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Temporal trends of perfluoroalkyl substances (PFAS) in individual serum samples from first-time mothers in Uppsala 1996-2016

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Sammanfattning
Sedan 1996 har Livsmedelsverket regelbundet samlat in blodprover från förstföderskor i Uppsala för analys av persistenta halogenerade organiska miljöföroreningar (POP). Poly- och perfluorerade alkylsyror (PFAS) är en sådan substansgrupp. I vårt projekt undersöks hur exponering för PFAS har förändrats sedan stora förändringar i produktion av kemikalierna skedde runt millennieskiftet. I följande rapport redovisas tidstrenderna av perfluorerade alkylsyror (PFAA) och perfluoroktansulfonamid (FOSA) i blodserum insamlade 3 veckor efter förlossningen 1996-2016, baserat på kemisk analys av enskilda prover från deltagarna. PFBS, PFHxS, PFNA, PFDA, PFUnDA och PFTrDA ökade under studieperioden, med en uppskattad fördubblingstid på mellan 12 och 32 år. Efter justering för faktorer som kan tänkas påverka trenderna ökade fördubblingstiden för PFHxS från 16 år till 24 år. Den ökande trenden av PFBS och PFHxS beror med stor sannolikhet på den förorening av dricksvatten i Uppsala stad som pågått under lång tid. En uppdelning av deltagarna efter hur länge de bott i Uppsala stad resulterade i kortare fördubblingstider för de som bott i Uppsala de senaste åren jämfört med de som inte bott i staden. De kvinnor som bott i Uppsala hade också 40 % högre halter av PFHxS. PFOS, PFHpA och PFOA sjönk med justerade halveringstider på mellan 8 till 24 år under studieperioden. Resultaten visar att utfasning av PFOS och PFOA har resulterat i minskande exponering i befolkningen. Kvinnor med högst utbildning (mer än 3 år efter gymnasiet) hade 10-60 % högre PFAA-halter än kvinnor med lägst utbildning (gymnasieskola). Störst skillnad observerades för PFBS och PFHxS som till viss del sannolikt beror på att kvinnor med högst utbildning i högre grad bott i Uppsala stad än kvinnor med lägst utbildning och därigenom fått högre exponering via dricksvattnet. Serumhalterna av flera av de långkedjiga karboxylsyrorna minskade med 1-4 % per enhetsökning av BMI, vilket antyder att överviktiga kvinnor hade något lägre halter av dessa PFAA än kvinnor med lågt BMI.

Temporal trends of perfluoroalkyl substances (PFAS) in individual serum samples from first-time mothers in Uppsala 1996-2016

Background

Poly- and perfluoroalkyl substances (PFASs) have been manufactured world-wide for many decades, for uses 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). Environmentally persistent perfluoroalkyl acids (PFAAs), that have fully fluorinated carbon backbones, are found globally in wildlife and in humans (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 since then declined in Sweden, as shown by decreasing serum levels of PFOS and PFOA among first-time mothers from Uppsala 1996-2012, with a faster decline of PFOS (halftime ~9 years) compared to PFOA (~20 years) (Glynn et al. 2012; Gebbink et al. 2015). However, not all PFASs are showing a decline. A temporal increase in levels of perfluorohexane sulfonic acid (PFHxS) was observed (doubling time ~10 years), as well as increases of longer-chained carboxylic acids perfluorononanoic acids (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA) and perfluoorotridecanoic acid (PFTrDA) (doubling time ~15-20 years) (Glynn et al. 2012; Gebbink et al. 2015). A follow-up study of PFAS temporal trends up to 2014 strongly indicates that the increasing trends of PFHxS and the long-chain PFAS in human serum are levelling off (Glynn et al. 2015), suggesting that exposure is not increasing anymore.

The aforementioned studies of first-time mothers from Uppsala, participating in the POPUP cohort, are limited by the use of pooled samples. This type of study gives no information about the variation in exposure within a studied population, which is important for risk assessment purposes. Moreover, in the case of the POPUP study, some participants lived in areas with PFAS-contaminated drinking water, whereas others did not. Consequently it may be possible that temporal trends of some PFASs differ depending on where the participants lived. Data from individual samples also makes it possible to identify dietary/life style factors that may explain some of the observed variation in exposure, thus giving information about possible sources of exposure.

