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Temporal trends of poly- and perfluoroalkyl substances (PFASs) in serum from children at 4, 8, and 12 years of age, in Uppsala 2008-2019

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Sammanfattning
Projektet undersökte halterna av 38 poly- och perfluorerade alkylsubstanser (PFAS) i blodserum i 4-, 8- och 12-åriga barn från Uppsala provtagna under perioden 2016-2019. PFAS är långlivade kemikalier som har stor användning i konsument- och kemikalieprodukter. Barnens mammor deltog, vid barnens födelse, i en undersökning av gravida och ammande kvinnors exponering för miljöföroreningar som genomförs av Livsmedelsverket, med finansiering av Naturvårdsverkets Hälsorelaterade miljöövervakning. Barnen rekryterades och provtogs i en uppföljningsstudie 4, 8 eller 12 år efter födseln. Uppföljningen av barnen har godkänts av den regionala etikprövningsnämnden i Uppsala och barnens mammor har gett skriftligt samtycke gällande barnens deltagande. Resultaten visar att de flesta analyserade PFAS, 27 av 38 ämnen, inte hade mätbara halter i serum. Bland de detekterbara PFAS hade PFHxS, PFOS och PFOA de högsta halterna följt av de långkedjiga karboxylsyrorna PFNA, PFDA och PFUnDA. För att studera tidstrender av PFAS slogs resultaten ihop med redan insamlad data från barn i samma studie från 2008-2015. Resultaten visar nedåtgående tidstrender för fem PFAS-ämnen under perioden 2008-2019. Medelhalterna minskade med 7 % per år för PFHpA, 6 % för PFOA, 3 % för PFNA, 4 % för PFDA och 6 % för PFOS. För PFUnDA och PFHxS fanns ingen signifikant trend.

Temporal trends of poly- and perfluoroalkyl substances (PFASs) in serum from children at 4, 8, and 12 years of age, in Uppsala 2008-2019

Background

In recent years, poly- and perfluorinated alkyl substances (PFASs) have attracted much attention as emerging environmental health risks to wildlife and humans around the world. PFASs are highly fluorinated organic compounds that have been manufactured for more than 60 years and are used in industrial processes (e.g. production of fluoropolymers), as water and stain proofing agents, and in lubricants, paints and fire-fighting foams (Kissa 2001; Prevedouros et al. 2006). Over 4000 PFASs are known to exist on the global market (OECD 2018). Some PFAS, such as perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonic acids (PFSAs) are persistent in the environment and are detected worldwide in humans and wildlife (Giesy and Kannan 2001; Kissa 2001; Kannan et al. 2004; Houde et al. 2006).

Since the start of the 21st century measures have been taken to decrease/stop production and use of the most widely distributed PFASs, perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). Human exposure to PFOS and PFOA have subsequently declined in Sweden, as shown by decreasing serum levels of PFOS and PFOA among first-time mothers from Uppsala from 1996 to 2017, and in their first born children (2008-2015) in the POPUP study (Persistent Organic Pollutants in Uppsala Primiparas) (Miaz et al 2020, Gyllenhammar et al 2016). A temporal increase in levels of perfluorohexane sulfonic acid (PFHxS) as well as increases of longer-chained PFCAs perfluorononanoic acids (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA) and perfluoorotridecanoic acid (PFTrDA) was observed in previous studies from the POPUP mothers (Glynn et al. 2012; Gebbink et al. 2015). A new study of PFAS temporal trends up to year 2017 observed increasing trends in the beginning of the study for PFHxS and long-chained PFCAs and change point around 2010-11 and 2004-2008 respectively, with decreasing trends after that (Miaz et al 2020).

In the present report we updated PFAS data from children in the POPUP study for the period 2008-2019, expanding on the previous temporal trend study reported in 2016 (Gyllenhammar et al. 2016).

Table 1. Personal characteristics of the participating children 2016-2019.

