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Estimating historical PFAS exposures in Ronneby, Sweden using biobanked dried blood spots from newborns

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ABSTRACT

Background: In 2013, it was discovered that a subset of the population in Ronneby, Sweden was exposed to high levels of perfluorinated compounds (PFAS) from drinking water that had been provided by the local Brantafors waterworks and was contaminated by fire-fighting foam from a nearby airport. The start and time-course of population exposures are not known.
Objective: To investigate the start of PFAS exposures in the Ronneby population and changes over time by measuring PFAS in dried blood spots (DBS) collected from infants after birth and biobanked at the Swedish Phenylketonuria (PKU) Biobank.
Methods: We measured PFAS in DBS from 288 infants born between 1985 and 2013 using liquid chromatography-tandem mass spectrometry. Brantafors subjects (N = 246) were infants whose mothers lived at an address that received Brantafors water, while non-Brantafors subjects (N = 42) were infants whose mothers lived in the same county but never lived in Ronneby. We compared PFAS concentrations between the two groups using Welch's t-tests for unequal variance and investigated trends in PFAS concentration over time using generalized additive models with a non-linear term for year of birth.
Results: Mean PFAS concentrations were significantly higher in Brantafors subjects born in 1985 (N = 10) compared to non-Brantafors subjects born 1985–1989 (N = 19) for all PFAS. The concentration of all PFAS measured in Brantafors subjects increased from 1985, with most PFAS reaching an expected maximum in 2007. For example, non-Brantafors subjects born between 1985 and 1995 had a median PFOS concentration of 4.0 ng/mL (IQR: 3.6–4.3), while Brantafors subjects born 1985–1995 had a median concentration of 18 ng/mL (IQR: 14–26) and Brantafors subjects born 1996–2013 had a median concentration of 42 ng/mL (IQR: 29–64).
Discussion: These results suggest that population-wide PFAS exposures were already present in Ronneby in 1985 and increased over the subsequent 30 years, and demonstrate how DBS can be used for historical exposure assessment.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a class of synthetic compounds that are widely used in industry and consumer products because of their desirable chemical properties, including oil and water repellency, chemical and thermal stability, and surfactant properties

Abbreviations: Per- and polyfluoroalkyl substances, (PFAS); aqueous film-forming foams, (AFFF); perfluorooctanoic acid, (PFOA); perfluorooctane sulfonic acid, (PFOS); perfluorohexane sulfonic acid, (PFHxS); dried blood spots, (DBS); phenylketonuria, (PKU); liquid chromatography-tandem mass spectrometry, (LC-MS/MS); perfluorobutane sulfonic acid, (PFBS); perfluoropentane sulfonic acid, (PFPeS); perfluoroheptane sulfonic acid, (PFHpS); perfluorohexanoic acid, (PFHxA); perfluoroheptanoic acid, (PFHpA); perfluorononanoic acid, (PFNA); perfluorodecanoic acid, (PFDA); perfluoroundecanoic acid, (PFUnDA); perfluorohexanesulfonamide, (PFHxSA).

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(EFSA Panel on Contaminants in the Food Chain, 2020). Many PFAS are highly persistent in the environment due to their strong carbon-fluorine bonds, which, combined with their extensive use, has led to widespread environmental contamination and human exposures (EFSA Panel on Contaminants in the Food Chain, 2020). Epidemiological studies have linked PFAS exposures to adverse health effects, including immunotoxicity, high cholesterol, and increased risk of cancer (EFSA Panel on Contaminants in the Food Chain, 2020; Fenton et al., 2021).

Point sources of PFAS contamination, including manufacturing facilities and landfills, can lead to high environmental concentrations of PFAS and eventual human exposures through drinking water and food (De Silva et al., 2021). Many common PFAS are highly mobile in aquatic environments and cannot be treated or removed by conventional wastewater treatment, making them a significant threat to clean water supplies (Banzhaf et al., 2017).

One common source of PFAS contamination is the use of aqueous film-forming foams (AFFF) at military bases, commercial airports, and fire-training areas (De Silva et al., 2021). When mixed with water, AFFF forms an aqueous film that is spread over flammable fuel to extinguish the fire and prevent re-ignition (ITRC, 2023). PFAS act as the thermally-stable surfactant in AFFF and typically account for several percent of its formulation by weight (ITRC, 2023). AFFF can be accidently discharged to the environment after its application, and water systems adjacent to areas of AFFF use often have high PFAS levels (De Silva et al., 2021). There are over 4000 military and airport sites in the U.S. and 1620 military and airport sites in Europe where AFFF contamination is likely (Forever Pollution Project, 2023; Salvatore et al., 2022). Although AFFF formulations containing perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and perfluorohexane sulfonic acid (PFHxS) have been phased out, new formulations still rely on other PFAS (ITRC, 2023, ITRC, 2022; Nicol et al., 2022; U.S. Federal Aviation Administration, 2023). Even if all AFFF is eventually replaced by fluorine-free foam, contamination from its past use will persist indefinitely and continue to cause environmental and human exposures.

Communities with high internal PFAS concentrations from contaminated drinking water have been identified globally, including in the U. S. (Daly et al., 2018; McDonough et al., 2021; Nair et al., 2021), Sweden (Miaz et al., 2020; Xu et al., 2021), Australia (Smurthwaite et al., 2021), Germany (Hölzer et al., 2008), Taiwan (Lin et al., 2020), and Jersey (States of Jersey, 2024). While population biomonitoring programs are able to assess the scale and magnitude of current community exposures (De Brouwere et al., 2023), identifying the start of exposures and characterizing historical exposure levels over time is much more difficult. Accurate historical exposure estimates are necessary for epidemiological studies of PFAS-associated effects in highly-exposed communities, as exposure misclassification can reduce power and potentially bias associations (Armstrong, 1998). Epidemiological studies of the effect of cumulative exposures or exposures during important developmental periods (e.g., prenatal exposures) particularly require accurate historical exposure estimates. However, historical reconstruction of PFAS exposure and serum levels has only been modeled for one highly-exposed epidemiological cohort (the C8 cohort in West Virginia and Ohio in the United States) (Shin et al., 2011). Understanding historical PFAS exposures is also important for addressing community concerns and informing potential public health actions.

