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Serum perfluoroalkyl substances in residents following long-term drinking water contamination from firefighting foam in Ronneby, Sweden

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ABSTRACT

Background: In December 2013, it was discovered that drinking water supplied to one third of the households in Ronneby, southern Sweden, was highly contaminated by PFAS (sum level >10,000 ng/L) originated from firefighting foams used at a nearby military airport.
Objectives: To report serum PFAS levels of Ronneby residents participating in a biomonitoring program, and to describe the variation by age, sex and calendar period for residential exposure. In addition, a reference group living in a neighboring municipality without PFAS contaminated drinking water was examined.
Methods: Blood samples and demographic data were collected for 3297 Ronneby residents and 226 individuals from the reference group. Yearly residence addresses were available for 3086 Ronneby residents from the national population registry. Serum concentrations of PFHxS, PFOS and PFOA were determined in all participants, with additional PFHpA, PFNA and PFDA in subsets of the participants.
Results: The population geometric means for serum PFHxS, PFOS and PFOA were 114, 135 and 6.8 ng/mL for all Ronneby residents, i.e.135, 35 and 4.5 times higher than for the reference group. Ronneby residents who resided in the area with contaminated water supply during 2005–2013 showed much higher PFAS levels in 2014 than those exposed only before 2005. Ronneby residents who never resided in the area with contaminated water supply also had higher serum PFAS levels than the reference group. All three PFAS were highly correlated (r_s > 0.9 for each pair). Serum PFAS levels were lowest in teenage years and then increased with age. Adult females had lower PFAS levels on average than males under the age of 60 but higher above 60.
Discussion: The results reveal high serum PFAS levels dominated by PFHxS and PFOS in the Ronneby residents highly exposed to PFAS originated from firefighting foams. The PFAS exposure in Ronneby permits studies of associations to a range of health parameters, as well as studies of the toxicokinetics of PFAS exposure.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a group of thousands of synthetic chemicals that have been used since the early 1950s (Buck et al., 2011). Their structure with a fluorinated carbon chain of varying length and functional groups make them highly stable and thermally resistant. Because of their stability and water, dirt and grease-resistant properties they have been widely used in a multitude of technical applications and are now ubiquitous in the environment. Generally, humans are exposed to PFAS through diet, indoor air and dust (Begley et al., 2005; Berger et al., 2009; Falandysz et al., 2006; Shoeib et al., 2005). In areas with PFAS point-source contamination, the exposure

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from contaminated drinking water is of major importance (Domingo and Nadal, 2019). It was recently found that drinking water with PFAS well below current guidelines contributes to elevated PFAS levels in the general population (Glynn et al., 2020).

International biomonitoring programs and cross-sectional studies show that general populations have detectable levels of PFAS in serum worldwide (Buck et al., 2011; Houde et al., 2006; Ingelido et al., 2018). The widespread PFAS contamination, together with the bioaccumulation properties and long half-lives of these substances, and experimental data on toxicity have raised concerns of environmental and human adverse effects. The first drinking water guidelines were issued in Germany, 2006 (Drinking Water Commission, 2006); since then many countries have followed. In Sweden, first action limits for PFAS in drinking water was issued in 2014, with levels of 90 ng/L for sum of seven PFAS [perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), perfluorobutane sulfonic acid (PFBS), perfluorohexane sulfonic acid (PFHxS) and perfluorooctane sulfonic acid (PFOS); Livsmedelsverket, 2014].

In December 2013, before any action limits had been issued in Sweden, it was unexpectedly discovered that one out of two municipal waterworks in Ronneby, southern Sweden, had a sum of PFAS level above 10,000 ng/L in the outgoing drinking water (Table 1). The contaminated waterworks was closed on December 16, 2013, immediately after the exposure was discovered, and clean water was distributed from the other municipal waterworks.

Table 1
PFAS levels in drinking water from contaminated waterworks (Brantafors), minimally contaminated waterworks (Kärragården), and from the main waterworks in Karlshamn, a neighboring municipality without PFAS in drinking water.

PFAS	Brantafors, Contaminated Waterworks in Ronneby (ng/L)[a]	Kärragården, Minimally contaminated waterworks in Ronneby (ng/L) [a]	Main waterworks in Karlshamn (ng/L) [b,c]
PFPeA	38	10	<0.6
PFHxA	320	3.6	<0.3
PFHpA	32	1.4	<0.3
PFOA	100	1.0	<0.3
PFNA	<1	<1	<0.6
PFDA	<1	<1	<0.6
PFUnDA	<10	<10	<2
PFDoDA	<10	<10	<2
PFBS	130	<2.6	<0.3
PFHxS	1700	4.6	<0.3
PFHpS	60	<1	<0.3
PFOS	8000	27	<0.2
Sum of PFAS [d]	10,380	47.6	<5

Note: PFAS, perfluoroalkyl substances; PFPeA, perfluoropentanoic acid; PFHxA, perfluorohexanoic acid; PFHpA, perfluoroheptanoic acid; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFUnDA, perfluoroundecanoic acid; PFDoDA, perfluorododecanoic acid; PFBS, perfluorobutane sulfonic acid; PFHxS, perfluorohexane sulfonic acid; PFHpS, perfluoroheptane sulfonic acid; PFOS, perfluorooctane sulfonic acid.

[a] Multiple water samplings were performed. Here lists the data from water sampled on December 10th 2013, the very last sampling before the contaminated waterworks was closed.

[b] Water sampled on January 15th 2020

[c] PFAS analysis in drinking water was performed by a commercial water analysis company, SYNLAB (SYNLAB Analytics & Services Sweden AB, Linköping, Sweden), according to German standard methods for determination of selected polyfluorinated compounds in water using liquid chromatography-tandem mass spectrometry (LC/MS/MS) after solid-liquid extraction (F 42) (DIN 38407-42). SYNLAB is accredited by SWEDAC according SS-EN ISO/IEC 17025.

[d] Sum of all PFAS with levels above LOD for waterworks in Ronneby. For Karlshamn, the sum of PFAS was reported by the water analysis company.

The PFAS exposure in Ronneby is thus a "natural experiment", where a segment of the population had long-term exposure to PFAS from drinking water without knowing it, and with an abrupt end of exposure. In this paper, we report serum PFAS levels in the Ronneby residents who participated in a biomonitoring program, and in a reference group from a neighboring municipality with uncontaminated drinking water supply. We also describe how serum levels varied by age, sex and calendar period for residential exposure.