Age category	Variable		n	Mean	±SD	Median	Range
4	Age (year)		30	3.9	0.3	3.9	3.4 – 4.6
	Weight (kg)		28	17	2	17	13 – 22
	Length (cm)		28	104	5	104	89 – 113
	Variable		**n**	**%**			
	Sex	Female	15	50			
		Male	15	50			
Age category	**Variable**		**n**	**Mean**	**±SD**	**Median**	**Range**
8	Age (year)		41	7.9	0.4	7.4	7.36 – 8.8
	Weight (kg)		38	28	4	25	22 – 39
	Length (cm)		39	131	5	132	120 – 140
	Variable		**n**	**%**			
	Sex	Female	23	56			
		Male	18	44			
Age category	**Variable**		**n**	**Mean**	**±SD**	**Median**	**Range**
12	Age (year)		25	12.0	0.4	12.0	11.5 – 12.8
	Weight (kg)		20	42	6	40	31 – 55
	Length (cm)		20	154	4	155	142 – 160
	Variable		**n**	**%**			
	Sex	Female	8	32			
		Male	17	68			

Material and methods

Recruitment and sampling

First-time mothers were randomly recruited during pregnancy (1996-99) or shortly after pregnancy (2000-2019). In 2008 a follow-up study on the mothers and their first-born children was initiated. A self-administered questionnaire including questions about anthropometry (Table 1) was answered by the mothers when the child was aged 4, 8, and 12 years. A nurse took blood samples from the children at home (age 4, N=30, age 8, N=41, age 12, N=25) using 9 ml Vacutainer® or Vacuette® serum tubes and serum was stored at -20°C. The study was approved by the local ethics committee in Uppsala, Sweden, and the participating women gave informed consent prior to the inclusion of the children in the study.

PFAS analyses

PFASs (Table 2) were analyzed in 30 samples from 4-year-old children, 41 samples from 8-year-old children and 25 samples from 12-year-old children as described in Gyllenhammar et al. (2015). In short, 0.5 g serum was spiked with internal standards and extracted with acetonitrile in an ultrasonicating bath. The concentrated extract underwent dispersive clean-up with graphitized carbon. Aqueous ammonium acetate and volumetric standards were added before instrument analysis on an Acquity ultra performance liquid chromatography system (UPLC) coupled to a Xevo TQ-S tandem mass spectrometer (MS/MS (both Water Corp., Milford, MA, U.S.) operated in negative electrospray ionization, multiple reaction monitoring mode. The instrumental method including optimized parameters is described in detail in Miaz et al. (2020). Quantification was performed by isotope dilution using a 5-point calibration curve (linear, 1/x weighting) which was run before and after samples. For most targets, exactly matched isotopically labelled internal standards were available. For PFBS, PFTriDA, PFTeDA, and PFPeDA, a structurally similar internal standard was used (Table 2). For PFHxS and PFOS, branched and linear isomers were quantified separately. The limits of quantification (LOQ) were 0.08 ng/g serum for PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTriDA, and PFHxS. The LOQ were 0.14 ng/g for PFOS, 0.29 ng/g for PFTeDA, and PFPeDA and 0.25 ng/g for PFBS.

Table 2. PFASs included in the study.