Here we report PFAA concetrations in individual serum samples, and temporal trends of PFAA, in POPUP mothers for the period 1996-2016. Trends are compared between women living in areas receiving PFAS contaminated water and women not living in these areas.

Material and methods

Recruitment and sampling

In the POPUP study (Persistent Organic Pollutants in Uppsala Primiparas) (Table 1) first-time mothers from the general population living in Uppsala County were recruited between 1996 and 2016 as described in Glynn et al. (2012). The participants donated a blood sample 3 weeks after delivery. Blood sampling was carried out using 9 ml Vacutainer® or Vacuette® serum tubes, and serum was stored at -20°C. The study was approved by the local ethics committee of Uppsala University, and the participating women gave informed consent prior to the inclusion in the study.

Table 1. Personal characteristics of the participating mothers.

Variable			**N**	**Mean**	**Median**	**Range**
Age (yr)			639	29.3	29,4	17.3-41.3
Pre-pregnancy BMI (kg/m^2)			637	23.4	22.7	15.9-40.0
Weight gain during pregnancy (% of initial weight)			636	23.0	22.4	-5.94-54.4
Weight reduction from delivery to sampling (%)[a]			594	9.46	9.31	-0.961-24.6
Variable			**N**	**%**		
Education	max 3-4 yr high school		192	31		
	1-3 yr higher education		126	20		
	>3 yr higher education		306	49		
Smoking	never		420	66		
	stopped before pregnancy		128	20		
	smoked during pregnancy		88	14		
Living in City of Uppsala ≥5 years last 10 years		yes	375	64		
		no	215	36		

Those that stopped smoking during the first trimeser were included in the smoking group

PFAS analyses

PFASs (Table 2) were analyzed as described in Gyllenhammar et al. (2015). In short, 0.5g of serum was spiked with internal standards and extracted with acetonitrile. The concentrated extract underwent dispersive clean-upon with graphitized carbon. Aqueous ammonium acetate and volumetric standards were added before instrumental analysis on an Acquity ultraperformance liquid chromatography system (UPLC) coupled to a Xevo TQ-S tandem mass spectrometer (MS/MS) (both from Waters 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 Vestergren et al. (2012). Quantification was performed by isotope dilution using a 5-point calibration curve (linear, 1/x weighting, excluding the origin) 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.

Table 2. PFAS included in the study.

Substance	No of carbons in fluorinated chain	Acronym[1]	Internal Standards
Perfluoroalkyl sulfonic acids (PFSA)			
Perfluorobutane sulfonic acid	4	PFBS	$^{18}O_2$-PFHxS
Perfluorohexane sulfonic acid[a]	6	PFHxS	$^{18}O_2$-PFHxS
Perfluorooctane sulfonic acid[a]	8	PFOS	$^{13}C_4$-PFOS
Perfluorooctane sulfonamidoacetic acid	8	FOSA	$^{13}C_8$-FOSA
Perfluoroalkyl carboxylic acids (PFCA)			
Perfluorohexanoic acid	5	PFHxA	$^{13}C_2$-PFHxA
Perfluoroheptanoic acid	6	PFHpA	$^{13}C_4$-PFHpA
Perfluorooctanoic acid	7	PFOA	$^{13}C_4$-PFOA
Perfluorononanoic acid	8	PFNA	$^{13}C_5$-PFNA
Perfluorodecanoic acid	9	PFDA	$^{13}C_2$-PFDA
Perfluoroundecanoic acid	10	PFUnDA	$^{13}C_2$-PFUnDA
Perfluorododecanoic acid	11	PFDoDA	$^{13}C_2$-PFDoDA
Perfluorotridecanoic acid	12	PFTriDA	$^{13}C_2$-PFDoDA
Perfluorotetradecanoic acid	13	PFTeDA	$^{13}C_2$-PFDoDA
Perfluoropentadecanoic acid	14	PFPeDA	$^{13}C_2$-PFDoDA

[1]Buck et al. (2011)

A procedural blank and control sample were included in each batch of samples. The samples were analyzed in different batches and Table 3 gives the method quantification limits (MQLs) for the different analytical batches. Absolute recoveries of the internal standards (determined relative to $^{13}C_8$-PFOA) were on an average between 60% and 69%. Further method validation parameters are provided in Glynn et al. (2012).

