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Level and temporal trend of perfluoroalkyl acids in Greenlandic Inuit

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***Objectives*:** Perfluoroalkyl acids (PFAAs) have been detected in human blood, breast milk and umbilical cord blood across the globe. PFAAs do accumulate in the marine food chain in Arctic regions. In Greenland, increasing PFAA concentrations were observed during 1982–2006 in ringed seals and polar bears. However, until now, no data have been reported for PFAAs in Greenlandic Inuit. This study assesses the level and temporal trend of serum PFAAs in Greenlandic Inuit.

***Study design*:** Cross-section and temporal time trend survey.

***Methods*:** Serum PFAA levels were determined in 284 Inuit from different Greenlandic districts using liquid chromatography-tandem mass spectrometry with electrospray ionization. The temporal time trend of serum PFAAs in Nuuk Inuit during 1998–2005 and the correlation between serum PFAAs and legacy persistent organic pollutants (POPs) were explored.

***Results*:** Serum PFAA levels were higher in Nuuk Inuit than in non-Nuuk Inuit. Within the same district, higher PFAA levels were observed for males. An age-dependent, increasing trend of serum PFAA levels in the period from 1998–2005 was observed for Nuuk Inuit. For the pooled gender data, no significant association between PFAAs and legacy POPs was observed for Nuuk Inuit while for non-Nuuk Inuit this correlation was significant. No correlation between PFAAs and legacy POPs was found for male Inuit, whereas significant correlation was observed both for pooled female Inuit and for non-Nuuk Inuit females.

***Conclusions*:** We suggest that sources other than seafood intake might contribute to the observed higher PFAA levels in Nuuk Inuit compared to the pooled non-Nuuk Inuit.

Keywords: *Perfluoroalkyl acids (PFAAs)*; *Greenlandic Inuit*; *persistent organic pollutants (POPs)*; *time trend.*

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Poly- and perfluorinated compounds (PFCs) are a large group of chemicals employed in different industrial and commercial applications (1). Two groups of PFCs, the perfluoro-carboxylated acids (PFCAs) and perfluorosulfonated acids (PFSAs), are together commonly referred to as perfluoroalkyl acids (PFAAs). These compounds have received attention in recent years as a novel group of persistent organic pollutants (POPs) (2,3). Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are the 2 most studied PFAAs. Adverse outcomes of exposure to PFOS and PFOA have been reported in animal studies; these outcomes have included decreased serum cholesterol, hepatotoxicity, thyroid hormone alterations, developmental toxicity, immuno-toxicity, neurotoxic effects and tumorigenicity (3–5). For humans, positive associations were observed between PFOA serum levels and cholesterol, uric acid and liver enzymes (6). Due to their resistance against degradation in the environment, their bioaccumulation in the food chain, their global distribution and their adverse health potentials, a series of governmental regulations have been taken by North American (7) and European authorities (8) on the use and production of PFOS and PFOA. PFOS and its salts

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have recently been added to Annex B of the Stockholm Convention on POPs (9).

PFAAs have been found in human blood, breast milk and livers (2) with half-lives of 4–10 years (10). The developing fetus is especially sensitive to exposure to PFAAs. PFOA and PFOS exposure during fetal development has inverse effects on birth weight and length, as well as on head and abdominal circumference (11,12). It has been reported that PFOA and PFOS exposure at general population levels can reduce female fecundity (13).

Biomonitoring studies have been carried out in almost all parts of the world in order to assess PFAA levels and temporal trends in the general population (2,14). During 1997–2006, European studies reported median serum and plasma concentrations of PFOS and PFOA ranging from 3.5 to 34.2 ng/ml and from 3.4 to 6.8 ng/ml, respectively (14). The average plasma levels of PFOS and PFOA in pregnant Danish women during 1996–2002 was 35.3 and 5.6 ng/mL, respectively (11), similar to most levels reported for Western populations during the same decade (15). Mean and median concentrations from North American populations appear to be slightly higher than European, Asian and Australian populations (14). As a consequence of U.S. EPA and European regulations, and of ceased production of PFOS-based products from the world's formerly largest producer (3M), human serum levels of PFOS and PFOA have shown a decreasing trend in studies from the United States and Norway (10,16,17). However, an increasing trend has been reported in studies from Japan and China (18,19).