One community that has been highly exposed to PFAS from AFFF-contaminated drinking water is in the municipality of Ronneby, located in Blekinge county, Sweden. Since the 1980s, public drinking water in Ronneby was provided by two municipal water supplies: Brantafors waterworks, which provided water to approximately $^{1}/_{3}$ of the population, and Kärragården waterworks, which provided water to the remaining $^{2}/_{3}$ of the population (Mussabek et al., 2023). In December 2013, it was unexpectedly discovered that the water provided by Brantafors was highly contaminated by PFAS, with a total PFAS concentration greater than 10,000 ng/L (Xu et al., 2021). Subsequent testing in Kärragården also identified slightly elevated PFAS concentrations, with a total PFAS concentration of 48 ng/L. In comparison, the total PFAS concentration in the water supply of a nearby municipality was <5 ng/L (Xu et al., 2021). After the high level of contamination was discovered, the Brantafors water supply was shut off and all water for the area was provided by Kärragården.

The contamination source was traced back to AFFF runoff from a military airport, which has been active since 1994 and was located upstream of the groundwater reservoir (Mussabek et al., 2023). Military records documented that AFFF usage at the airport began in the mid-1980s primarily for fire training activities (Mussabek et al., 2023). However, the exact start of AFFF use at the airport and changes in its use patterns over time are not known. It is also not known how long it took the AFFF contamination to reach the drinking water source.

Population biomonitoring in 2014 and 2015 found high serum levels of PFOS (geometric mean, GM: 114 ng/mL) and PFHxS (GM: 135 ng/mL) in 3297 Ronneby residents. In 2016, an additional 219 residents from a nearby municipality also provided serum samples as a comparison group. The geometric mean concentrations in this population was 3.9 ng/mL for PFOS and 0.84 ng/mL for PFHxS (Xu et al., 2021). Previous epidemiological studies of Ronneby adults have assumed that exposure began in 1985 and, based on this assumption, categorized exposure as never-high/ever-high using subject-specific residential history and water supply maps (H. Li et al., 2022a; Xu et al., 2020b). Studies of health outcomes in pregnancy, delivery and early-childhood have similarly categorized exposure based on maternal residential history the five years before delivery (Ebel et al., 2023; Nielsen et al., 2022). However, the true start of population-wide PFAS exposures is unknown and could be earlier or later than its assumed start in 1985. Furthermore, PFAS concentrations in the aquifer and in Brantafors' provided drinking water likely fluctuated over time due to changes in fire training activities, AFFF formulations, and water withdrawal patterns at Brantafors, thus changing exposures to the community and resulting population serum levels. These time-dependent changes have not been incorporated in previous exposure assessments for epidemiology studies.

To better profile historical PFAS exposures in Ronneby, we measured PFAS concentrations in whole blood from dried blood spots (DBS) collected from newborns as part of the Swedish phenylketonuria (PKU) screening program between 1985 and 2013. PFAS are transferred from mother to child during gestation by the placenta (Liu et al., 2021). Therefore, PFAS concentrations measured in newborn serum reflect maternal PFAS serum levels before delivery. Several previous studies have developed and validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods for quantifying PFAS in DBS (Spliethoff et al., 2008; Kato et al., 2009; Ma et al., 2013; Poothong et al., 2019; Koelmel et al., 2023; Lin et al., 2023).

The primary objective in the study was to investigate differences in early exposure by comparing PFAS concentrations in DBS collected as part of the Swedish routine phenylketonuria (PKU) screening program in newborns whose mothers received Brantafors water to newborns whose mothers never lived in Ronneby. Based on military records of AFFF use, we expected that population exposures would begin sometime between 1985 and 1990. The secondary objective of the study was to investigate changes over time in PFAS levels and PFAS mixtures in exposed newborns until 2013, when the contamination at Brantafors was identified.

2. Materials and methods

2.1. Subject selection and sample collection

The study protocol was approved by the Regional Ethical Review Board in Lund (2016/366 and amendment 2021-06184-02).

2.1.1. Subject selection

Study subjects were identified from a previously established register cohort (Ebel et al., 2023). This cohort included women with a residential

address in Blekinge county at least once between 1980 and 2013 and who gave birth between 1985 and 2013. Yearly residential addresses, assessed on December 31st of each year, were retrieved from the Total Population Register (Ludvigsson et al., 2016) and were linked to the annual Ronneby municipal water distribution list to identify each individual's annual water source.

Subject selection is illustrated in Fig. 1. We limited all subjects in our study to primiparous, singleton newborns. For the years 1985–1995, we selected 10 newborns annually whose mothers resided at a Ronneby address served by the Brantafors waterworks on the year of birth and the year prior to delivery. In years with more potential subjects than we required, we prioritized selecting newborns whose mothers had lived at Brantafors-serviced addresses for 3 to 5 consecutive years before delivery in order to make the exposure duration as comparable as possible across subjects. We refer to these subjects as "Brantafors" for the remainder of this article. As a reference group, we also selected 4 newborns per year whose mothers lived in Blekinge county the year of delivery but had never lived in Ronneby. We refer to these subjects as "non-Brantafors" for the remainder of the article.

For the years 1996–2013, we selected 8 newborns per year who met the criteria for the Brantafors group to evaluate how PFAS exposures may have changed over time in this population. We did not include a non-Brantafors reference group for these years.

2.1.2. Newborn sample collection

As part of the national PKU screening program, DBS are collected from all newborns in Sweden as soon as possible after 48 h of age. The site is disinfected and dried and then blood is dripped directly onto the center of the collection spot on the filter paper and allowed to diffuse outwards until the entire spot is filled. This is repeated four times. The samples are air dried and sent the same day to the PKU laboratory for analysis and biobanking (Karolinska Universitetslaboratoriet, 2023).