Table 3. Method quantification limits for the different analytical batches.

PFASs	Analytical batch				
	2013	**2014**	**2015**	**2016**	**2017**
PFHxA	0.30	0.10	0.020	0.080	0.16
PFHpA	0.040	0.10	0.030	0.14	0.14
PFOA	0.20	0.25	0.30	0.030	0.14
PFNA	0.050	0.10	0.010	0.030	0.040
PFDA	0.050	0.070	0.010	0.070	0.15
PFUnDA	0.050	0.050	0.010	0.020	0.060
PFDoDA	0.050	0.050	0.010	0.030	0.060
PFTrDA	0.050	0.050	0.030	0.020	0.040
PFTeDA	0.050	0.050	0.10	0.070	0.060
PFPeDA	0.050	0.030	0.40	0.060	0.050
PFBS	0.010	0.010	0.15	0.090	0.10
PFHxS (br/lin)	0.010/0.010	0.010/0.10	0.050/0.060	0.020/0.020	0.040/0.040
PFOS (br/lin)	0.010/0.010	0.20/0.50	0.020/0.10	0.030/0.030	0.040/0.040
FOSA (br/lin)	na/0.01	0.01/0.01	0.01/0.01	0.01/0.01	

na=not analyzed

Statistical analyses

For PFHpA only data from the analyses 2013 were used, since almost all other data were below MQL. Similarly for PFBS data from 2013 and 2014 were used. Data for PFTrDA came from analyses in 2015, 2016 and 2017. In the statistical analyses concentrations below MQL were substituted with imputed concentrations. Temporal trends of PFAA were investigated by linear regression analysis. Multiple regression analyses included the covariates age, BMI, weight gain during pregnancy, weight loss after delivery, education level and maternal smoking.

Results and discussion

Analyses were performed in different batches during a 5 year period and the MQLs varied between analytical runs (Table 3). Concentrations were below the MQL in the majority of samples in the case of PFHxA (0.02-0.3 ng/g), PFDoDA (0.01-0.06 ng/g), PFTeDA (0.05-0.1 ng/g), PFPeDA (0.03-0.4 ng/g) and branched/linear FOSA (0.01 ng/g). For PFBS results from the analyses 2013 and 2014 were used, and the median concentration was more than 200-fold lower than medians of PFHxS and PFOS (Table 4). PFOS concentration was 6-fold higher than the median of PFHxS, when looking at the whole study period (Table 4). PFOA showed the highest median concentration among PFCAs, being similar as that of PFHxS. Median concentration of long-chain PFCAs decreased with increasing carbon chain length from 0.4 ng/g for PFNA to 0.03 ng/g for PFTrDA (Table 4). Median concentration of PFHpA was close to that of PFTrDA.

Table 4. Concentrations of perfluoroalkyl sulfonic acids (PFSA) and perfluoroalkyl carboxylic acids (PFCA) (ng/g) in individual serum samples from nursing primiparous women in Uppsala County 1996-2016.

Substance	N	N<LOQ	Mean	Median	Range
PFBS	413	181	0.029	0.012	<0.01-0.80
PFHxS	624	0	3.9	2.5	0.32-34
PFOS	623	0	14	9.0	0.21-61
PFHpA	297	113	0.062	0.052	<0.04-0.40
PFOA	626	0	2.4	2.2	0.20-13
PFNA	626	0	0.51	0.44	0.062-2.9
PFDA	626	24	0.24	0.20	<0.01-1.3
PFUnDA	626	61	0.22	0.19	<0.01-1,3
PFTrDA	214	83	0.038	0.029	<0.02-0.19

PFBS: samples analysed 2013 and 2014; PFHpA: samples analysed 2013; PFTrDA: samples analysed 2015, 2016 and 2017. When calculating means data below MQL was replaced with imputed data.

Table 5. Annual change in PFAS concentrations in blood serum 1996–2016.