Compound	Abbreviation	IS
Perfluorobutanoate	PFBA	M4PFBA
Perfluoropentanoate	PFPeA	M2PFDoDA
Perfluorohexanoate	PFHxA	M4PFHpA
Perfluoroheptanoate	PFHpA	M4PFHpA
Perfluorooctanoate linear isomer	PFOA	M4PFOA
Perlfuorooctanoate branched isomers	PFOA-br	M4PFOA
Perfluorononanoate	PFNA	M5PFNA
Perfluorodecanoate	PFDA	M2PFDA
Perfluoroundecanoate	PFUnDA	M2PFUnDA
Perfluorododecanoate	PFDoDA	M2PFDoDA
Perfluorotridecanoate	PFTriDA	M2PFDoDA
Perfluorotetradecanoate	PFTeDA	M2PFDoDA
Perfluoropentadecanoate	PFPeDA	M2PFDoDA
Perfluorohexadecanoate	PFHxDA	M2PFDoDA
Perfluorooctadecanoate	PFOcDA	M2PFDoDA
Perfluorobutanesulfonate	PFBS	18O2-PFHxS
Perfluoropentanesulfonate	PFPeS	18O2-PFHxS
Perfluorohexanesulfonate lin.	PFHxS	18O2-PFHxS
Perfluorohexanesulfonate br.	PFHxS-br	18O2-PFHxS
Perfluoroheptanesulfonate	PFHpS	M4PFOS
Perfluorooctanesulfonate lin.	PFOS	M4PFOS
Perfluorooctanesulfonate br.	PFOS-br	M4PFOS
Perfluorononanesulfonate	PFNS	M4PFOS
Perfluorodecanesulfonate lin.	PFDS	M4PFOS
Perfluorodecanesulfonate br.	PFDS-br	M4PFOS
Perfluoroundecanesulfonate	PFUnDS	M4PFOS
Sodium Dodecafluoro-3H-4,8,-dioxanonanoate	NaDONA	M4PFOA
Potassium 9-chlorohexadecafluoro-3-oxanonanoe-1-sulfonate	9Cl-PF3ONS	M2PFDA
Potassium 11-chloroeicosafluoro-3-oxaundecane-1-sulfonate	11Cl-PF3OUdS	M2PFDA
3:3 Fluorotelomer carboxylic acid	3:3 FTA (FPrPA)	M2PFHxA
5:3 Fluorotelomer carboxylic acid	5:3 FTA (FPePA)	M4PFOA
7:3 Fluorotelomer carboxylic acid	7:3 FTA (FHpPA)	M2PFDA
4:2 Fluorotelomer sulfonate	4:2 FTS	M2 6:2 FTS
6:2 Fluorotelomer sulfonate	6:2 FTS	M2 6:2 FTS
8:2 Fluorotelomer sulfonate	8:2 FTS	M2 6:2 FTS
Perfluorooctane sulfonamide lin,	FOSA	M8FOSA
Perfluorooctane sulfonamide br.	FOSA-br	M8FOSA
Perfluorooctane sulfonamidoacetate lin.	FOSAA	d3-MeFOSAA
Perfluorooctane sulfonamidoacetate br.	FOSAA-br	d3-MeFOSAA
Methyl perfluorooctane sulfonamidoacetate lin.	MeFOSAA	d3-MeFOSAA
Methyl perfluorooctane sulfonamidoacetate br.	MeFOSAA-br	d3-MeFOSAA
Ethyl perfluorooctane sulfonamidoacetate lin.	EtFOSAA	d5-EtFOSAA
Ethyl perfluorooctane sulfonamidoacetate br.	EtFOSAA-br	d5-EtFOSAA
6:2 Fluorotelomer phosphate diester	6:2 diPAP	M4 6:2/6:2 diPAP
6:2/8:2 Fluorotelomer phosphate diester	6:2/8:2 diPAP	M4 8:2/8:2 diPAP
8:2 Fluorotelomer phosphate diester	8:2 diPAP	M4 8:2/8:2 diPAP

A procedural blank and QC serum sample was included with every batch of samples. For targets observable in method blanks, MQLs were based on 3× standard deviation of the blanks. For those with no observable blank contamination, MQLs were calculated based on a signal to noise ratio of 3 using the lowest calibration point. Further method validation parameters are provided in Glynn et al. (2012).

