (years), gender (male as reference), body mass index (BMI in kg/m2), residence type (permanent residence as reference) and serum sampling time (year).
[2] Goodness-of-fit is represented by the parameters degree of freedom (DF), adjusted coefficient of determination (Adj. R^2) and residual standard error (Residuals SE).
[3] A p-value of ≤0.05 for CB informs that the intercept of the background serum concentration is significant different from zero.
[4] A p-value of ≤0.05 for the coefficient values show that the associations between PFAA concentration changes and the predictors (i.e. DW concentration., age, gender, BMI, residence type and sampling time) are statistically significant.
C_B - background serum concentration, *SWR* - serum water ratio

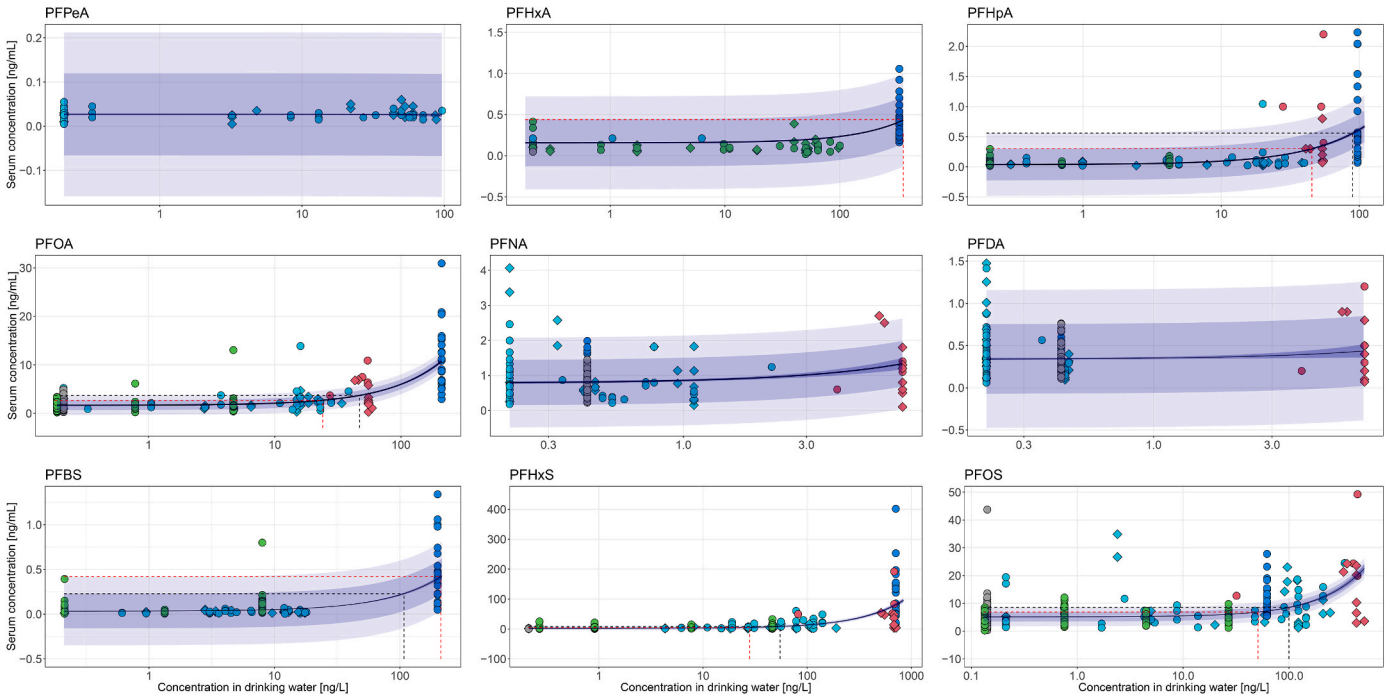

Fig. 2. Averaged population fits of the unadjusted linear regression models using individual weights of 1/abs (residuals) demonstrate the relationship between drinking water concentrations and serum concentrations for nine PFAAs (black solid line). Colored symbols represent measured serum concentrations in subjects and their consumed drinking water concentrations at the 5 Swedish sites (dark blue – Arvidsjaur, grey - Karlshamn, red - Lulnäset, green – Uppsala, turkish blue – Visby). Note that there may be considerable overlap of individual data points at some concentrations in drinking water. Subjects permanently living at the site of contamination are indicated by dots and subjects with temporary residence are depicted by diamonds. Interval bands represent 95% confidence interval (dark purple), 68% prediction interval (medium purple) and 95% prediction interval (light purple). Lowest drinking water concentrations associated with observable elevated serum concentrations above background variability are indicated for the averaged population serum concentrations that are equal to the 68% (red dotted line) and 95% (black dotted line) upper prediction interval for serum background exposure. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

highly exposed residents of Little Hocking (Ohio), Lubeck (West Virginia) (Seals et al., 2011) and Ronneby (Sweden) (Li et al., 2022).