2. Material and methods

2.1. Study area

Ronneby is a municipality with approximately 28,000 inhabitants in 2013. Two waterworks (Brantafors and Kärragården) provided drinking water to the whole municipality. In September 2013, sampling in a glaciofluvial water reservoir indicated PFAS contamination in the groundwater. From then on to December 2013, repeated water samplings were performed, confirming very high PFAS levels in both the aquifer and the wells of one of the two waterworks in Ronneby (Brantafors). No measurements before 2013 exist.

The PFAS contaminated waterworks (Brantafors) distributed drinking water to approximately one third of the households in Ronneby (Fig. 1). The source of the contamination was confirmed to be AFFF firefighting foams used at a nearby military airport, situated approximately 2 km from the waterworks wells. Information from the airport indicated that the use of AFFF foams started in the mid-1980s. No information was available on the formulations in the foams or changes over time.

Table 1 shows the PFAS levels in the drinking water sampled at the two Ronneby waterworks on December 10 (i.e. the very last water sampling before the contaminated waterworks was closed). The contaminated waterworks had very high levels of multiple PFAS in the outgoing drinking water with sum of PFAS above 10,000 ng/L. The other waterworks, from which water was redirected to the contaminated waterworks district from December 16, had sum of PFAS below the action limits, 90 ng/L, but still higher than the waterworks in the neighboring municipality, Karlshamn. Private wells in the vicinity of the airport were also investigated, with some contamination but no indications of elevated PFAS levels above the action limits.

2.2. Study population

In February 2014, i.e. two months after provision of clean water, we performed a pilot study including 11-year-old children from a school in the area with previous contaminated drinking water supply (n = 20) and from a school in the area supplied from the other waterworks (n = 17). High serum levels of PFAS in the 20 children who had been exposed to contaminated drinking water (Table S1) were found, which prompted extensive population biomonitoring in the municipality.

The biomonitoring started in June 2014, i.e. six months after provision of clean water. All residents in the municipality were invited to free-of-charge blood samplings. Information on the samplings was repeatedly given through local media, the municipality website, announcements in libraries and the town hall, and through schools and workplaces. Over 20 sampling occasions were arranged between June 2014 and December 2015 to recruit as many participants as possible. Inhabitants living in the area with drinking water supplied by the minimally contaminated waterworks were explicitly invited. In total there were 3507 participants, about 13% of the entire Ronneby population at the time. The participation rates from contaminated and minimally contaminated areas were approximately 30% and 5%, respectively. All participants received written information about their serum PFOS, PFHxS and PFOA levels. Informed consent for participation in further studies and biobanking of serum samples was given by 3297 (94%) of participants (aged 0–92 years). Thus, this open sampling is the

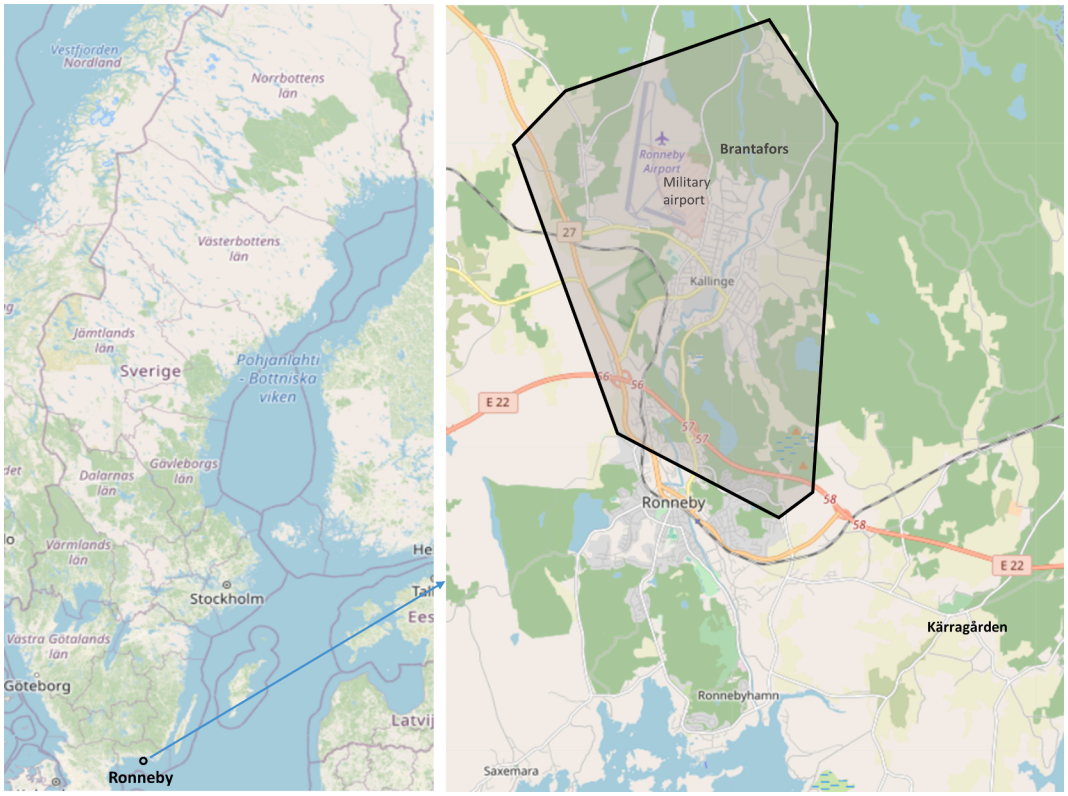

Fig. 1. The left map shows the location of Ronneby municipality in Sweden. The right map of Ronneby municipality shows the district with PFAS-contaminated drinking water supply in 2013 (area within solid black lines with gray gradient), together with the locations of the military airport, the contaminated waterworks Brantafors and the uncontaminated waterworks Kärragården. Background map data: © OpenStreetMap contributors, CC BY-SA.

baseline investigation for the *Ronneby Biomarker Cohort*. Information on smoking history, self-reported water and fish intake, pregnancy and breast feeding, firefighting experience, and addresses of daycare, school and work from 1985 and on were obtained from a short questionnaire. Height and weight were self-reported, with the possibility to measure height and weight at the sampling site. In addition, we retrieved yearly residential and workplace addresses during 1980–2013 from the Total Population Register (Statistics Sweden, www.scb.se) for 3086 participants. The address data were linked to detailed municipal lists of water supply.