It is well known that the Indigenous populations in the Arctic are particularly exposed to legacy POPs, such as polychlorinated biphenyl (PCBs) and organochlorine pesticides, through the intake of marine mammals. Recent studies have indicated that the consumption of local traditional food among Indigenous populations in Greenland has decreased by about 25% over the last 30 years, and that these foods now make up only approximately 20% of the total dietary intake (20,21). Women generally consume less local traditional food than men (21). The Arctic Monitoring and Assessment Programme (AMAP) has in the past 20 years assessed the concentration of legacy POPs in the different parts of the circumpolar region, as well as their spatial distributions and temporal trends in the Indigenous populations (20,22). These studies indicate that Inuit populations in Greenland, Canada and Alaska continue to have high concentrations of the legacy POPs (22), although recent data show a slight decreasing trend in concentrations for some legacy POPs, such as 2,2-bis(p-chlorophenyl)-1,11-trichloroethane (DDT), PCBs and oxychlordane in some Arctic regions, including Greenland (20–23).

In addition to legacy POPs, emerging contaminants including PFAAs are currently being detected in humans from the Arctic regions (20,22). Unlike legacy POPs, the level of PFAAs in marine mammals from Greenland has continued to show an increase over the past few years (24,25). Very sparse data on PFAA levels in humans from Arctic regions are available (20,26–28). The largest study on PFAAs was performed in the Arctic Canada (26) and included a data set for PFOS serum concentrations from 883 Canadian Inuit adults from Nunavik. The other published studies on human levels of PFOS and/or PFOA in the Arctic are mainly based on small-sample data sets (sample size ≤ 25) and are often performed on maternal blood. At present, the level of PFAAs has not yet been investigated for the Indigenous population in Greenland.

In this paper we present the level of 10 different PFAAs in serum from 284 adult Inuit belonging to 10 different Greenlandic districts. Moreover, we present the correlation between serum PFAAs and legacy POPs, and the temporal trend of PFAAs covering the period 1998–2005 for the district of Nuuk.

Material and methods

The participants and sample collection

All participants were of Inuit descent, defined as having more than 2 grandparents born in Greenland. The participants were randomly selected from 10 Greenlandic districts – Qaannaq, Upernavik, Ummannaq, Qeqertarsuaq, Ilulissat, Sisimiut, Nuuk, Narsaq, Tasiilaq and Ittoqqor-toormitt – in the period from 1997–2006 (Fig. 1). Participants from Nuuk during 2000–2002 were randomly selected from a cross-sectional study assessing legacy POP exposure on osteoporosis-related ultrasound bone measurements in Greenlandic Inuit women (29), and the rest of the participants were randomly selected from projects in the human health program of the ongoing circumpolar AMAP (21,30,31). The participation rate was more than 80% (21,29–31). Venous blood samples and questionnaires about demographic and lifestyle factors were collected. The serum was prepared and frozen at -80°C for further measurement (21,29,30).

The proposed protocols of the studies were accepted by the Ethical Committee for Scientific Investigations in Greenland and all the participants gave written informed consent.

PFAAs analysis

The following compounds were analysed in serum samples: perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnA), perfluorododecanoic acid (PFDoA), perfluorotridecanoic acid (PFTrA), perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS) and perfluorooctane sulfonamide (PFOSA). The following compounds from Wellington Laboratories were used