For PFOA, PFNA, PFHxS and PFOS, Lu and Bartell (2020) estimated *SWR* values to be 118, 202, 129 and 201, respectively, based on published central tendency measures of daily DW consumption, half-lives and volumes of distribution. These estimates were 2- to 4-fold higher than our estimates (Table 4), which might be a result of using default central tendency measures of clearance factors and daily DW consumption collected from different studies. Furthermore, the use of different central tendency measures (i.e. arithmetic mean, median, geometric mean, etc.) may result in different *SWR* estimates.

DWES values, calculated for the eight PFAAs displaying a significant association between DW and serum concentrations, are presented in Table 5. $DWES_{68}$ increased in the order PFOA (24 ng/L) <PFHxS < PFHpA < PFOS < PFBS < PFHxA (approx. 357 ng/L) (Table 5). For five PFAAs, $DWES_{95}$ were approximately twice the $DWES_{68}$ values. Both *DWES* values were higher than PFAA DW concentrations generally observed in municipal DW in Sweden (Lindfeldt et al., 2021). The high *DWES* values are most likely due to a large variation in the background exposure from other sources than DW. For instance, PFOS concentrations in fish vary considerably in Sweden (Augustsson et al., 2021), and high consumers of PFOS-contaminated fish can reach PFOS exposures that are on average more than 20-fold higher than those of the general population (Augustsson et al., 2021).

3.4.2. Adjusted regression analysis

As in the unadjusted regression analyses, the associations between DW and serum concentrations remained significant for seven of the eight PFAAs in the adjusted regression analyses, excluding potential confounding by co-variates (Table 4, SI Fig. 5). The unadjusted and adjusted estimates of C_B and *SWR* differed less than two- and three-fold, respectively (SI Fig. 6). Notably, adjusted *SWR* values were higher than the unadjusted *SWR* values, except in the cases of PFNA, PFDA and PFOS, leading to lower *DWESs* (Table 5). Higher adjusted *SWR* values were likely estimated since male subjects were referents in the adjusted regression model. Despite this difference, trends of unadjusted and adjusted *SWR* estimates in relation to carbon-chain length were similar (SI Fig. 6).

Co-variates for population characteristics (i.e. gender, BMI) and proxy measurements of cumulative exposure (i.e. age, residence type and serum sampling time) were significantly associated with PFAA concentrations in serum (Table 4). No multi-collinearity between the co-variates was identified in any of the regression analyses (VIF<10). Age was significantly associated with higher serum concentrations for all PFAAs besides PFPeA and PFHxS. Concentrations of PFOA, PFNA, PFHxS, and PFOS in serum were significantly higher among males than among females. These results are in line with previous observations in adult populations (Hölzer et al., 2008; Nair et al., 2021; Ingelido et al., 2020). In agreement with Barton et al. (2020), Hölzer et al. (2008) and Nair et al. (2021), BMI showed both positive and negative associations with PFAA concentrations in serum, suggesting that BMI is not a strong predictor for serum concentrations. As expected, subjects living temporarily in contaminated study areas had significantly lower concentrations of PFHpA, PFOA, PFBS, PFHxS and PFOS in serum than subjects living there permanently. Concentrations of PFHxA, PFHpA, PFOA, PFBS and PFOS in serum were inversely related with serum sampling year, in line with the observed decrease in background exposure in Sweden during the study period (Miaz et al., 2020; Nyberg et al., 2018). Overall, DW concentrations were the strongest predictor of PFAA serum concentrations besides for PFNA and PFDA for which a huge improvement of the fit was demonstrated when including co-variates.