The *Ronneby Biomarker Cohort* includes not only residents living in the areas with heavily contaminated drinking water but also those living in parts of Ronneby supplied by minimally contaminated waterworks. The latter ones were likely, to a varying extent, to drink contaminated water at work, at school, or during visits in the areas supplied by the contaminated waterworks. Therefore, in 2016, we also recruited 226 individuals (aged 5–59 years) from a neighboring municipality, Karlshamn, with PFAS-uncontaminated drinking water supply, as a reference group. Drinking water in Karlshamn had all PFAS levels below limit of detection (Table 1).

Fig. 2 illustrates the composition of the *Ronneby Biomarker Cohort and its reference group*. The study was approved by the Regional Ethical Review Board in Lund, Sweden (approved, date: 2014-04-22, approval number: 2014/4).

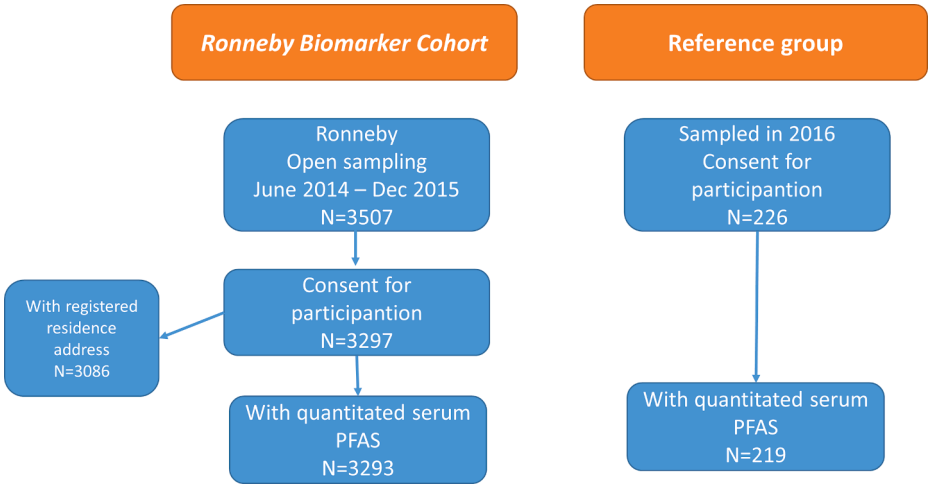

Fig. 2. The illustration of the *Ronneby Biomarker Cohort and its reference group*.

2.3. Serum PFAS analysis

Venous blood was collected in 5 ml Becton Dickinson vacutainer blood collection tubes (BD, Belliver Industrial Estate, Plymouth, UK) without gel. When venous blood sampling could not be performed (mainly for very small children), capillary sampling was performed. The blood samples were left in room temperature for at least 30 min before being centrifuged, then, serum was immediately transferred to storage tubes, transported on dry ice to the laboratory at Occupational and Environmental Medicine, Lund University, Lund, Sweden, and frozen at −80 °C (Lindh et al., 2012).

In the pilot study with 37 children, 15 different PFAS: PFBS, PFHxS, PFOS, perfluorodecane sulfonic acid (PFDS), as well as PFHxA, PFHpA, PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorotridecanoic acid (PFTrDA), perfluorotetradecanoic acid (PFTeDA), perfluorohexadecanoic acid (PFHxDA) and perfluorooctadecanoic acid (PFODA) were quantitated. The low levels found for PFAS with longer carbon chain (Table S1) led to selection of a limited set of compounds for quantitation in the main study. In the first 901 samples obtained in June 2014 from the *Ronneby Biomarker Cohort*, six PFAS: PFHxS, PFOS, PFHpA, PFOA, PFNA and PFDA were selected to be quantitated (Table S2). The results showed that the levels of PFHxS, PFOS and PFOA were much higher than the other three PFAS in serum, therefore, only PFHxS, PFOS and PFOA were decided to be quantitated for all study participants (N = 3523, 3297 *Ronneby Biomarker Cohort* participants and 226 reference group) due to practical reason. PFHpA, PFNA and PFDA were also quantitated in 51 samples randomly selected from the reference group (sampled in October 2016) for comparison purpose.

PFHxS, PFOS and PFOA were determined as the total, non-isomer specific compounds according to the method described by Lindh et al. (2012) and Li et al. (2018). Briefly, after thawing and vortexing samples, the proteins were precipitated using acetonitrile by vigorous shaking for 30 min. The samples were then centrifuged, and an aliquot of the supernatant was analyzed using liquid chromatography (LC) (UFLCXR, SHIMADZU Corporation, Kyoto, Japan) connected to tandem mass spectrometry (MS/MS) (QTRAP 5500 and 6500+, Sciex Framingham, MA, USA). Serum samples from populations expected to have high exposure to PFAS were prepared using diluted aliquots of 25 μl serum added with 75 μl of water and isotopically labeled internal standards for all compounds, and 1 μl of the samples were analyzed using LC/MS/MS. If lower levels were expected, aliquots of 100 μl serum were used and 4 μl of the samples were analyzed. In all batches, chemical blanks and three quality control (QC) samples, prepared in-house from serum spiked with different PFAS were included. The limit of detection (LOD) and detection frequency of all PFAS reported in this paper are listed in Table 2.

The analyses of PFOS and PFOA are part of a quality control programme between analytical laboratories coordinated by Professor Hans Drexler, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University of Erlangen-Nuremberg, Germany. The laboratory also participated in the HBM4EU QA/QC programme, and its successful performance has resulted in its qualification as HBM4EU laboratory for the analysis of: PFPeA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFBS, PFHxS, PFHpS and PFOS.

In addition to each PFAS, we also calculated the sum of three PFAS on weight basis for all study participants, and sum of four PFAS (i.e. PFOS, PFHxS, PFOA and PFNA) for participants with quantitated PFNA. Reporting sum of PFAS is scientifically sound and reasonable for regulatory purpose to protect our health and environment now and in the future (Kwiatkowski et al., 2020). In the recent report, EFSA assessed and set PFAS tolerable weekly intake as 4.4 ng/kg bw per week based on sum of four PFAS and called for reporting results for the sum of several PFAS for risk assessment (EFSA, 2020).

2.4. Drinking water exposure groups, based on address data

For the participants from Ronneby, we assessed the historical residential exposure based on information on registered yearly residence addresses. We linked all addresses to data on yearly water supply obtained from the municipality water company. Thus, we were able to identify, for each calendar year, if the address was supplied with high or low PFAS concentrations in the drinking water. Based on source of drinking water at residency, we assigned Ronneby residents to mutually exclusive groups: never-high (i.e. always low), and ever-high, with the latter group further separated into early-high and late-high (Table 3). All residential addresses with private wells were assumed to have had low contamination. The reference group consists of all participants from Karlshamn.