Compound	N	Univariate Change (%) Mean (SE)	p	½ time/*doubling* (yrs) Mean	Multivariate N	Change (%) Mean (SE)	p	½ time/*doubling* (yrs) Mean
PFBS	412	5.8 (1.2)	<0.001	*12*	369	5.1 (1.4)	<0.001	*14*
PFBS 0					119	3.2 (2.4)	0.187	
PFBS 1					250	6.5 (1.8)	<0.001	*11*
PFHxS	622	4.3 (0.50)	<0.001	*16*	613	2.9 (0.50)	<0.001	*24*
PFHxS 0					203	2.3 (0.93)	0.015	*30*
PFHxS 1					346	3.0 (0.73)	<0.001	*23*
PFOS	621	-8.7 (0.29)	<0.001	7.9	612	-9.3 (0.30)	<0.001	7.5
PFOS 0					204	-9.7 (0.49)	<0.001	7.1
PFOS 1					346	-8.8 (0.45)	<0.001	7.9
PFHpA	297	-2.3 (0.64)	0.001	30	275	-2.8 (0.77)	<0.001	24
PFOA	624	-4.6 (0.29)	<0.001	15	615	-4.3 (0.29)	<0.001	16
PFOA 0					189	-4.6 (0.48)	<0.001	15
PFOA 1					347	-4.2 (0.40)	<0.001	16
PFNA	623	2.2 (0.34)	<0.001	*32*	615	2.0 (0.36)	<0.001	*35*
PFDA	624	2.3 (0.36)	<0.001	*30*	614	2.0 (0.40)	<0.001	*35*
PFUnDA	624	3.4 (0.39)	<0.001	*20*	615	3.0 (0.44)	<0.001	*23*
PFTrDA	213	2.1 (0.74)	0.004	*32*	208	1.7 (0.79)	0.034	*41*

SE=standard error. The multivariate annual change was adjusted for age, BMI, weight gain during pregnancy, weight change between delivery and sampling, educational level and smoking.

PFAA 0 = subjects living in Uppsala for at least 5 of the last 10 years.

PFAA 1 = subjects living in Uppsala for less than 5 of the last 10 years.