Calculations and statistical analyses

When PFAS concentrations were below the LOQ, LOQ/√2 was used as an estimated value in the statistical analyses. Multiple linear regressions (STATA version 14.2, StatCorp. College Station, Texas, USA) were used to analyze associations between PFAS concentrations in child serum and sampling year for the whole period, 2008-2019. Logarithmically-transformed PFAS concentrations were used, since the distribution of data closely followed a log-normal distribution. Child age, weight and height at sampling were included as covariates in the analyses. Trends in the whole cohort were analyzed (N=330) and also for the three age groups 4, 8 and 12 years separately (N= 85 for 4-year-olds, N= 91 for 8-year-olds, and N=133 for 12-year-olds).

As a consequence of the logarithmic transformation, the associations between sampling year and PFAS concentrations are presented as percent change of concentrations per year, and not as change in absolute levels.

Table 3. Concentrations of perfluoroalkyl carboxylic acids (PFCAs) and MeFOSAA (ng/g) in serum samples from children at 4, 8, and 12 years of age from Uppsala, Sweden 2016-2019.

Substance	Age	n	<LOQ (%)	Mean	±SD	Median	Range
PFHpA	4	30	80				<LOQ – 0.17
	8	41	85				<LOQ – 0.22
	12	25	92				<LOQ – 0.13
lin-PFOA	4	30	0	2.09	0.7	2.06	1.08 – 3.85
	8	41	0	1.73	0.59	1.56	<LOQ – 3.35
	12	25	0	1.18	0.39	1.06	0.60-2.07
PFNA	4	30	0	0.58	0.3	0.48	0.27 – 1.2
	8	41	0	0.60	0.25	0.53	0.29 – 1.25
	12	25	4	0.50	0.27	0.43	<LOQ – 1.46
PFDA	4	30	3	0.22	0.1	0.20	<LOQ – 0.53
	8	41	2	0.25	0.10	0.23	<LOQ – 0.48
	12	25	8	0.17	0.08	0.16	<LOQ – 0.41
PFUnDA	4	30	17	0.18	0.1	0.17	<LOQ – 0.40
	8	41	2	0.22	0.11	0.21	<LOQ – 0.52
	12	25	24	0.15	0.10	0.12	<LOQ – 0.49
PFDoDA	4	30	100				<LOQ
	8	41	100				<LOQ
	12	25	96				<LOQ – 0.10
lin-MeFOSAA	4	30	97				<LOQ-0.11
	8	41	98				<LOQ- 0.11
	12	25	84				<LOQ-1.46
br-MeFOSAA	4	30	100				<LOQ
	8	41	100				<LOQ
	12	25	96				<LOQ-0.18

Results and discussion

PFAS levels in children

Among perfluoroalkyl carboxylic acids (PFCAs) the median level was highest for PFOA (1.1-2.1 ng/g serum) and declined in the order PFOA>PFNA>PFDA~PFUnDA (Table 3). For PFHpA, PFDoDA and MeFOSAA most children had levels below LOQ. All children had levels above LOQ for the sulfonic acids, PFOS and PFHxS with median levels ranging from 1.2 to 3.7 ng/g (Table 4). For the first time PFPeS and PFHpS was analysed in POPUP children the results showed that most children had levels below LOQ (Table 4). In all children, 4, 8 and 12 years old, the levels of PFBA, PFPeA, PFHxA, br-PFOA, PFTriDA, PFTeDA, PFPeDA, PFHxDA, PFOcDA, PFBS, PFNS, lin-PFDS, br-PFDS, PFUnDS, lin-

FOSA, br-FOSA, lin-FOSAA, br-FOSAA, lin-Et-FOSAA, br-Et-FOSAA, 9Cl-PF3ONS, 11Cl-PF3OUdS, NaDONA, FPrPA, FPePA, FHpPA, 4:2 FTS, 6:2 FTS, 8:2 FTS, 6:2 diPAP, 8:2 diPAP and 6:2/8:2 diPAP were below LOQ.

Table 4. Concentrations of perfluoroalkyl sulfonic acids (PFSA) (ng/g) in serum samples from children at 4, 8, and 12 years of age from Uppsala, Sweden 2016-2019.