Residential addresses thus allowed a crude classification of the population by different potential for exposure to PFAS in drinking water. While we cannot know for sure when the contamination reached the water supply, we are confident that it was not prior to the mid-1980s when PFAS containing AFFF was first used. Moreover, we can safely assume that the levels in the contaminated aquifer rose over the subsequent years, being highest in the last decade prior to its discovery, and had arrived at the waterworks wells prior to 2004, our tentative cut-off for early and late exposure. The early-high group had moved out of the contaminated water distribution district by 2004, thus allowing for a 10 year elimination period, or even longer.

2.5. Statistical analysis

Study subjects were grouped into eight age strata by 10-year intervals (i.e. 0–10, 11–20, 21–30, 31–40, 41–50, 51–60, 61–70 and >70 years-old). For the reference group, only six age strata were available, up to age 60. For those in the early-high and late-high groups, total numbers of years of exposure was calculated as total years of residence in the area with contaminated water supply. Numbers of years since exposure stopped was calculated as elapsed years between end of exposure to contaminated water at residency (i.e. in 2013 when the

Table 2
List of PFAS, their corresponding acronyms, limit of detections (LOD), number of samples (n) and detection frequencies (df) in the *Ronneby Biomarker Cohort* and its reference group.

		Ronneby Biomarker Cohort			Reference group		
Analyte [a]	Acronym	LOD (ng/mL)	n	df (%)	LOD (ng/mL)	n	df (%)
Perfluoroheptanoic acid	PFHpA	0.05	901	56	0.02	51	73
Perfluorooctanoic acid	PFOA	0.4	3293	100	0.2	219	100
Perfluorononanoic acid	PFNA	0.05	901	100	0.08	51	100
Perfluorodecanoic acid	PFDA	0.09	901	89	0.04	51	100
Perfluorohexane sulfonic acid	PFHxS	0.5	3293	100	0.02	219	100
Total Perfluorooctane sulfonic acid	PFOS	0.5	3293	100	0.05	219	100

[a] PFAS were analyzed with the original method used from June 2014 to 2018. Details of the original method were reported by Lindh et al. (2012), Li et al. (2018) and Glynn et al. 2020.

Table 3
Drinking water exposure groups, definition, counts and exposure characteristics in each group.

Drinking water exposure groups [a]	Definition	Counts [b]	Total years of exposure[c] Median (P_5, P_{95})	Total years since exposure stopped[d] Median (P_5, P_{95})
Late-high	Resided in Ronneby, in the area with water supply from the highly contaminated waterworks at home address in 2005–2013, may also resided in same area in 1985–2004	2219	16 (2, 29)	1 (1, 6)
Early-high	Resided in Ronneby, in the area with water supply from the highly contaminated waterworks at home address in 1985–2004, but not later.	283	6 (1, 18)	18 (11, 28)
Ever-high	Resided in Ronneby, in the area with water supply from the highly contaminated waterworks at home address any time in 1985–2013	2502	14 (2, 29)	1 (1, 19)
Never-high	Resided in Ronneby, but never resided in the area with water supply from the highly contaminated waterworks at the home address or had own well in 1985–2013	582	–	–
Reference	Resided in neighboring municipality, Karlshamn. Never resided in Ronneby during 1985 to 2013	226	–	–

[a] Through linkage between registered yearly residence addresses and the data on yearly water supply area obtained from the municipality water company, we were able to identify, for each calendar year, if the address was supplied with contaminated or minimally contaminated drinking water. Then we assigned individuals to four exposure groups according to their historical residence addresses.

[b] If someone moved out from the contaminated area in the early period and never moved in again, this person only contributes counts for the Early-high group. If one person moved out from the contaminated area in the early period and moved in again (e.g. moved out in 1990 and moved in again in 2010), this person only contributes counts for the Late-high group.

[c] Total number of years of residence in the area with contaminated water supply. If a person has moved out and moved in again, the years in between were not summed up.

[d] Total number of years between the last time a person moved out from the area with contaminated water supply and the time of sampling (i.e. 2014–2015).

contaminated waterworks shut down, or year when moved out from the area with contaminated water supply) and blood sampling. PFAS levels were log-transformed in all regression models to improve the model fit.

Since our study population had a very wide age range, a generalized additive model was used to produce smooth splines to visualize the non-linear relationship between serum PFAS levels and age (Wood, 2017). In the regression models that compare the serum PFAS levels between the *Ronneby Biomarker cohort* and the reference group, as well as across exposure groups, log-transformed PFAS levels were estimated as smooth functions (thin plate splines) of age and BMI, with sex as a covariate in the models. In the regression models comparing sex-specific serum PFAS levels in each age stratum, age and BMI were included as continuous variables. Spearman's correlation coefficient was used for correlations between serum levels of pairs of each PFAS compound in the *Ronneby Biomarker Cohort*. Generalized additive model was performed in R using the 'mgcv' package. Linear regression and correlation analysis were performed using IBM SPSS 26.0 (IBM, Armonk, NY, USA). All p values were two-sided.

3. Results

3.1. Serum PFAS levels in the Ronneby Biomarker Cohort and its reference group

Population summary statistics for PFHxS, PFOS, PFOA and sum of three PFAS from the *Ronneby Biomarker Cohort* and the reference group, stratified by sex and age groups are given in Table 4. The population geometric means (GM) were 114 ng/mL for PFHxS, 135 ng/mL for PFOS and 6.8 ng/mL for PFOA, which were 135, 35 and 4.5 times higher than the reference group.

In the *Ronneby Biomarker Cohort*, the relations between PFHxS, PFOS, sum of three PFAS levels and age groups were J-shaped, with the age group 11–20 having lowest population GM of serum PFAS in both sexes. In the age groups between 20 and 50, females had clearly lower serum levels than males, in models adjusted for age and BMI. Above and below this age range the contrasts were small and confidences intervals were wide, although the results suggest that females had higher levels than males above age 60 (Table 5). Such pattern by age and sex was further highlighted using smooth splines (Fig. 3A) based on sum of three PFAS, showing that serum PFAS slightly decreased from childhood to teenage years and then increased with age. The difference between males and females in PFAS levels had a turn over point at around age 55. In the reference group, children aged 0–10 and 11–20 showed quite similar serum PFAS levels between sexes. From age 20 to 60, females constantly showed lower PFAS levels than males in all age groups (Table 5, Fig. 3B).