We additionally explored the influence of exposure duration and

Table 5
Estimations of drinking water concentrations causing observable elevated serum concentrations above variability of background serum concentrations (*DWES*) (mean ± confidence interval). Estimations are based on unadjusted and adjusted weighted linear regression models for eight PFAAs that showed a significant positive association of drinking water contamination level on serum concentrations. Drinking water concentrations and the corresponding lowest elevated serum concentrations ($C_{s,\text{elevated}}$) were based on the 68% and 95% upper prediction value for serum concentrations at background at 0 ng/L drinking water concentration.

PFAA	Model	*DWES* [ng/L]		$C_{S.\ elevated}$ [ng/mL][d]	
		68%	95%	68%	95%
PFHxA	unadjusted	~357	ND[b]	0.44	0.72
	adjusted[a]	178 ± 15	349 ± 18	0.37	0.55
PFHpA	unadjusted	45 ± 3	89 ± 5	0.30	0.56
	adjusted[a]	29 ± 1	55 ± 1	0.22	0.46
PFOA	unadjusted	24 ± 1	47 ± 2	2.70	3.70
	adjusted[a]	18 ± 1	35 ± 2	2.29	3.22
PFNA	unadjusted	ND[b]		1.44	2.07
	adjusted[a]			1.47	2.10
PFBS	unadjusted	108 ± 6	212 ± 11	0.23	0.42
	adjusted[a]	71 ± 4	136 ± 8	0.21	0.37
PFHxS	unadjusted	28 ± 3	55 ± 4	5.39	8.41
	adjusted[a]	24 ± 17	48 ± 16	7.04	10.50
PFOS	unadjusted	51 ± 4	100 ± 7	6.87	8.54
	adjusted[a]	79 ± 19	134 ± 19	6.32	7.89

DWES – minimum drinking water concentrations that caused observable elevated serum concentrations above background exposure variability in the observed Swedish populations. $C_{s,elevated}$ – Lowest elevated serum concentration that was observable above either the 68% or 95% prediction interval of the background serum concentration.

[a] Co-variates used in the adjusted weighted linear regression included age (years), gender (male as reference), body mass index (BMI in kg/m2), residence form (permanent residence as reference) and serum sampling time (years).

[b] *DWES* was not determined (ND) as population mean of regression fit did not exceed 68% or 95% prediction interval of background serum concentration in the range of drinking water measurements.

daily consumption of DW on estimated cumulative exposures. Serum concentrations were significantly lower with shorter exposure durations for PFHxA, PFOA and PFHxS (SI Table 7), indicating that apparent steady-state serum concentrations might have not been reached. In general, apparent steady-state serum concentrations will be reached after exposure to approximately five half-lives (Benet and Zia-Amirhosseini, 1995), i.e. about 160 days for PFHxA, between 6 and 42.5 years for PFOA and between 9.5 and 90 years for PFOS according to ranges of estimated half-lives in humans summarized by EFSA (2020) (SI Table 16). Furthermore, serum concentrations were significantly increased for PFBS and PFHxS or showed a positive trend in subjects from Arvidsjaur; Lulnäset and Visby, who consumed more than 7 glasses/day of either pure DW (Arvidsjaur subjects) or pure DW and DW used for home-made lemonade and hot beverages (Lulnäset and Visby subjects) (SI Table 8). This finding confirms results published by Hölzer et al. (2008), Hu et al. (2019) and Nair et al. (2021) that increased DW consumption is likely associated with increased PFAA concentration in serum. Notably, harmonized questionnaires for subjects living in different PFAA hotspot areas need to be applied in order to enable a better estimate of the total consumed DW including plain DW as well as DW used for other beverages and food preparation. In our study, the number of participants with information on exposure duration as well as daily consumed DW was limited (N < 87), making the results uncertain.

3.5. Gender-stratified adjusted regression

Gender-stratified adjusted regression analysis revealed that female subjects had lower *SWR* estimates for all PFFAs with exception of PFHpA than male subjects (SI Table 10). PFAA bioaccumulation from DW differed at most three-fold between genders and differences became less obvious when excluding females over 50 years of age besides for PFBS and PFOS (SI Table 10). One explanation of the lower *SWR* among women for most PFAAs could be that pre-menopausal women excrete PFAAs through bleeding during menstruation in addition to other excretion pathways (Wong et al., 2014; Li et al., 2022). Another contributing factor may be PFAA excretion due to childbirth and breastfeeding (Verner et al., 2016). Thus, having at least one child was significantly associated with decreased serum concentrations of PFHpA and PFOA (SI Table 11). Breastfeeding duration was not included in the regression analyses as serum samples from first-time mothers in Uppsala, the majority of female subjects with breastfeeding information (Table 1), only had breast-fed for 3 weeks when serum was sampled.