Substance	Age	n	<LOQ (%)	Mean	±SD	Median	Range
PFPeS	4	30	100				<LOQ
	8	41	98				<LOQ – 0.29
	12	25	96				<LOQ – 0.23
lin-PFHxS	4	30	0	3.49	3.1	2.75	0.89 – 15.43
	8	41	0	4.41	4.29	2.45	0.64-17.79
	12	25	0	3.24	3.68	1.17	0.30-14.03
br-PFHxS	4	30	60				<LOQ-0.87
	8	41	59				<LOQ-0.59
	12	25	64				<LOQ-0.55
PFHxS[a]	4	30		3.63	3.3	2.80	0.94-16.30
	8	41		4.56	4.45	2.50	0.70-18.38
	12	25		3.38	3.82	1.23	0.35-14.58
PFHpS	4	30	63				<LOQ-0.47
	8	41	78				<LOQ-0.35
	12	25	84				<LOQ-0.22
lin-PFOS	4	30	0	2.44	1.8	1.83	0.73-7.46
	8	41	0	2.83	1.26	2.47	1.12-6.86
	12	25	0	2.26	1.28	1.85	0.83-6.04
br-PFOS	4	30	0	1.11	0.6	0.94	0.41-2.81
	8	41	0	1.25	0.49	1.20	0.54-2.55
	12	25	0	1.02	0.65	0.81	0.41-3.64
PFOS[a]	4	30		3.54	2.4	2.77	1.14-10.27
	8	41		4.08	1.75	3.66	1.66-9.42
	12	25		3.28	1.93	2.66	1.24-9.68

[a]Sum of linear and branched isomers

Temporal trends

Declining temporal trends of PFHpA, PFOA, PFNA, PFDA, and PFOS were found in POPUP children during 2008-2019 (Table 5). Similar trends were observed among individual PFASs when data from the whole cohort and different age groups were compared, except for PFNA and PFOS where the trends were not significant for 4-year-old children (Table 5). PFHxS and PFUnDA did not show any statistically significant trends during the time period. In the previous study of temporal trends, 2008-2015, similar decreasing trends was shown for

PFHpA, PFOA, PFDA, and PFOS (Gyllenhammar et al 2016). PFNA did not have a significant trend 2008-2015 but when including the new data from 2016-2019, a declining trend was observed. Both PFUnDA and PFHxS had significant increasing trends 2008-2015 (Gyllenhammar et al 2016) but in the present study, no trends were found. For PFUnDA the LOQ was lower in the present study, which might affect the results (Fig. 1). For PFHxS it is known that the previous PFAS contamination of the drinking water in Uppsala has contributed to elevated serum levels in mothers and children in the POPUP study (Gyllenhammar et al 2015, Gyllenhammar et al 2016). As the contamination was mitigated in 2012 it is expected that the serum levels will decrease after that. For PFBS all levels were below LOQ in the present study and the LOQ was also higher compared to the previous study period 2008-2015 (Fig. 1) it was therefore not possible to perform a trend analysis.

The significant declining temporal trends observed for PFHpA, PFOA, PFNA, PFDA, and PFOS suggests that there has been a decrease in exposure of Uppsala children to these PFASs during this period.

Table 5. Percent change in concentrations of PFAS per year in serum from children in Uppsala 2008-2019, at 4, 8, and 12 years of age. Adjusted for exact age, weight, and length.