2.1.3. Sample retrieval from the PKU biobank

The Swedish PKU biobank is located at the Karolinska University Hospital, Region Stockholm. The PKU screening program has been conducted since 1965. It currently tests for 26 rare diseases and includes greater than 99.9 % of births in Sweden each year (Biobank Sverige, 2023). DBS collected as part of the PKU screening program have been stored in the PKU biobank since 1975. Filter papers are stored directly in stacks in a cold room with a temperature of 4 ± 2 °C and a humidity level below 30 %. The PKU screening program has used several similar brands of filter papers over the duration of the study for blood spot collection (1985–2001: Whatman Schleicher & Schuell 2292; 2001–2009: Whatman Schleicher & Schuell 903; 2009 and later: Ahlströmer 226; note that changes were gradually implemented across sites) (L. Sörensen, personal communication, May 24, 2024).

Sample collection was completed in January and February 2023 by a staff member from the PKU biobank. First, two duplicate 3 mm punches were taken from each DBS sample (McGill hole puncher) and packaged individually in a plastic bag. Next, two blank punches (field blanks) were collected from the blank area on the same filter paper to assess potential PFAS contamination in the filter paper and sample contamination from the collection, storage and handling. Each blank was collected in a separate plastic bag. While a blank punch was taken after every sample punch for all study subjects, the step of saving each subject-specific field blank was added after sample collection had already started and the first 59 subjects are missing field blanks. All punches were taken from approximately the same position on each filter paper to maximize comparability. Following collection, samples were pseudonymized and given a sample number. The samples were sent by priority mail to the Division of Occupational and Environmental Medicine, where they were stored at 4 °C until analysis.

2.2. Chemical analysis

Laboratory staff were blinded to the exposure group of each sample. Each DBS was analyzed for 12 PFAS (perfluorobutane sulfonic acid, PFBS; perfluoropentane sulfonic acid, PFPeS; perfluorohexane sulfonic acid, PFHxS; perfluoroheptane sulfonic acid, PFHpS; perfluorooctane sulfonic acid, PFOS; perfluorohexanoic acid, PFHxA; perfluoroheptanoic acid, PFHpA; perfluorooctanoic acid, PFOA; perfluorononanoic acid, PFNA; perfluorodecanoic acid, PFDA; perfluoroundecanoic acid, PFUnDA; and perfluorohexanesulfonamide, PFHxSA) using liquid chromatography-tandem mass spectrometry (LC-MS/MS; QTRAP 7500, AB Sciex, Framingham, MA, USA). Concentrations were determined as the total non-isomer-specific compounds.

The method is a modified version of the method previously described by Norén et al. (2021), and is described in detail in the Supplemental Material. In brief, each 3 mm punch was extracted in 96-well plates using methanol and acetonitrile. The samples were sonicated in an ultrasonic bath and shaken vigorously for 30 min. The duplicate 3 mm punches from each DBS sample and two paper blanks from the same filter paper (field blanks) were analyzed separately but adjacent on the 96-well plates. Two quality control (QC) samples were prepared by spotting whole blood on paper. Two 3 mm punches from each QC

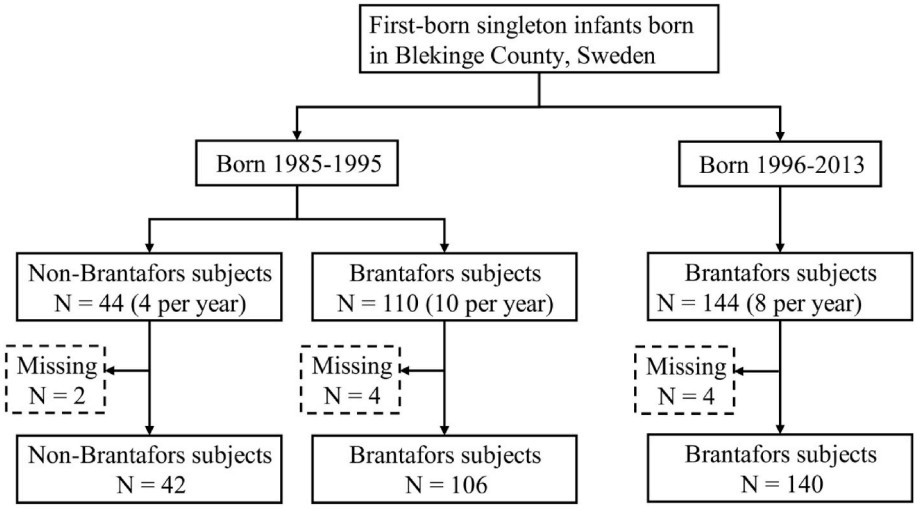

Fig. 1. Subject selection for the study. Brantafors subjects are newborns whose mothers lived at an address receiving Brantafors water in the year of delivery and for at least one consecutive year prior to delivery. Non-Brantafors subjects are infants whose mothers lived in Blekinge county during the year of delivery but had not lived in Ronneby.

sample, a paper blank from each QC paper (method blanks), and two sets of chemical blanks were added to each batch in the 96-well plates. For the quantification of PFAS, it was assumed that each 3 mm punch corresponded to 3.3 μL of blood (Poothong et al., 2019) and concentrations were normalized to ng/mL blood.

The limit of detection (LOD) was defined based on the analysis of the field blanks (n = 501) and was calculated as three times the standard deviation of the concentration corresponding to the peak with the same retention time as each PFAS. The LOD was determined to be 0.02 ng/mL for PFHxSA, 0.05 ng/mL for PFHpS, 0.08 ng/mL for PFBS and PFPeS, 0.17 ng/mL for PFHxS, 0.4 ng/mL for PFOS, 0.5 ng/mL for PFHpA and PFNA, and 0.6 ng/mL for PFOA. Three PFAS (PFDA, PFUnDA, and PFHxA) were analyzed but were not quantifiable because the levels were not discernible.