3.6. Sensitivity analysis

The associations between PFAAs in DW and serum remained highly significant when outliers (SI Table 12) or single study sites (SI Tables 13 and 14) were excluded from the unadjusted as well as adjusted regression analyses, except for PFNA and PFDA. *SWR* values were highly similar for PFHpA, PFOA and PFBS or varied less than 2-folds for PFHxA, PFHxS and PFOS compared with the full regression model, even when we excluded subjects from Karlshamn alone or Arvidsjaur and Lulnäset combined. Only PFNA and PFDA displayed high uncertainty in *SWR* estimates and became even negative, which most likely resulted from differences in LOD for DW concentrations between study sites. Notably, C_B estimates of PFHxA, PFHpA, PFHxS and PFOS became either insignificant or negative when the Uppsala subpopulation was excluded from the adjusted but not from the unadjusted regression analyses. As we observe a similar pattern in the gender-stratified multiple linear regression model (SI Table 10), we suspect that this might indicate gender-specific sensitivity because Uppsala subpopulation contributed to 53% of the total number of women (Table 1). Overall, the associations between concentrations in DW and serum were not markedly driven by any single subpopulation, suggesting that our population-based estimates are robust, except for PFNA and PFDA.

3.7. Comparison with published data from other PFAA hotspots

We tested the predictability using the unadjusted regression models for PFOA, PFHxS and PFOS by comparing model predictions with previously reported data on concentrations in DW and serum (Fig. 3, SI Table 15). The ratios between measured and predicted mean serum concentrations for the different hotspot populations ranged between 0.2 and 4.9 (Fig. 3D), demonstrating an acceptable agreement when taking the uncertainties in the comparisons into account. The “serum PFAS calculator for adults” published by Lu and Bartell (2020) predicted serum concentrations that differed up to 8.4-fold to the published population serum concentrations (Fig. 3A–C). Here, a larger discrepancy between measured and predicted serum concentrations was found for populations being exposed to high PFAA levels in DW, likely due to much higher *SWR* estimates than our estimates. This larger over-prediction might have resulted from using default values of central tendency measures to predict individual serum concentrations instead of population-mean serum concentrations. Thus, a combination of our population estimates of *SWR* with Monte Carlo simulation of the toxicokinetics might overcome the over-prediction and would also reflect the population variability. Such a framework integrates probability distribution of input parameters (i.e. *SWR*, C_B values, DW consumption and DW concentrations) to predict uncertainties and inter-individual variability in serum concentrations. This contrasts the Lu and Bartell (2020) calculator that uses single point estimates of the input parameters.

In addition, other uncertainties in model predictions resulted from input data reported for the different populations such as quality of DW concentration data including unknown temporal fluctuations, exposure duration and lag time between exposure stop and serum sampling (Nair

et al., 2021; Landsteiner et al., 2014; Hu et al., 2019; Zhang et al., 2019). Differences of population characteristics in the previously reported studies such as age and gender composition as well as variability between daily DW consumptions at different PFAA hotspots might further contribute to uncertainties in the predictions.

3.8. Study limitations

In the regression analyses, several uncertainties should be considered when interpreting the results. Different analytical methods were used to measure PFAA concentrations in serum and DW in this and previous hotspot studies introducing uncertainty in the results. Specifically, differences in LODs in DW between the study sites introduced high uncertainty in the *SWR* estimates for PFNA and PFDA. Improved (with lower LODs) and harmonized (with the same LOD across laboratories) analytical methods would help to better assess the impact of low PFAA concentrations in DW on serum concentrations. In this study, we evaluated the impact of different analytical methods to be statistical insignificant for quantified PFOA, PFNA and PFOS serum concentrations, but not for PFHxS. Furthermore, possible long-/short-term fluctuations in PFAA exposure from DW (concentration and/or consumption) were disregarded in our regression models and in previous hotspot studies. Another uncertainty included missing information on subjects' mobility (e.g. history of change in area of residence, commuting to work) as this is an important co-variate shown by our observation that subjects living temporarily in PFAA hotspot areas had significantly lower concentrations of many of the studied PFAAs compared to permanent residents (Table 4). Moreover, serum was sampled months or even years after implementing remediation measures (e.g. drinking bottled water) in other studies that have likely contributed to a decline of PFAAs in serum. While these lag times had minimal impact on serum concentrations of the long-chained PFAAs with half-lives spanning over years in humans in this study, they might have decreased concentrations in serum of the short-chained PFAAs