Serum levels of PFHpA, PFNA and PFDA were only quantitated in the first 901 samples from *Ronneby Biomarker Cohort*, and 51 samples from the reference group (Table 6). The GM of PFHpA was on average 4.3 (95%CI: 2.7, 6.9) times higher in the Ronneby participants than in the reference group. On the contrary, PFNA and PFDA were lower in the Ronneby participants [ratio 0.8 (95%CI: 0.7, 0.9) for PFNA, and 0.6 (95%CI: 0.5, 0.8) for PFDA] adjusted for age, BMI and sex. Including PFNA into the sum of 4 PFAS only increased the GM of sum by 0.2% in the Ronneby participants. In the reference group, the inclusion of PFNA increased the GM of sum by 12%, compared to the sum of 3 PFAS.

Serum levels of PFHxS, PFOS and PFOA were very highly correlated (Spearman's $r_s > 0.9$, $p < 0.001$ for all pairs) in the *Ronneby Biomarker Cohort*. The pairwise correlations to PFHpA, PFNA and PFDA were weaker and r_s were generally around 0.2–0.4. The weakest correlations were found between PFHpA and PFDA or PFNA (Table 7).

3.2. Serum PFAS levels in the drinking water exposure groups based on residential address

The total numbers of years of exposure and years since exposure stopped are given in Table 2. The median number of years of exposure was 16 years for the late-high group, and 6 years for the early-high group. In the late-high group, the majority of participants (1937; 87%) had contaminated drinking water at home until December 2013.

Ronneby residents, no matter where they had resided, the serum PFAS levels exceeded the findings in the reference group (Table 8). The largest difference was observed for PFHxS, where the late-high group had a GM of 210 ng/mL, >190 times higher than the GM in reference group. Smaller but still substantial differences were also observed for PFOA, where the Ronneby participants (all three groups) had about 1.9 to 7.3 time higher.

Table 4
Geometric mean (GM), 5 and 95 percentiles of serum PFAS levels (ng/mL) in the *Ronneby Biomarker Cohort* and in the reference group, stratified by sex and age group.

		PFHxS			PFOS			PFOA			Sum of 3 PFAS [a]		
	Count	GM	P_5	P_{95}	GM	P_5	P_{95}	GM	P_5	P_{95}	GM	P_5	P_{95}
Ronneby Biomarker Cohort	3293	114	7.0	715	135	12	718	6.8	1.4	37	262	21	1465
Female	1795	102	5.6	758	124	11	743	8.1	1.3	38	239	19	1539
0–10	155	89	19	303	98	14	315	8.9	1.9	26	199	37	617
11–20	162	54	5.5	249	70	6.9	291	5.2	1.3	19	131	13	559
21–30	206	60	6.6	334	79	9.0	331	5.0	1.0	19	146	16	670
31–40	257	61	5.6	357	82	9.7	421	5.1	1.0	22	150	18	783
41–50	348	85	4.0	525	109	8.3	552	6.9	1.1	30	206	14	1105
51–60	266	130	4.3	800	157	10	779	9.8	1.6	37	304	17	1631
61–70	263	220	10	944	240	16	911	15	1.8	48	483	30	1810
>70	138	341	21	1078	349	25	1053	20	2.7	55	716	49	2066
Male	1497	129	9.5	658	149	15	698	9.6	1.9	37	292	27	1393
0–10	183	103	18	324	113	18	362	10	2.5	28	230	34	700
11–20	178	65	3.6	300	85	5.5	360	6.3	1.2	21	159	9.6	666
21–30	138	110	14	395	133	22	440	8.2	2.3	24	255	41	825
31–40	208	96	5.0	483	114	12	540	7.0	1.7	27	221	20	1060
41–50	267	155	14	688	170	17	687	10	2.0	38	341	31	1412
51–60	204	146	6.9	629	163	16	668	10	2.1	34	325	28	1429
61–70	196	183	7.3	792	210	21	831	13	2.7	43	416	31	1653
>70	123	299	24	932	330	32	1001	18	2.7	59	653	64	1956
Reference Group	219	0.84	0.33	3.5	3.9	1.6	11	1.5	0.74	3.4	6.6	3.0	17
Female	120	0.76	0.33	2.4	3.5	1.3	9.1	1.5	0.66	3.3	6.0	2.7	14
0–10	37	0.57	0.31	2.3	3.0	1.2	6.2	1.5	0.90	2.9	5.2	3.0	9.2
11–20	7	0.59	0.36	1.2	2.2	1.4	3.6	1.2	0.74	2.1	4.0	2.7	5.7
21–30	21	0.89	0.33	2.7	3.2	1.2	6.0	1.4	0.66	3.2	5.8	2.3	10
31–40	16	0.85	0.22	2.1	3.2	0.23	8.5	1.2	0.30	3.6	5.7	1.5	11
41–50	16	0.87	0.41	3.6	4.4	2.1	13	1.6	0.65	4.4	7.1	4.0	20
51–60	23	0.94	0.50	2.2	5.4	2.5	10	1.7	1.1	2.8	8.1	3.9	15
Male	99	0.96	0.34	8.2	4.5	1.7	12	1.7	0.95	3.4	7.5	3.3	21
0–10	35	0.48	0.33	0.9	3.0	1.3	6.3	1.6	1.2	2.7	5.2	3.0	9.0
11–20	8	0.64	0.37	1.0	3.7	1.6	5.5	1.3	0.62	2.2	5.7	2.6	8.5
21–30	16	1.2	0.61	8.0	4.8	2.0	9.1	1.8	0.95	4.2	8.0	3.9	18
31–40	9	1.8	0.35	19	5.1	1.5	15	1.8	1.2	3.4	9.9	3.3	26
41–50	19	1.4	0.32	12	5.7	1.9	13	1.5	0.79	3.1	9.0	3.2	26
51–60	12	2.4	1.0	28	9.6	4.8	49	2.3	1.2	4.9	15	8.5	81

Note: PFAS, perfluoroalkyl substances; PFHxS, perfluorohexane sulfonic acid; PFOS, perfluorooctane sulfonic acid, PFOA, perfluorooctanoic acid; GM, geometric mean; P_5 and P_{95}, 5 and 95 percentiles.
[a] Sum of concentrations of PFHxS, PFOS and PFOA.

Table 5
The ratios in serum PFAS levels (ng/mL) between sexes in each age strata of the *Ronneby biomarker Cohort* and reference group.