The precision of the method was assessed by calculating the coefficient of variation (CV) from the duplicate 3 mm punches from each DBS sample, and was between 10 and 20 % (Table S1). The between-run precision, calculated as the CV of the two QC samples, was between 15 and 41 % (Table S2). We also assessed the agreement between the two duplicate punches from each DBS using correlation plots (Fig. S2) and Bland-Altman plots (Fig. S3). Final PFAS concentrations for each subject were calculated as the mean PFAS concentration measured from the duplicate DBS punches.

The mass spectrometry laboratory participates in G-EQUAS interlaboratory exercises for PFAS analysis in serum.

2.3. Statistical analysis

We limited our statistical analyses to PFAS that were above the LOD in at least 70 % of all subjects. Machine-read values were used when concentrations were below the LOD. The following information was available for each sample: the subject's year of birth, the mother's age at delivery, and the number of years that the mother lived continuously (i.e., without interruption) at an address receiving water from the Brantafors waterworks preceding the subject's year of birth. No other personal identifiable data were collected as part of this study.

We first investigated potential selection bias by comparing the characteristics of our study subjects with available DBS samples to the few individuals where samples were unavailable. Next, we summarized PFAS concentrations in the Brantafors and non-Brantafors exposure groups using descriptive statistics. We estimated pairwise correlation of PFAS within each group using Spearman rank-order correlation statistics.

We compared PFAS concentrations measured in newborns born in 1985 from the Brantafors group (N = 10) to newborns born in 1985–1989 in the non-Brantafors reference group (N = 19), after confirming that PFAS concentrations did not change over this five-year period in the non-Brantafors group. Given the difference in the variance of PFAS concentrations between the two exposure groups and the log-normal distribution of PFAS concentrations, we used Welch's unequal variance two-sided t-tests of natural log-transformed concentrations to formally test whether the two population means were equal for each PFAS (Fagerland and Sandvik, 2009). As a sensitivity analysis, we also compared concentrations from newborns in the Brantafors group born in 1985 (N = 10) to concentrations measured in newborns in the non-Brantafors reference group born in 1985 (N = 4).

In Brantafors subjects, we investigated time-trends in PFAS by modeling PFAS concentrations as a non-linear function of year of birth. PFAS concentrations were natural log-transformed to improve model fit and ensure homoskedasticity of the model residuals. The effect of birth year was modeled using penalized thin-plate splines with the degree of smoothing estimated using restricted maximum-likelihood. The models were also adjusted for maternal age at delivery and the number of years that the mother lived at an address receiving Brantafors water as continuous linear terms.

All statistical analyses were conducted in R version 4.4.2 (R Core Team, 2024) using the Tidyverse (Wickham et al., 2019). Models of PFAS concentration over time were fitted using the R package "mgcv" version 1.9.1 (Wood, 2017).

3. Results

We were able to find and collect DBS samples from 288 of the 298 (97 %) requested subjects. Subject characteristics (age and year of delivery) were similar for those with samples compared to those who were missing samples (Table S3). Of the 288 subjects with samples, 42 were in the non-Brantafors reference group and 246 were in the Brantafors exposure group (Fig. 1).

The mean maternal age of the study subjects was 27 years and was similar in Brantafors subjects (26 years) and non-Brantafors subjects (27 years). The mothers of Brantafors subjects received water from the Brantafors waterworks for a median of three consecutive years before the year of the subject's birth (IQR: 2–5, range: 1–22 years) (Fig. S1).

Three of the 12 PFAS (PFDA, PFUnDA and PFHxA) were analyzed but were not quantifiable. Seven PFAS were above the LOD in at least 70 % of all subjects (PFBS, PFPeS, PFHxS, PFHxSA, PFHpS, PFOS and PFOA). For these seven PFAS, the concentration measured in the two duplicate DBS punches for each subject were strongly correlated (Spearman correlation coefficient r_s between 0.87 and 0.99; Fig. S2) and showed high agreement (Fig. S3). All subsequent analyses are limited to PFAS above LOD in at least 70 % of subjects.

3.1. PFAS concentrations by exposure group

In non-Brantafors subjects, PFAS concentrations were highest for PFOS (Median: 4.0 ng/mL, IQR: 3.6–4.3) and PFOA (Median: 1.2; IQR: 0.92–1.4). The mixture was similar across subjects (Fig. S4) and PFAS concentrations were not highly correlated within subject (range of r_s: −0.33 to 0.47, Fig. S5).

In contrast, Brantafors subjects had high concentrations of PFOS (Median: 30 ng/mL; IQR: 18–51) and PFHxS (Median: 20; IQR: 9.5–39). PFAS concentrations were highly correlated (e.g., $r_s = 0.98$ for PFHpS and PFOS and $r_s = 0.97$ for PFHxS and PFOS; Fig. S6). Brantafors subjects with a high total PFAS concentration had a larger relative contribution of PFHxS than subjects with less total PFAS (Fig. S7).

When we compared PFAS concentrations from subjects born 1985–1995 in the Brantafors exposure group to the non-Brantafors group, the median concentration was higher in Brantafors subjects for all PFAS (Table 1). For example, the median PFHxS concentration in the Brantafors group was 94 times higher than the non-Brantafors group, and the median PFHpS concentration was 18 times higher.

Welch's t-tests comparing Brantafors subjects born in 1985 (N = 10) to non-Brantafors subjects born between 1985 and 1989 (N = 19) found significant differences for all PFAS (Fig. 2; p-value <0.001 for all tests). Non-linear tests for time trends in PFAS concentrations measured in non-Brantafors subjects born between 1985 and 1989 confirmed that concentrations did not significantly change by year of birth for all PFAS except PFOA, which showed a marginal increase over the five-year period (Table S4). In our sensitivity analysis, Welch's t-tests comparing Brantafors subjects born in 1985 (N = 10) to non-Brantafors subjects born in 1985 (N = 4) found similar significant differences for all PFAS (Table S5).