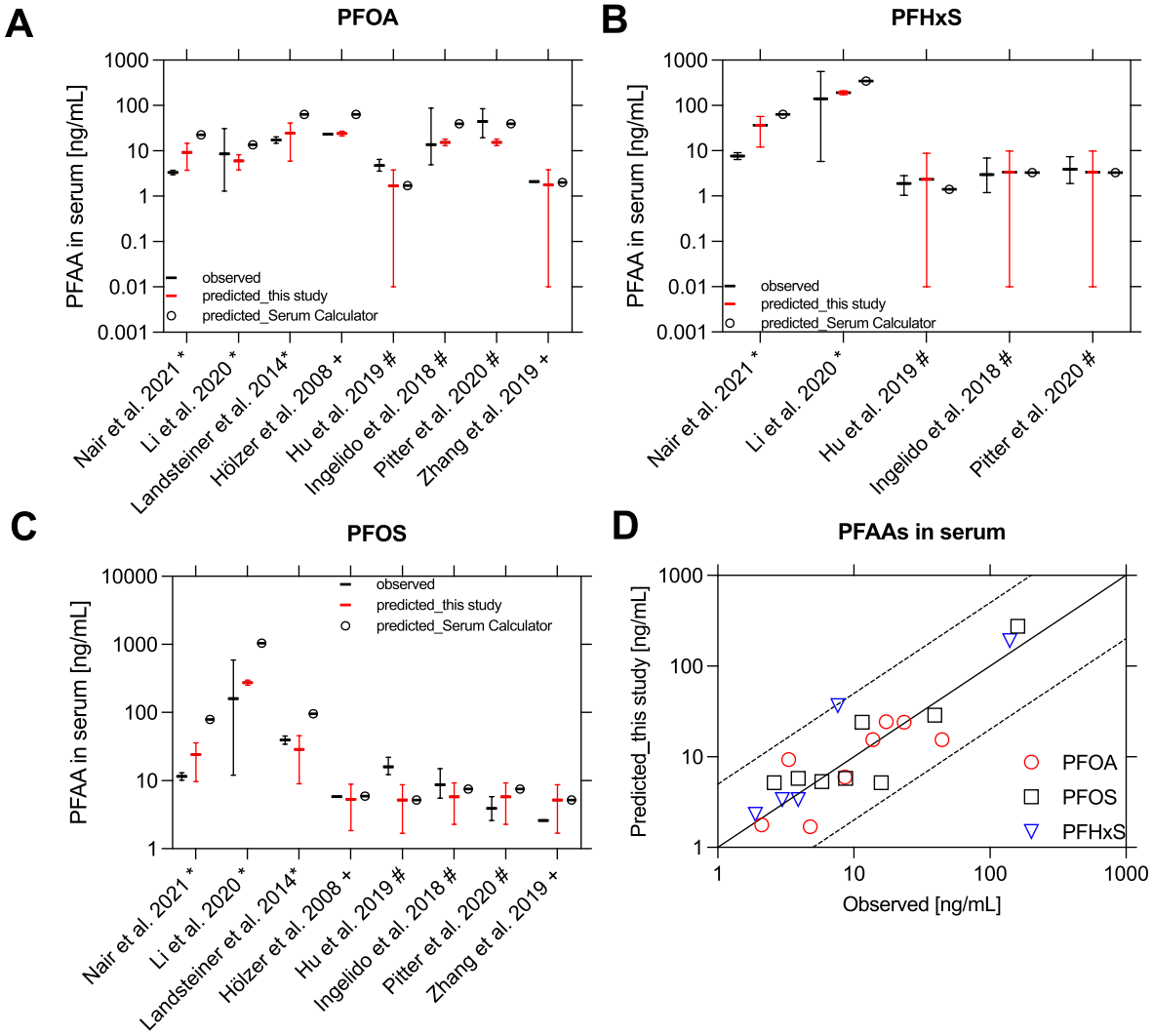

Fig. 3. Comparison of predicted (both mean and 95% predicted interval (PI) (red symbols) and mean (open black dots)) and observed (published data, black symbols) concentrations of the most studied PFAAs A) PFOA, B) PFHxS and C) PFOS in serum from people living near PFAA hotspots. Two predictions are carried out using the here established unadjusted regression results (red symbols) and the "serum PFAS calculator for adults" (open black dots) from Lu and Bartell (2020). Both tools predict mean serum concentrations based on reported DW concentrations given as geometric mean or median (Hu et al., 2019; Ingelido et al., 2018; Pitter et al., 2020; Zhang et al., 2019), point measurements (Li et al., 2020; Hölzer et al., 2008) as well as a range (Nair et al., 2021; Landsteiner et al., 2014). Observed serum concentrations were reported as geometric mean or median and 95% confidence interval (CI) (*: Nair et al., 2021; Li et al., 2020; Landsteiner et al., 2014), median and interquartile range (#: Hu et al., 2019; Ingelido et al., 2018; Pitter et al., 2020) or geometric means (+: Hölzer et al., 2008; Zhang et al., 2019). Please see also SI Table 15 for the numerical values. Based on the here established regression analyses, Fig. 3D summarizes the comparison of population averaged predicted and observed serum concentrations of PFOA, PFHxS and PFOS. Dashed lines represent 5-fold differences. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

PFHxA and PFBS in Lulnäset and Arvidsjaur subjects due to their shorter half-lives of about a month (SI Table 16). Repeated measurements of PFAAs in serum in Arvidsjaur workers after cessation of exposure revealed a faster decline of short-chained PFAAs than long-chained PFAAs, attributed to their different half-lives (Xu et al., 2020). For Visby, we therefore included self-reported change in consumption behavior after subjects had been informed about DW contamination (SI Table 9). Our analysis indicates that the subjects, who reduced their DW-intake had significantly lower concentrations of PFHpA, PFOA, PFNA, PFDA and PFBS in serum than those who did not change or even increased their intake. However, our results on the impact of exposure duration and self-reported DW consumption should be interpreted with caution as the sample size is low (N = 62). Lastly, serum sampling spanned over 10 years (2008–2018), and temporal changes of background exposure were not accounted for in the unadjusted models used for comparing predicted and observed serum PFAA concentrations in hotspot populations (Fig. 3). Despite those limitations, the sensitivity analysis gave robust estimations of *SWR* values except for PFNA and PFDA. In addition, the unadjusted regression models for PFOA, PFHxS and PFOS predicted reported population serum concentrations based on measured DW concentrations with the majority of predicted serum concentrations falling within an acceptable 2-fold-error, illustrating that DW concentration is a robust predictor.