	PFHxS		PFOS		PFOA		Sum of 3 PFAS	
Age group	Ratio (95%CI) [a,b]	P [a]	Ratio (95%CI) [a,b]	P [a]	Ratio (95%CI) [a,b]	P [a]	Ratio (95%CI) [a,b]	P [a]
Ronneby Biomarker cohort								
0–10	0.86 (0.68, 1.08)	0.18	0.86 (0.69, 1.06)	0.15	0.88 (0.75, 1.04)	0.14	0.86 (0.70, 1.06)	0.16
11–20	0.84 (0.62, 1.12)	0.24	0.82 (0.63, 1.09)	0.17	0.84 (0.69, 1.02)	0.08	0.83 (0.63, 1.09)	0.17
21–30	0.55 (0.42, 0.72)	<0.001	0.59 (0.47, 0.75)	<0.001	0.61 (0.51, 0.74)	<0.001	0.57 (0.45, 0.73)	<0.001
31–40	0.65 (0.51, 0.83)	<0.001	0.73 (0.58, 0.91)	0.01	0.73 (0.61, 0.87)	<0.001	0.69 (0.55, 0.87)	<0.001
41–50	0.55 (0.43, 0.69)	<0.001	0.64 (0.52, 0.79)	<0.001	0.68 (0.57, 0.80)	<0.001	0.61 (0.49, 0.75)	<0.001
51–60	0.86 (0.66, 1.14)	0.29	0.95 (0.75, 1.19)	0.63	0.96 (0.79, 1.16)	0.66	0.91 (0.72, 1.17)	0.47
61–70	1.21 (0.94, 1.57)	0.14	1.15 (0.92, 1.44)	0.21	1.12 (0.94, 1.33)	0.20	1.17 (0.93, 1.47)	0.18
>70	1.19 (0.90, 1.56)	0.23	1.10 (0.85, 1.42)	0.48	1.15 (0.91, 1.45)	0.24	1.14 (0.88, 1.48)	0.33
Reference group								
0–10	1.19 (0.93, 1.51)	0.16	1.00 (0.8, 1.26)	0.99	0.91 (0.79, 1.04)	0.16	0.99 (0.83, 1.19)	0.93
11–20	1.00 (0.55, 1.81)	0.99	0.76 (0.42, 1.38)	0.33	1.19 (0.66, 2.12)	0.53	0.90 (0.53, 1.52)	0.66
21–30	0.75 (0.48, 1.19)	0.21	0.68 (0.48, 0.96)	0.03	0.81 (0.55, 1.17)	0.25	0.73 (0.53, 1.00)	0.05
31–40	0.30 (0.14, 0.67)	0.01	0.57 (0.25, 1.31)	0.18	0.77 (0.44, 1.35)	0.34	0.48 (0.25, 0.92)	0.03
41–50	0.63 (0.37, 1.08)	0.09	0.76 (0.53, 1.10)	0.14	1.10 (0.80, 1.51)	0.55	0.80 (0.56, 1.13)	0.2
51–60	0.40 (0.24, 0.64)	<0.001	0.55 (0.38, 0.78)	<0.001	0.73 (0.55, 0.97)	0.03	0.54 (0.38, 0.77)	<0.001

Note: PFAS, perfluoroalkyl substances; PFHxS, perfluorohexane sulfonic acid; PFOS, perfluorooctane sulfonic acid, PFOA, perfluorooctanoic acid.
[a] From linear regression model: ln_PFAS = a + β1*sex + β2*age + β3*BMI. Age and BMI were treated as continuous variable in the model. Ratio = exp(β1).
[b] The ratio was females vs. males. For example: females had average 0.55 times lower serum PFHxS than males in age group 21–30 in the *Ronneby Biomarker Cohort*.

4. Discussion

The PFAS contaminated drinking water from a municipal waterworks led to globally unique serum levels in the local population, not only regarding the high concentrations but also concerning the composition of different PFAS, reflecting contamination from AFFF firefighting foam (Rotander et al., 2015). The dominating PFAS were PFHxS and PFOS, which led to population GM about 135 and 35 times higher in the Ronneby participants than a reference population with background exposure. In contrast, PFOA levels were 4.5 times higher than the reference population.

The increasing awareness of widespread PFAS contaminated

Fig. 3. Smooth spline of sum of 3 PFAS with 95% confidence intervals in (A) *Ronneby Biomarker Cohort* and (B) Reference group, stratified by age and sex in. The points on the graph are the original data.

Table 6
Geometric mean (GM), Median, 5 and 95 percentiles of serum concentrations (ng/mL) of PFHpA, PFOA, PFNA, PFDA, PFHxS and PFOS in first 952 samples obtained from Ronneby Biomarker Cohort and the reference group.

PFAS	Ronneby Biomarker Cohort (n = 901)				Reference Group (n = 51)					
(ng/mL)	GM	P_5	Median	P_{95}	GM	P_5	Median	P_{95}	Max	Ratio (95%CI) [c]
PFHpA	0.11	<LOD	0.06	0.8	0.04	0.01	0.04	0.2	0.20	4.3 (2.7, 6.9)
PFOA	15	3.0	17	47	1.5	1.0	1.4	2.9	3.8	8.1 (6.5, 10)
PFNA	0.67	0.3	0.7	1.8	0.50	0.3	0.5	1.0	1.3	0.8 (0.7, 0.9)
PFDA	0.24	0.04	0.3	0.8	0.22	0.1	0.2	0.4	0.6	0.6 (0.5, 0.8)
PFHxS	229	33	280	866	0.49	0.3	0.5	1.0	6.9	298 (220, 403)
PFOS	262	42	303	874	3.0	1.2	2.9	6.2	13.1	57 (43, 75)
Sum of three PFAS [a]	511	82	606	1770	5.1	3.0	4.8	9.0	22.9	65 (49, 86)
Sum of four PFAS [b]	512	82	607	1771	5.7	3.3	5.3	9.8	24.2	59 (45, 78)

Note: PFHpA, perfluoroheptanoic acid; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFOS, perfluorooctane sulfonic acid.

[a] Sum of concentrations of PFHxS, PFOS, PFOA.

[b] Sum of concentrations of PFHxS, PFOS, PFOA and PFNA.

[c] Ratio (95%CI) were from thin plate regression spline: ln_PFAS = a + β1*(Ronneby vs. reference) + β2*sex + β3*BMI + β4*age. Age and BMI were treated as smooth functions in the model. The ratio = exp (β1).