3.2. PFAS concentrations in brantafors subjects over time

The results of our non-linear models of PFAS concentrations in Brantafors subjects suggest similar time trends for all PFAS. In general, concentrations began to increase rapidly in the 1990s and then either increased slowly or plateaued in the 2000s (Fig. 3; trends and measured data are shown in Fig. S8). Predicted concentrations reached a maximum in 2007 for all PFAS except PFBS (maximum in 2002) and PFOA (maximum in 2001). PFHxS had the greatest relative increase

Table 1
Measured PFAS concentrations (ng/mL, whole blood) by exposure group summarized as N > LOD (%), Median (IQR) and Range.

PFAS	PFAS Exposure Category		
	Non-Brantafors born 1985–1995 (N = 42)	Brantafors born 1985–1995 (N = 106)	Brantafors born 1996–2013 (N = 140)
PFBS			
N > LOD	2 (4.8)	69 (65)	130 (93)
Median	<LOD (<LOD-<LOD)	0.15 (<LOD-0.21)	0.29 (0.18–0.4)
Range	<LOD-0.17	<LOD-0.52	<LOD-2.3
PFPeS			
N > LOD	1 (2.4)	102 (96)	140 (100)
Median	<LOD (<LOD-<LOD)	0.58 (0.35–0.87)	1.5 (0.96–2.3)
Range	<LOD-0.12	<LOD-2.6	0.14–6
PFHxS			
N > LOD	21 (50)	106 (100)	140 (100)
Median	<LOD (<LOD-0.28)	9.2 (5.7–16)	34 (20–55)
Range	<LOD-0.69	1.1–69	2.5–160
PFHpS			
N > LOD	13 (31)	106 (100)	140 (100)
Median	<LOD (<LOD-0.064)	0.48 (0.32–0.79)	1.4 (0.84–2.3)
Range	<LOD-0.12	0.13–3.2	0.16–8
PFOS			
N > LOD	42 (100)	106 (100)	140 (100)
Median	4 (3.6–4.3)	18 (14–26)	42 (29–64)
Range	1.9–6.8	5.9–77	5.9–170
PFHpA			
N > LOD	0 (0)	18 (17)	49 (35)
Median	<LOD (<LOD-<LOD)	<LOD (<LOD- < LOD)	<LOD (<LOD-0.63)
Range	<LOD- < LOD	<LOD-0.9	<LOD-1.7
PFOA			
N > LOD	38 (90)	106 (100)	140 (100)
Median	1.2 (0.92–1.4)	3.7 (2.6–5.4)	5.6 (3.6–7.5)
Range	<LOD-2.6	1.3–12	1.1–18
PFNA			
N > LOD	0 (0)	11 (10)	30 (21)
Median	<LOD (<LOD-<LOD)	<LOD (<LOD-<LOD)	<LOD (<LOD-<LOD)
Range	<LOD- < LOD	<LOD-0.77	<LOD-1.2
PFHxSA			
N > LOD	3 (7.1)	73 (69)	132 (94)
Median	<LOD (<LOD-<LOD)	0.041 (<LOD-0.059)	0.075 (0.049–0.15)
Range	<LOD-0.051	<LOD-0.15	<LOD-0.74

from 1985 to its peak in 2007, increasing by an estimated 480 % (95 % CI: 310, 720). PFHpS had the second greatest relative increase from 1985 to 2007, increasing by an estimated 340 % (95 % CI: 210, 530). Concentrations of most PFAS were elevated at the end of the study in 2013 compared to concentrations in 1985. Estimated changes in PFAS concentrations over time are summarized in Table 2. The number of years a mother lived continuously at a Brantafors-supplied address before delivery was significantly associated with all PFAS except PFBS and PFHxSA, while maternal age was not significantly associated with any PFAS (Table S6).

The PFAS mixture in Brantafors subjects changed over the duration of the study period (Fig. S9). The relative contribution of PFHxS to the total PFAS concentration increased from a median of 24 % in 1985 (IQR: 22, 27) to 38 % in 2013 (IQR: 35, 44). Meanwhile, although the absolute concentration of PFOS generally increased over the study period, the relative contribution of PFOS to the total PFAS mixture decreased from a median of 58 % (IQR: 55, 60) to 53 % (IQR: 49, 55). The relative contribution of PFOA also decreased from a median of 12 % (IQR: 11, 16) to 5.5 % (IQR: 4.1, 6.8).

4. Discussion

This study measured PFAS concentrations in DBS from 288 firstborn singleton newborns born between 1985 and 2013 in Blekinge County, Sweden. Brantafors subjects, whose mothers lived at an address that received water from the Brantafors waterworks for at least one continuous year before the year of delivery, generally had higher PFAS concentrations than non-Brantafors subjects, whose mothers never lived at an address receiving Brantafors water. When we compared Brantafors subjects born in 1985 to non-Brantafors subjects born 1985–1989, the mean difference in PFAS concentrations was statistically significant for all PFAS. These results suggest that population-wide exposures to AFFF-associated PFAS via the drinking water began before 1985. The strong correlations in PFAS concentrations (Fig. S6) and the similar time trends in AFFF-associated PFAS (Fig. 3) over the study duration also support the importance of AFFF as the primary exposure source in the Brantafors population.

According to the Swedish Armed Forces, AFFF use at Ronneby began in the mid-1980s (Xu et al., 2021), but our findings indicate a potential earlier introduction. This earlier timing is possible, given that AFFF formulations were put on the U.S. market in the 1960s (Cousins et al., 2016) and that there is documented use of AFFF at Swedish military airports in the 1970s (Filipovic et al., 2015). Although the exact time required for PFAS to migrate via surface water and groundwater from the airport to the groundwater wells for the Brantafors waterworks is unknown (Mussabek et al., 2023), many PFAS are highly mobile in water (ECHA, 2022).