Compound	**Age**	**n**	**Change (%)** Mean (SE)	**R^2**	**P**
PFHpA	**4**	**85**	**- 10.4 (2.4)**	**21**	**<0.001**
	8	**91**	**- 4.6 (2.1)**	**19**	**0.027**
	12	**133**	**- 4.3 (1.3)**	**14**	**0.001**
	All	**309**	**- 6.7 (1.0)**	**21**	**<0.001**
PFOA	**4**	**85**	**- 4.3 (1.4)**	**20**	**0.003**
	8	**91**	**- 5.1 (1.4)**	**29**	**<0.001**
	12	**133**	**- 7.4 (1.0)**	**36**	**<0.001**
	All	**309**	**- 6.1 (0.7)**	**29**	**<0.001**
PFNA	4	85	-2.1 (2.0)	12	0.287
	8	**91**	**- 3.8 (1.6)**	**9**	**0.016**
	12	**133**	**- 3.5 (1.6)**	**5**	**0.025**
	All	**309**	**- 3.2 (0.9)**	**4**	**<0.001**
PFDA	**4**	**85**	**- 3.4 (1.6)**	**20**	**0.031**
	8	**91**	**- 5.1 (1.6)**	**14**	**0.001**
	12	**133**	**- 4.5 (1.3)**	**9**	**<0.001**
	All	**309**	**- 4.2 (0.8)**	**9**	**<0.001**
PFUnDA	4	85	- 0.3 (2.0)	1	0.863
	8	91	- 0.9 (1.7)	7	0.587
	12	133	- 0.6 (1.3)	1	0.629
	All	309	0.0 (0.9)	2	0.991
PFHxS[a]	4	85	- 3.6 (3.4)	2	0.283
	8	91	- 0.8 (3.6)	5	0.812
	12	133	0.8 (3.2)	7	0.803
	All	309	0.7 (1.8)	9	0.717
PFOS[a]	4	85	- 3.5 (2.0)	7	0.067
	8	**91**	**- 5.2 (1.7)**	**28**	**0.002**
	12	**133**	**- 6.5 (1.3)**	**20**	**<0.001**
	All	**309**	**- 5.5 (0.9)**	**18**	**<0.001**