Table 7
Spearman's correlation coefficients and p-values between each PFAS compound in the *Ronneby Biomarker Cohort.*

	PFOA [a]	PFOS [a]	PFHpA [b]	PFNA [b]	PFDA [b]
PFHxS [a]	0.93 (<0.001)	0.98 (<0.001)	0.22 (<0.001)	0.37 (<0.001)	0.19 (<0.001)
PFOA [a]		0.95 (<0.001)	0.37 (<0.001)	0.40 (<0.001)	0.21 (<0.001)
PFOS [a]			0.24 (<0.001)	0.39 (<0.001)	0.22 (<0.001)
PFHpA [b]				0.13 (<0.001)	0.07 (0.035)
PFNA [b]					0.73 (<0.001)

Note: PFAS, perfluoroalkyl substances; PFHxS, perfluorohexane sulfonic acid; PFOS, perfluorooctane sulfonic acid, PFOA, perfluorooctanoic acid; PFHpA, perfluoroheptanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid.

[a] Correlations were based on 3293 participants in the *Ronneby Biomarker Cohort.* 4 participants did not have quantitated PFAS in serum.

[b] Correlations were based on 901 Ronneby participants with PFHpA, PFNA and PFDA quantitated in serum.

drinking water originated from AFFF has led to increase numbers of studies investigating such exposure. Many countries have launched nation-wide exposure assessments focusing on the communities near current or former military airbase. For instance, Agency for Toxic Substances and Disease Registry (ATSDR) together with the Centers for Disease Control and Prevention (CDC) initiated exposure assessments in eight US communities in 2018 (https://www.atsdr.cdc.gov/pfas/activities/assessments.html). In Sweden, water sampling and biomonitoring of residents have been performed in four municipalities (including Ronneby) with military or civil airports nearby (Jakobsson et al., 2019). However, the published studies on general population exposure after AFFF contamination is still scarce, as are reports of health effect (Gyllenhammar et al., 2015; Daly et al., 2018; Barton et al., 2020; Nair et al., 2020). The Ronneby exposure scenario, dominated by PFOS and PFHxS, differs from populations with PFOA-dominating exposure from industrial sources (Frisbee et al., 2009; Hölzer et al., 2008; Ingelido et al., 2018). The serum PFAS levels comparison between studies are summarized in Table 9.

PFAS with less than eight carbons in the chain length (e.g. PFPeA, PFHxA, PFHpA and PFBS, PFPeS, PFHpS) were present in the drinking water in Ronneby municipality. Correspondingly, serum PFHpA was found to be considerably higher in Ronneby participants than in the reference group, together with serum PFBS to be higher in the 20 students living within exposed area than those living outside exposed area from the pilot study (Table S1). Notably, the serum levels of these shorter chain PFAS during exposure are underestimated due to the lag of two to six months between when the external exposure stopped and the first blood sampling, given their relatively faster elimination rate (Xu

Table 8
Serum PFAS levels (ng/mL) in the drinking water exposure groups.

	Drinking water exposure groups (based on registered address) [a]	n	GM	P_5	P_{95}	Ratio (95% CI) [b,c]	Ratio (95% CI) [b,d]
PFHxS	Late-high	2219	210	43	777	193 (169, 220)	6.7 (6.1, 7.3)
	Early-high	283	43	5.1	246	36 (31, 43)	1.3 (1.1, 1.5)
	Never-high	582	30	2.9	204	29 (25, 33)	1
	Reference	226	0.84	0.33	3.5	1	–
PFOS	Late-high	2219	239	55	783	48 (43, 54)	5.8 (5.3, 6.2)
	Early-high	283	48	9.9	226	9.0 (7.7, 10)	1.1 (1.0, 1.2)
	Never-high	582	40	5.5	218	8.4 (7.4, 9.5)	1
	Reference	226	3.9	1.6	11	1	–
PFOA	Late-high	2219	13	3.6	40	7.3 (6.6, 8.1)	3.7 (3.4, 3.9)
	Early-high	283	3.6	1.1	12	1.9 (1.7, 2.2)	1.0 (0.9, 1.1)
	Never-high	582	3.5	0.94	13	2.0 (1.8, 2.2)	1
	Reference	226	1.5	0.74	3.4	1	–
Sum of 3 PFAS	Late-high	2219	466	104	1614	56 (50, 62)	5.9 (5.5, 6.4)
	Early-high	283	97	17	474	11 (9.2, 12)	1.1 (1.0, 1.3)
	Never-high	582	74	11	455	9.3 (8.2, 11)	1
	Reference	226	6.6	3	17	1	–

Note: PFAS, perfluoroalkyl substances; PFHxS, perfluorohexane sulfonic acid; PFOS, perfluorooctane sulfonic acid, PFOA, perfluorooctanoic acid; GM: geometric mean; P_5, P_{95}: 5 and 95 percentiles.

[a] Detailed definition of groups see Table 4.

[b] Ratio and 95% CI were obtained from regression model: ln_PFAS = a + β1*exposure groups + β2*sex + β3*BMI + β4*age. Age and BMI were treated as smooth functions (thin plate splines) in the model. The ratio = exp (β1).

[c] Comparison was late-high/early-high/never-high groups vs. Reference. For instance: Late-high group had average 193 times higher PFHxS than the reference group.

[d] Comparison was late-high/early-high groups vs. Never-high group. For instance: Late-high group had average 6.8 times higher PFHxS than the never-high group.

et al., 2020b). Approximately, in December 2013 the GM of serum PFHpA would have been 0.88 ng/mL, based on level measured in June 2014 (GM = 0.11 ng/mL, Table 6) and mean observed half-life as 62 days reported by Xu et al. (2020b).

In a recent EFSA draft opinion on PFAS, PFNA was included, in addition to PFOS, PFHxS and PFOA for calculation of tolerable weekly intake (EFSA, 2020). In our reference group, where background exposure levels were comparable or even slightly lower than the European general population summarized by EFSA and the US population reported by NHANES 2015–2016 (Table 9), we found that PFNA constituted 10% of the sum of four PFAS. In contrast, the contribution of PFNA to the sum of four PFAS in the *Ronneby biomarker cohort* was negligible. Similar findings of low levels of PFNA in serum, as well as in water samples, were observed around another two airports in Sweden (Xu et al., 2020b; Livsmedelsverket, 2017). Moreover, in two studies with US residents exposed to AFFF contaminated drinking water, PFNA was also detected in most of the serum samples, but showed a relatively lower concentrations (median = 0.4 ng/mL in Barton et al. (2020) and GM = 0.7 ng/mL in Nair et al. (2020)) compared to PFHxS, PFOS and PFOA (Table 9), and such levels were comparable or even slightly lower than those reported in the U.S. general population. Taken together, it is reasonable to assume that other sources (e.g. dietary, residential) than AFFF are more important for PFNA exposure at background level.