Our study found similar time trends for most PFAS with a rapid increase in concentration during the 1990s and a slower increase or plateau in the early 2000s. This trend may be determined in part by changes in training protocols and/or the frequency of large-scale training events at the military airport, which would impact both the quantity of AFFF released into the environment and the frequency of release events. Historical training protocols from the site are not publicly available. However, it is known that firefighting training of conscripts was conducted by the military up to 2003, after which firefighting responsibilities for the airport were transferred over to permanently-employed civil firefighters (Christer Lindgren, 2022;

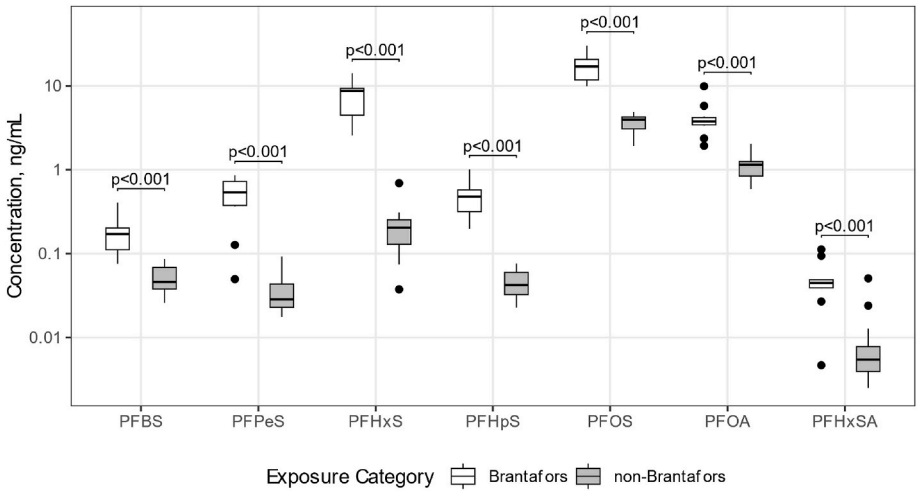

Fig. 2. Welch's t-tests comparing natural-log PFAS concentrations in Brantafors subjects born in 1985 (N = 10) to non-Brantafors subjects born in 1985–1989 (N = 19). Concentrations on the y-axis are shown using a natural-log scale.

Sundén, Göran, 2001). This shift likely reduced the amount of training conducted at the site, which would have also reduced AFFF usage. All AFFF applications were stopped in 2014 after the water contamination was discovered (Mussabek et al., 2023).

The formulation of AFFF used at the Ronneby airport may also have changed over the study period, both due to general changes in purchasing and potentially due to restrictions on the use of PFOS in AFFF. PFOS was first restricted in the EU in 2006 under Directive 2006/122/EC (European ParliamentCouncil of the European Union, 2006), which specified that PFOS-containing AFFF that was already on the market could be only used until June 2011. In 2009, PFOS and its salts were added to Annex B (Restriction) of the Stockholm Convention (UN Environment Programme, 2009), which was implemented in the EU as part of the EU POP Regulation (Regulation (EC) No 850/2004) with the same exception for AFFF as in the original directive ("Fire-fighting foams that were placed on the market before December 27, 2006 may be used until June 27, 2011") (European Commission, 2010). In a survey of firefighting foam use in Sweden in 2014, all major producers for the Swedish market reported that their current products did not contain PFOS or its precursors (KEMI, 2014). Any specific effects of regulations on AFFF formulations used at the Ronneby miliary airport are unknown.

Several additional factors may have also contributed to the PFAS concentrations in the water that was ultimately distributed by the Brantafors waterworks. These include the speed of environmental transport to the aquifer, which can vary by PFAS (Mussabek et al., 2023), and the accumulation of PFAS in the aquifer over time. The Brantafors waterworks also used several different groundwater wells to extract water from the aquifer source over the study period, and a recent study found that PFAS concentrations varied significantly across the different wells (Mussabek et al., 2023). This suggests that the relative contribution of groundwater from different wells, which varied based on well-specific water flow, also may have impacted PFAS concentrations in the provided drinking water.

The PFAS concentrations in DBS measured in this study are influenced by the biological elimination half-life of each PFAS (i.e., the time required for the PFAS concentrations in serum or plasma to decrease by half from its starting concentration). PFAS with longer elimination half-lives have lower excretion rates and are more likely to bioaccumulate with continuous exposure and persist following a decrease in exposure (Rosato et al., 2023). Although previous studies of PFAS half-lives have found high interstudy and interindividual heterogeneity, long-chain PFAS generally have longer half-lives than short-chain PFAS. Of the PFAS included in this study, PFBS and PFPeS have the shortest half-lives, while PFOS and PFHxS have the longest half-life. Previous studies have reported an estimated half-life ranging from 26 to 44 days for PFBS (Olsen et al., 2009; Xu et al., 2020a), 0.63–0.94 years for PFPeS (Y. Li et al., 2022b; Xu et al., 2020a), 1.0–6.5 years for PFOS, including both branched and linear isomers (Y. Li et al., 2022a; Nilsson et al., 2022; Xu et al., 2020a, p. 20), and 2.9–7.8 years for PFHxS (Y. Li et al., 2022b; Nilsson et al., 2022; Xu et al., 2020a). PFAS-specific half-lives impact the time trends observed in our studies, as PFAS with longer half-lives may have accumulated over time in the general Ronneby population. For example, PFHxS, which has a long half-life, also had the greatest increase over the study duration in Brantafors subjects. In contrast, PFBS, which has a short half-life, peaked earlier than the other PFAS included in this study. Because of its shorter half-life, this earlier maximum in PFBS may reflect more accurately the timing of maximum PFBS contamination in the drinking water, compared to the estimated maximum of long-chain PFAS in DBS. However, without more information on the use of AFFF and its formulation at the airport, we cannot disentangle the effect of bioaccumulation from other potential contributing factors.