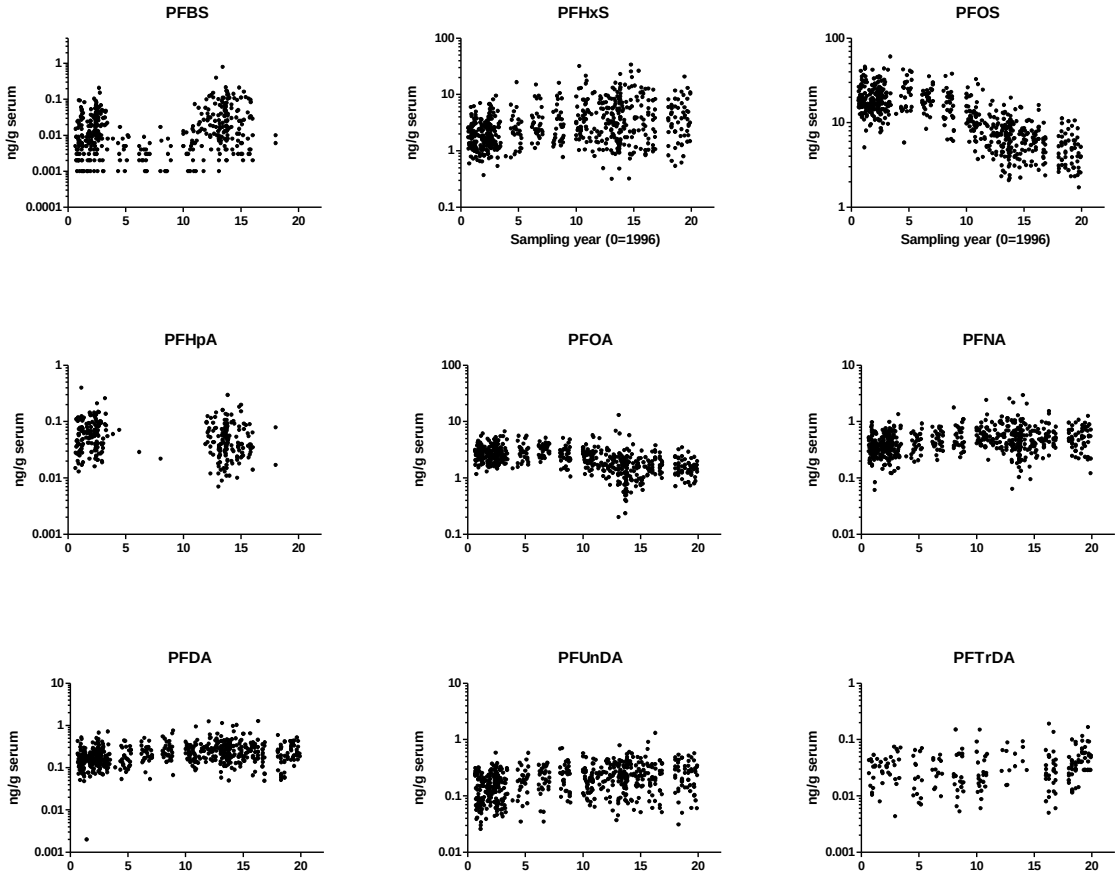

Figure 1. PFAA concentrations in serum from first-time mothers living in Uppsala County 1996-2016.

Temporal trends were analyzed by univariate and multiple linear regression. The results of the univariate analyses show temporal trends as they are observed in the population of young Uppsala women (Figure 1, Table 5), and the results of the multivariate analyses show temporal trends adjusted for possible temporal changes in personal characteristics associated with serum PFAA concentrations (Table 5). PFBS, PFHxS, PFNA, PFDA, PFUnDA and PFTrDA all showed increasing temporal trends during the study period, with time for doubling of concentrations ranging from 12 years for PFBS to 32 years for PFTrDA in the univariate analyses. In the multiple regression analyses the doubling time of PFHxS became 1.5-fold longer (16 to 24 years), showing that some of the univariate temporal trend could be explained by temporal changes in personal characteristics associated with PFHxS concentrations.

For the other PFAA showing an increasing temporal trend lesser differences were observed between univariate and adjusted temporal trends (Table 5). PFHpA, PFOS and PFOA showed decreasing temporal trends that did not change markedly after adjustment for possible temporal trends in personal characteristics (Table 5). The half-time was considerably shorter for PFOS than for PFHpA and PFOA, although the biological half-life of PFOS in the body is longer than that of PFHpA and PFOA (Zhang et al. 2013). This suggests that PFOS exposure has decreased much faster than exposure to PFHpA and PFOA, which is consistent with the almost complete phase-out of PFOS and related compounds. Figure 1 shows that the results for PFBS, PFHpA and PFTrDA are more uncertain than the results for the other PFAA, due to generally very low concentrations and omission of data from analytical batches with high MQLs.

PFAA temporal trends have previously been studied in pooled samples from the POPUP cohort 1997-2014 (Glynn et al. 2015). In the present study the univariate temporal trend is comparable with the pooled trend. For PFHxS the increase was slightly faster in the pooled trend (6% per year) than in the univariate trend (4% per year), which could be due to differences in number of participants in the two studies and the inclusion of data from 2016 in the present study. This could, at least partly, also explain the slightly faster decline of PFOS and PFOA and the slower increase in PFNA-PFUnDA concentrations in the present study than in the pooled temporal trend (Glynn et al. 2015). In the present study we observed an annual 2% increase in PFTrDA concentration, whereas no temporal trend was observed in the pooled trend (Glynn et al. 2015).

In 2012 it was discovered that certain drinking water production wells in the City of Uppsala were contaminated with PFHxS, and to a lesser degree with PFOS, PFOA and PFBS (Gyllenhammar et al. 2015). When the study participants were divided in groups of women having lived in the City of Uppsala for at least 5 of the last 10 years (Uppsala group) and those having lived less than 5 years in Uppsala (Outside group), the adjusted temporal increase of PFBS and PFHxS was slower for the Outside group (Table 5). This suggests that consumption of PFBS- and PFHxS-contaminated drinking water in the City of Uppsala contributed significantly to the overall PFBS and PFHxS exposure of women living in the city. For PFOS and PFOA the differences in temporal trends were less obvious between the two groups, suggesting a small contribution from drinking water to the overall PFOS and PFOA exposure (Table 5).

Table 6. Percent change in PFAA serum concentration per unit change in covariates included in the multiple regression analyses (mean (standard error)), and coefficient of determination (R^2, %) of the whole regression model also including the covariate "sampling year".