4. Conclusion

In this study, we report for the first time the relationships between concentrations of nine PFAAs in DW and serum from four contaminated sites and one uncontaminated site in Sweden using regression analyses. In further development of modeling, better reporting of biomonitoring studies in PFAA hotspot areas are needed, including more comprehensive data on PFAA concentrations in DW and on factors affecting cumulative PFAA exposure from DW, such as duration of consumption of contaminated water before sampling of blood that determines whether apparent steady state serum concentrations have been reached or not. In the future, more precise tools such as toxicokinetic models are needed that allow predictions of serum concentrations in individuals. For this purpose, improved predictability would be gained by including information on (i) long-term changes in PFAA concentrations of DW, (ii) variation of individual consumption of PFAA contaminated and clean DW to estimate daily DW ingestion rates including all sources of DW usage (i.e. pure DW, food preparation as well as other beverages), (iii) inter-individual variation of clearance and volume of distribution since these parameters decide the elimination half-life, and (iv) temporal changes in background exposure. Awaiting such improvements, we propose the unadjusted regression model to be used as a reliable and simple tool to predict population-averaged serum concentrations from average PFAA concentrations in DW, thereby providing a non-invasive and cheap method for screening the impact of PFAA exposure from DW.

An important finding is that already at background exposure the estimated sum of PFOA, PFNA, PFHxS and PFOS in serum exceeds the critical level of 6.9 ng/mL (EFSA, 2020). We therefore suggest that PFAA concentrations in contaminated DW should be reduced as much as possible. We also want to point out that the established regressions models are valid for adult populations and might give false predictions for those born after 2000, i.e. when the background exposure of many of the legacy PFAAs started to decline. Hypothetically, elevated serum concentrations of PFAAs in young people might be observable already at much lower DW concentrations than observed for adults in the present study.

Author statement

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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

Data will be made available on request.

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Appendix A. Supplementary data

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