PFAS concentrations in newborn DBS are also determined in part by the transfer efficiency of different PFAS from mother to newborn across the placenta ("transplacental transfer efficiency"), which varies by PFAS compound and across individuals. Previous studies have found that perfluorocarboxylic acids (PFCAs) generally transfer across the placenta more efficiently than perfluorosulfonic acids (PFSAs). For example, a meta-analysis estimated a weighted transplacental transfer efficiency of 0.8 ± 0.25 for PFOA ($N_{studies} = 17$) compared to 0.44 ± 0.24 for PFOS ($N_{studies} = 19$) (Appel et al., 2022). Differences in placental transfer by PFAS compound would not have impacted the PFAS-specific time trends identified in this study. However, they may impact the PFAS mixture observed in newborn DBS, as PFAS with a higher transfer efficiency (e.g., PFOA) may represent a larger share of the total PFAS in newborn samples relative to the mixture in maternal blood. While PFAS concentrations in newborn DBS are an accurate reflection of prenatal PFAS exposures, any backwards estimation of maternal PFAS exposures would need to consider these differences in transplacental transfer efficiency.

This is the first study in Ronneby to quantify PFHxSA, a perfluoroalkane sulfonamide substance and known ingredient in legacy AFFF (Annunziato et al., 2020; D'Agostino and Mabury, 2017; Houtz et al., 2013; Xu et al., 2021). It was detectable at very low concentrations in Brantafors subjects (median: 0.06 ng/mL) but was below the LOD in most non-Brantafors subjects. This is also one of the first studies in Ronneby to quantify PFBS, a short-chain PFSA that was elevated in water samples from the Brantafors waterworks in 2013 (130 ng/L compared to <0.3 ng/L at a nearby waterworks). While a small

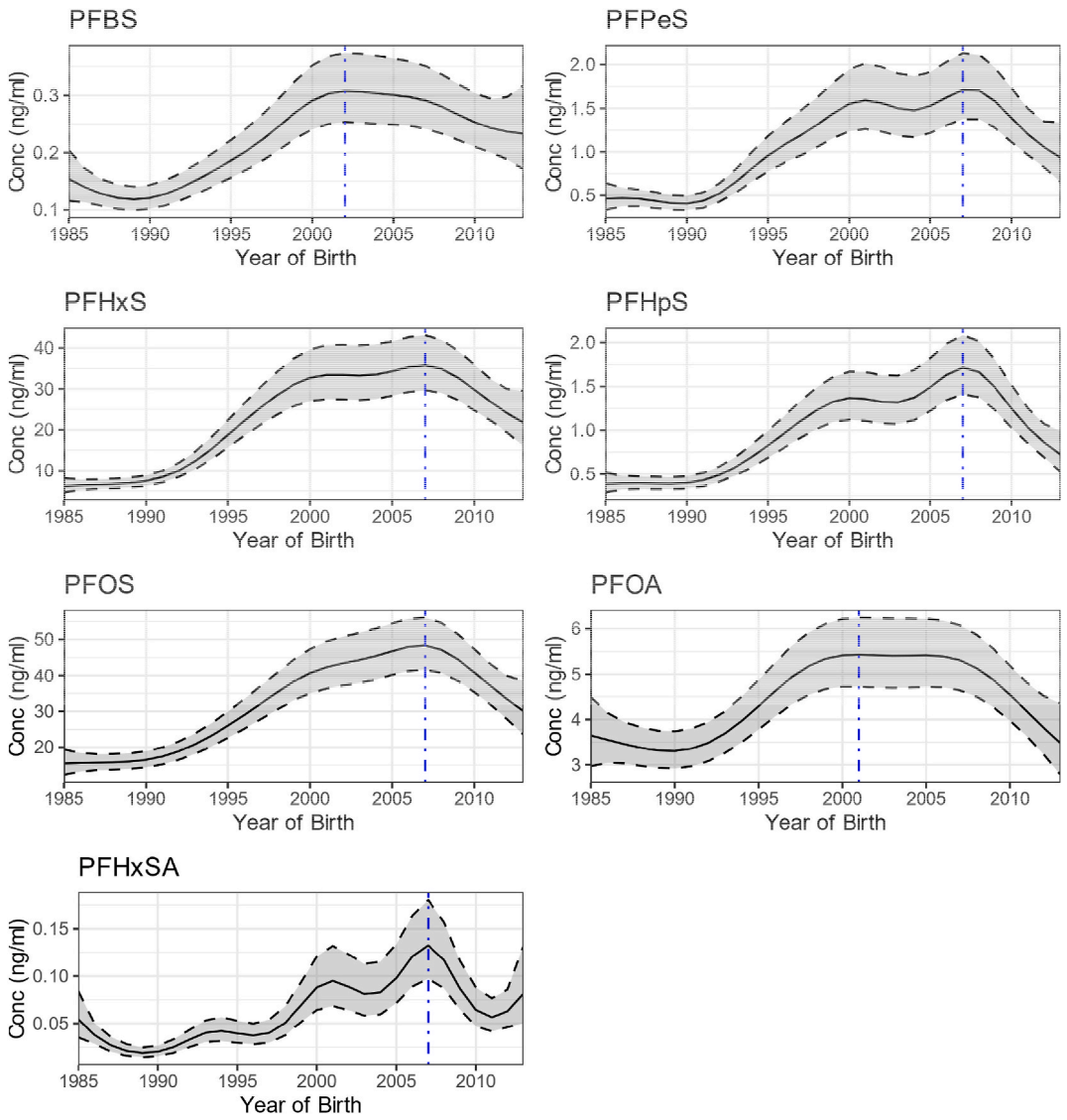

Fig. 3. Expected PFAS concentrations (ng/mL, whole blood) as a non-linear function of year of birth for Brantafors study subjects (N = 246). Predicted values are estimated at the median value of maternal age (26 years) and the number of years receiving contaminated water before delivery (3 years). The vertical dashed blue line indicates the year with the maximum modeled PFAS concentration. Underlying measured data is included in Fig. S8. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Expected percent change in the PFAS concentrations from 1985 to the year of estimated maximum concentration ($Year_{max}$) and the end of the study (2013) in Brantafors subjects (N = 246).