Compound	N	Age	Uppsala	BMI (kg/m^2)	Weight gain	Weight loss	Education		Smoking		R^2
			2				2	3	1	2	Including sampling year
PFBS	369	ns	ns	ns	ns	ns	ns	57 (19)	ns	ns	9.0
PFHxS	540	ns	41 (6.8)	ns	ns	ns	ns	49 (8.5)	ns	ns	25
PFOS	538	ns	ns	ns	ns	ns	ns	17 (5.0)	-18 (5.0)	-15 (5.6)	62
PFHpA	274	ns	ns	ns	ns	ns	ns	ns	ns	ns	6.7
PFOA	542	ns	8.3 (4.0)	-1.2 (0.61)	ns	ns	ns	11 (5.0)	-21 (4.9)	ns	31
PFNA	542	ns	ns	ns	ns	ns	ns	13 (5.6)	-16 (5.5)	ns	12
PFDA	542	ns	ns	-1.5 (0.74)	ns	1.7 (7.6)	ns	17 (6.1)	ns	ns	13
PFUnDA	542	2.1	ns	-2.2 (0.84)	ns	ns	ns	19 (6.9)	ns	ns	19
PFTrDA	174	2.8	ns	-4.4 (1.7)	ns	ns	ns	ns	ns	ns	17

For the variable "Uppsala" the reference group (1) was women living in Uppsala less than 5 years during the last 10 years and (2) was women living in Uppsala at least 5 years during the last 10 years. The variable "Education" included women with high school education (1, reference group), women with 1-3 years of higher eductation (2) and women with more than 3 years of higher education (3). Women that had never smoked was reference group for the variable "smoking", group (2) women who had stopped smoking before pregnancy and (3) women who smoked during pregnancy or stopped smoking during the 1st trimester of pregnancy. ns=not significant $p>0.05$.

In the multivariate regression analysis it is possible to determine the associations between personal characteristics, included as independent variables in the regression models, and PFAA concentrations. For each determinant the association with PFAA is adjusted for possible influence of the other covariates on the association. Women living in the City of Uppsala for at least 5 of the last 10 years had on average 40% higher PFHxS concentrations than women living in Uppsala less than 5 years (Table 6). This further strengthens the importance of PFHxS-contaminated drinking water as a source of exposure. This difference was not observed for PFBS, most probably due to its short half-life (less than a year) compared with PFHxS (several years) (Olsen et al. 2009). A different grouping of the participants into women living in Uppsala City during the year of sampling and women not living in the city during the sampling year may be more appropriate in the case of PFBS. For PFOS and PFOA there were only slight or no differences in serum concentrations between the two groups of women (Table 6), further highlighting that contaminated drinking water was a less important source of exposure to these targets.

Education level was positively associated with serum PFAA concentrations, with on average more than 10% higher concentrations among women with the highest education level (Table 6). PFBS and PFHxS showed the largest difference between women with only high school education and women with more than 3 years of higher education, 57% and 49% increase, respectively. Since these two PFAAs are associated with drinking contamination it may be speculated that some of the association with education may be related to place of living in Uppsala City. In fact 57% of the women living in Uppsala the recent years had more than 3 years of education after high-school compared to 38% among women from outside Uppsala City.

The PFCAs were inversely related to BMI, except in the case of PFHpA and PFNA (Table 6). The serum concentration decreased on average with 1-4% per unit increase in BMI, suggesting that obese women had slightly lower serum concentrations than women with low BMI. Women that reported stopping smoking before pregnancy had on average more than 15% higher PFOS, PFOA and PFNA serum concentrations than non-smoking women (Table 6). For PFOS women smoking during pregnancy had significantly higher serum concentrations than non-smoking women, not observed for PFOA and PFNA. This suggests smoking itself does not affect serum PFAA concentrations. There may be other personal characteristics among the former smokers and smokers (PFOS) that cause decreased PFAA concentrations in serum.

The variation of the independent variables in the regression model explained 7-60% of the variation in PFAA concentrations (Table 5), showing that there are important determinants of serum concentrations not studied by us. The highest R^2 was observed for PFOS and PFOA, mainly due to the large between-sampling year variation in concentrations.

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