Our baseline data for the *Ronneby Biomarker Cohort* showed that the serum PFAS levels decreased from early age through preteen to ten ages, with lowest levels at age 11–20 in both sexes, which is likely explained by the expansion of body volume as the child grows. After age 20, serum PFAS levels increased with age. Before age 60, females showed lower serum levels of all PFAS than males. The largest sex difference was seen in the age range 20–50, explained by PFAS elimination through menstruation, pregnancy and breast feeding (Li et al., 2018; Wong et al., 2014). The contrast in serum PFAS levels between men and women became smaller in 51–60 years old. Women had higher levels than men from 60 years and up, though these differences did not reach statistical significance. In the C8 study, a similar pattern was evident for women, with higher PFOA than men after around 65 years old, but not for PFOS and PFHxS (Frisbee et al., 2009). In another Swedish study including subjects aged 70 and above, with overall much lower serum levels, higher PFHxS in women than in men was reported, but no sex-difference for PFOA and PFOS (Salihovic et al., 2015). The underlying physiological mechanisms are not known, and the possibility of higher dependency on residential drinking water in women has not been ruled out. Additionally, it should be noted that these observations were based on cross-sectional, not longitudinal data.

External exposure assessment as a complement to direct measurement is important in cross-sectional studies, to help in identifying possible confounding or reverse causation (Weisskopf and Webster, 2017). Unfortunately, no water data before 2013 on PFAS in drinking water is available, therefore a relative crude exposure modelling based on yearly addresses and water distribution data was used to reflect the contamination accumulating over time (Andersson et al., 2019; Xu et al., 2020a),. The large contrast in serum levels in 2014 between the early-high and late-high groups reflects both excretion after stopping exposure (following the long half-lives) and assumed lower water concentrations in the past.

When the drinking water contamination was discovered in Ronneby in 2013, 6:2, and 8:2 fluorotelomer sulfonate (FTS) were not included in the water and serum analysis. These two compounds were observed at AFFF firefighter training areas after the shift from electrochemical fluorination to telomerization method for production (Schultz et al., 2004, Houtz et al., 2013, Buck et al., 2011). Future studies are needed to investigate serum levels of these compounds in the populations exposed to AFFF-related contamination.

The long half-life of PFAS that dominated in the Ronneby population indicates a large body burden of PFAS in the exposed population that will remain for decades (Li et al., 2018). Considering the large variation in PFAS elimination rate between persons, if an 11-years-old child who had been exposed to PFAS through drinking water and had PFHxS level as 270 ng/mL (the median level in Table S1), it will take him/her from 30 to 70 years to reach a level as 5 ng/mL, the median level found in the same age child without PFAS exposure in drinking water. During these years, although the external exposure has stopped, the body burden remains and may cause adverse health effects. More importantly, these years with internal exposure are also a problem for next one or even two generations since PFAS pass from mother to infant throughout pregnancy and breastfeeding (Mamsen et al., 2019; Mogensen et al., 2015; Mondal et al., 2014). In order to elucidate potential health effects in the Ronneby residents, an extensive research program with multiple ongoing studies has been established (Figure S1). The findings are

Table 9
Summary of PFAS levels in the present study and in other studies referred in the discussion.

Cohort	Area	PFAS origin	PFHxS (ng/mL)	PFOS (ng/mL)	PFOA (ng/mL)	ref
PFAS exposure through drinking water						
Ronneby Biomarker Cohort	Ronneby, Sweden	AFFF firefighting foam	GM: 114	135	6.8	Present study
C8	West Virginia, US	DuPont Industry	GM: 3.3	19	33	Frisbee et al. (2009)
Veneto	Veneto Region, Italy	Chemical plant producing herbicides	Median: 3.0	8.7	14	Ingelido et al. (2018)
Arnsberg	Arnsberg, Germany	Soil conditioner	GM: Children: 1.2 Mothers: 1.1 Men: 2.5	Children: 4.9 Mothers: 5.8 Men: 11	Children: 22 Mothers: 23 Men: 25	Hölzer et al. (2008)
Uppsala	Uppsala. Sweden	AFFF	Median: 1.8	18	2.6	Gyllenhammar et al. (2015)
New Hampshire	New Hampshire, US	AFFF	GM: 4.1	3.1	8.6	Daly et al. (2018)
Colorado	Colorado, US	AFFF	Median: 14.8	9.7	3.0	Barton et al. (2020)
Pennsylvania	Pennsylvania, US	AFFF	GM: 6.6	10.2	3.1	Nair et al. (2020)
Background PFAS exposure						
Reference group	Karlshamn, Sweden		Median: 0.7 GM:0.84	3.8 3.9	1.5 1.5	Present study
NHANES (2015–2016)	US		Median: 1.2 GM: 1.2	4.8 4.7	1.6 1.6	CDC (2018)
EFSA	European population		Median: children: 0.6 Adult: 0.7	Median: children: 3.2 Adult: 7.7	Median: Children: 3.3 Adult: 1.9	EFSA (2020)

important for further regulatory actions for the large class of PFAS.

5. Conclusion

The PFAS contamination in drinking water which occurred in Ronneby resulted in up to hundredfold or even higher serum levels than in a population with only background exposure. Contamination of drinking water with PFAS is not unique, but the very high serum levels in combination with a wide range, especially for PFHxS and PFOS, hitherto not reported from any other general population, enables in-depth studies of dose-response and dose-effect relationships. Ongoing studies have the potential to improve the current understanding of the biology of PFAS exposure and therefore inform future regulation to protect populations exposed to PFAS.

CRediT authorship contribution statement

Yiyi Xu: Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Christel Nielsen:** Conceptualization, Investigation, Project administration, Writing - review & editing. **Ying Li:** Formal analysis, Data curation, Writing - review & editing. **Sofia Hammarstrand:** Validation, Writing - review & editing. **Eva M. Andersson:** Data curation, Writing - review & editing. **Huiqi Li:** Validation, Writing - review & editing. **Daniel S. Olsson:** Resources, Writing - review & editing. **Karin Engström:** Resources, Writing - review & editing. **Daniela Pineda:** Resources, Writing - review & editing. **Christian H. Lindh:** Resources, Writing - review & editing. **Tony Fletcher:** Resources, Validation, Writing - review & editing. **Kristina Jakobsson:** Conceptualization, Supervision, Project administration, Funding acquisition, 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.

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Appendix A. Supplementary material

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