PFAS	$Year_{max}$	Estimated Percent Change (95 % CI)	
		1985 to $Year_{max}$	1985 to 2013
PFBS	2002	100 (42, 180)	52 (−0.53, 130)
PFPeS	2007	270 (150, 450)	100 (24, 230)
PFHxS	2007	480 (310, 720)	250 (130, 440)
PFHpS	2007	340 (210, 530)	87 (22, 190)
PFOS	2007	210 (140, 310)	95 (39, 170)
PFOA	2001	49 (16, 90)	−4.7 (−30, 29)
PFHxSA	2007	140 (42, 320)	49 (−22, 190)

biomonitoring study conducted approximately a month after closure of the Brantafors waterworks found elevated levels of PFBS in children living in the Brantafors waterworks area (N = 20) (Jönsson et al., 2016), it was undetectable in the main biomonitoring study that was initiated six months after the drinking water exposure had ended (Y. Li et al., 2022a; Xu et al., 2021), reflecting its short half-life (Xu et al., 2020a). In this current study, PFBS was detectable in almost all Brantafors subjects (median: 0.2 ng/mL) but was below the LOD in almost all non-Brantafors subjects. Given its short half-life, the detectable levels of PFBS in Brantafors subjects indicate that there was an ongoing PFBS exposure in this population for the duration of the study.

Several analytical and methodological considerations must be made when analyzing PFAS in DBS. First, the method must account for potential sample contamination, both directly from the filter and indirectly from sample collection and handling (e.g., potential cross-contamination during storage in the PKU biobank, or contamination during transport from storage in the plastic bags). In this study we estimated background contamination by measuring PFAS in chemical blanks, method blanks and field blanks. No contamination was observed in field blanks collected from each sample filter paper, but there was a variable noise level. The chemical blank samples show similar results (Supplemental Material). It is possible that, because the DBS samples were stored in stacks at the PKU biobank, some blood may have transferred from one sample to the sample lying directly on top of it. However, given that we did not detect PFAS in the field blanks, this suggests

that the DBS were not flaking or causing contamination outside of the sample spot. Second, our chemical analyses assumed that a 3 mm punch was equal to known volume of whole blood (3.3 μL) based on results from a previous study (Poothong et al., 2019). This study estimated the median volume of blood in a 3 mm diameter DBS subsample from 708 samples with a known blood volume. The authors found strong agreement in blood volume across all samples and concluded that a hematocrit adjustment was not necessary for DBS analysis. One limitation of this decision in our study is that the filter papers used in the PKU biobank are not the same as those used in Poothong et al., which may induce some non-differential error. The type of filter paper used at the PKU biobank also changed twice during the study period, so this error may also vary over time. However, the manufacturer remained the same for most of the study period (1985–2010) and the filter paper types were similar, so we do not expect these changes to have a major impact on our results. The volume of blood on each punch may also vary by the location that the punch is taken (i.e., in the center of the DBS sample vs. the edge of the sample), which we accounted for by taking our DBS punches in approximately the same location. The concentrations measured in the duplicate punches from each DBS sample generally showed strong agreement, indicating that the location of the DBS punches did not impact the repeatability of our measurements. Another possible limitation is that the PFAS-specific LODs in our study were calculated from the 3 mm field blank punches, and do not account for matrix effects from the dried blood spots. This may add additional uncertainty to our measured PFAS concentrations at values close to the LOD. The matrix may also impact the overall PFAS concentrations measured in our samples. A previous study of paired DBS and whole blood found that measured concentrations were generally lower in DBS compared to whole blood but that the two matrices had strong correlation and agreement, indicating that PFAS measurements from DBS are a robust and reliable indicator of exposure (Poothong et al., 2019). Future studies of paired DBS and PFAS measurements collected during pregnancy or at birth could provide additional information on the comparability of PFAS measurements in different sample types and its use for assessing prenatal exposure for epidemiological studies.

In addition to these methodological considerations, this study has several other limitations and strengths. Our existing registry cohort only included births from 1985 and onward and therefore we could not measure PFAS in DBS samples from any children born before 1985. This prevented us from conclusively identifying the first year of population-wide PFAS exposure in Ronneby. Future research should analyze PFAS concentrations in earlier samples so that the start of exposure can be identified and used to inform future epidemiology studies. Our study was also limited to first-born infants. This choice was made to minimize the factors impacting differences in PFAS exposure levels between the two exposure groups. However, the measured levels from this study cannot be generalized to later-born (i.e., not first-born) infants. We also did not measure PFAS concentrations in infants whose mothers lived in Ronneby but did not receive drinking water from the Brantafors waterworks. A previous biomonitoring study indicated that exposures in adults from this population had higher PFAS exposures than adults who did not live in Ronneby, but lower concentrations than adults receiving their drinking water from Brantafors (Xu et al., 2021). Future research could address this limitation by measuring PFAS concentrations in DBS from a broader sample of the infant population.

An important strength of this study is that we have demonstrated that we can measure PFAS in biobanked DBS and use these measurements to model the time-course of serum concentrations in an exposed population over many years, a major advancement in reconstructing exposure estimates for epidemiologic research on PFAS. These results will likely be of high interest to the Ronneby community, and will be used to improve future registry-based epidemiologic studies in this population. This method could potentially be used for historical exposure assessment in other communities located near known or suspected point-sources of PAS contamination.

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CRediT authorship contribution statement

Annelise J. Blomberg: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Christian Lindh:** Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Investigation. **Daniela Pineda:** Writing – original draft, Validation, Methodology, Investigation. **Tony Fletcher:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Kristina Jakobsson:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Christel Nielsen:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

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 data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2025.121397.

Data availability

The data that has been used is confidential.

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