[a]Sum of branched and linear isomers

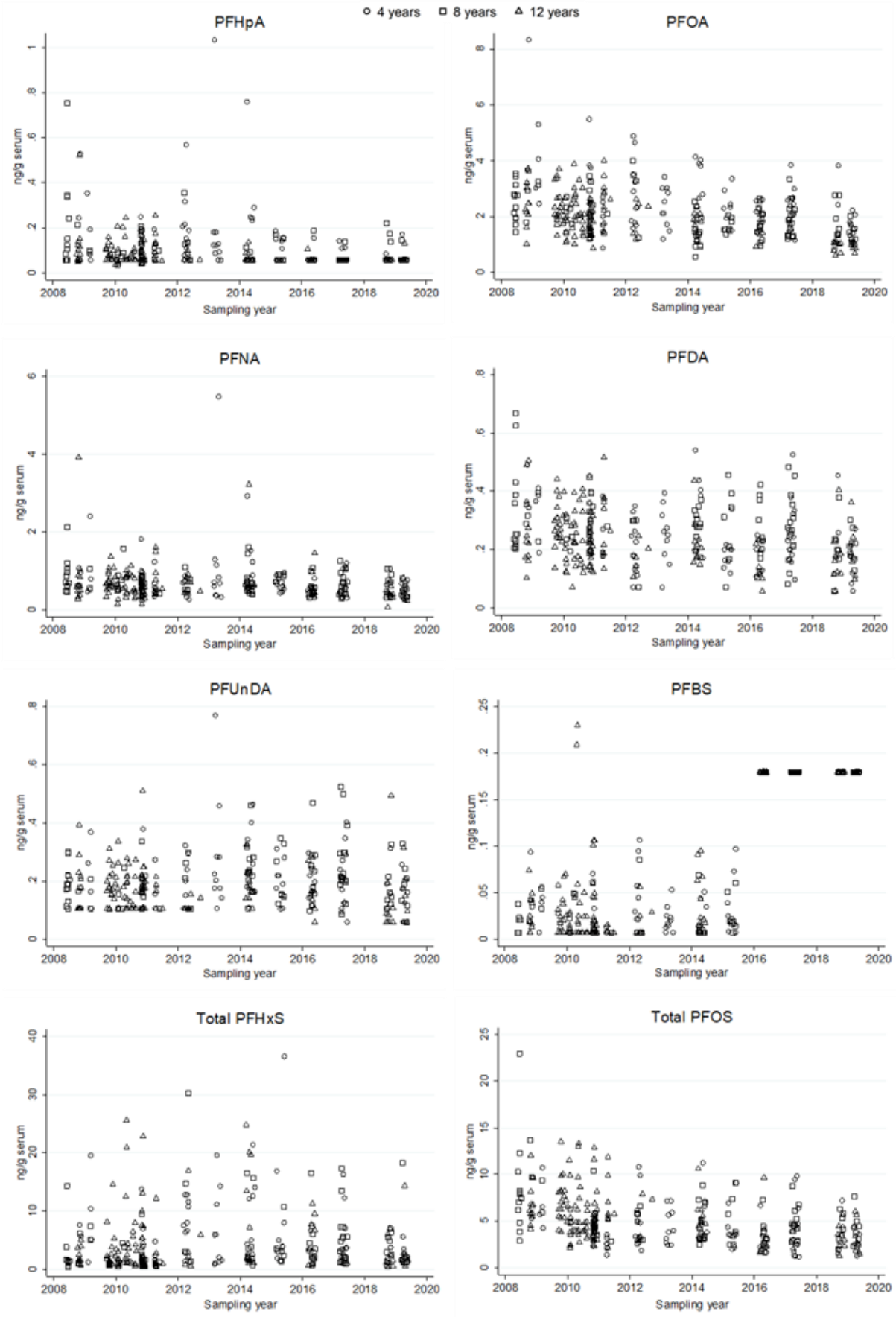

Figure 1. PFAS concentrations in POPOP children (N=303) during 2008-2019.

Levels in children from Uppsala compared to proposed TWI-levels from EFSA and the study Riksmaten Ungdom

In February 2020, EFSA released a new proposal for a TWI for four PFAS; PFOA, PFNA, PFOS and PFHxS. The opinion is now out on public consultation and the new TWI will be decided upon after summer 2020. Based on available studies in animals and humans, effects on the immune system were considered the most critical for the risk assessment. From two human studies, no observed adverse effect concentrations (NOAECs) of 31.9 and 27.0 ng/mL serum for the sum of the four PFASs were identified for 1- and 5-year-old children, respectively. Using physiologically-based pharmacokinetic (PBPK)-modelling, the serum level of 31.9 ng/mL in 1-year-old children was estimated to correspond to long-term maternal exposure to 1.16 ng/kg bw per day (EFSA, 2020).

Compared to data in the EFSA risk assessment, all children in this study have serum levels below the critical concentration of 31.9 ng/mL (Table 6). Compared to the NOAEC for five-year-old children in the EFSA-opinion (27.0 ng/mL serum), the maximum levels of the 4- and 8-year-olds in Uppsala is slightly exceeded (30.7 and 28.7 ng/mL, respectively). Median- and mean-levels of serum concentrations is well below the critical concentration for all age groups (Table 6). The levels found in these children are also comparable with the levels found in the study Riksmaten Ungdom (Livsmedelsverket 2020). The participants in the Riksmaten Ungdom study is slightly older than the children in this study, but the mean and median levels are in the same range.

Table 6. The sum of PFNA, lin-PFOA, total PFHxS and total PFOS concentrations (ng/mL) in serum from children in Uppsala 2016-2019.

Sum of PFNA, lin-PFOA, tot PFHxS and tot PFOS					
Age group (years)	Mean	±SD	Median	Min	Max
4	9.8	5.6	8.1	3.6	30.7
8	11.0	5.7	9.2	4.0	28.7
12	8.3	5.2	6.3	2.3	24.0

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