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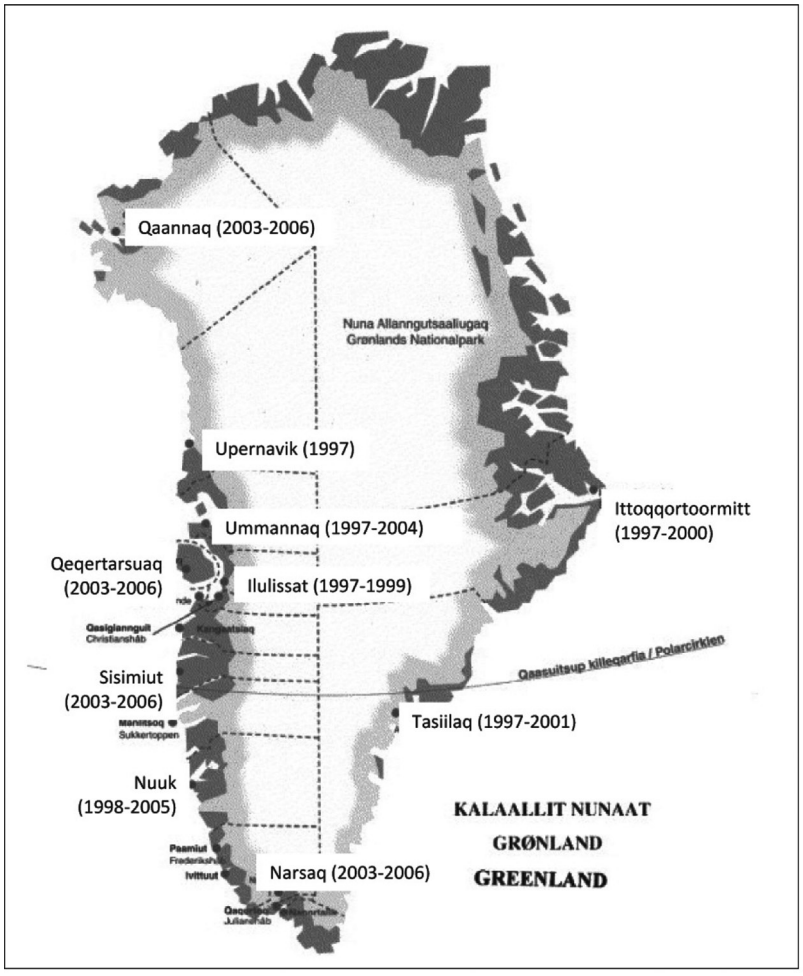

District	Qaannaq	Upernavik	Ummannaq	Qeqertarsuaq	Ilulissat	Sisimiut	Nuuk	Narsaq	Tasiilaq	Ittoqqortoormitt
n	29	2	24	20	19	7	142	10	13	18
∑PFSAs	12.0	92.3	14.0	6.5	44.1	8.3	32.7	4.6	62.5	15.2
∑PFCAs	1.8	11.3	2.8	1.8	6.0	1.5	6.2	1.4	8.1	2.2

Fig. 1. Map of Greenland showing the different districts and sampling periods, including the serum PFAAs median levels (ng/ml) for each district.

as surrogate standards: $^{13}C_8$-PFOA, $^{13}C_4$–PFOS and $^{13}C_2$-PFDA.

The extraction method was based on ion pairing as described by Hansen et al. (32). Instrumental analysis was performed by liquid chromatography-tandem mass spectrometry (LC-MS-MS) with electrospray ionization (ESI). The analytical method used here is described in detail in Bossi et al. (25). Method performance was tested through participation in inter-laboratory comparison studies organized by the Institute Nationale de Santé Publique du Québec for AMAP (33). Satisfactory z-scores were obtained in the inter-laboratory comparison studies from our laboratory.

Measurement of legacy POPs and fatty acids

Serum concentration of PCB congeners CB99, CB101, CB105, CB118, CB128, CB138, CB153, CB156, CB170, CB180, CB183 and CB187, and organochlorine pesticides including chlordanes, p,p'-dichlorodiphenyldichloroethane (p,p'-DDE), p,p'-dichlorodiphenyltrichloroethane (p,p'-DDT), oxychlordane, hexachlorobenzene (HCB), beta-hexachlorocyclohexane (β-HCH), mirex and toxaphene were measured at the certified laboratory, Le Centre Toxicologie, in Sainte Foy, Quebec, Canada (21,23,29,30).

The fatty acid profiles were determined in plasma phospholipids at the Biology Department of the University of Guelph, Ontario, Canada (23,34). The ratio between n-3 polyunsaturated fatty acids and n-6 fatty acids is known to be a strong indicator of seafood intake and thus is a good indicator of the relative consumption of traditional food versus imported food (35).

Statistical analysis

The statistical analysis of the data was performed in SPSS 13.0 (SPSS Inc., Chicago, IL) with a significance level of

$p < 0.05$. Half of the detection limit values were used in case of concentrations below the detection limit. Based on the chemical structure, the analysed PFAAs were grouped in perfluorosulfonated acids (ΣPFSAs) – as in, the sum of PFOS, PFHxS and PFOSA – and perfluorocarboxylated acids (ΣPFCAs), which were made up of the sum of PFHpA, PFOA, PFNA, PFDA, PFUnA, PFDoA and PFTrA. The legacy POPs were grouped in ΣPCBs (sum of 12 measured PCB congeners), Σpesticides (sum of 8 measured organochlorine pesticides) and Σlegacy POPs (sum of 12 PCB congeners and 8 pesticides). Due to the low number of samples collected from most districts and the different lifestyles among them (21), the data from non-Nuuk districts were grouped as pooled non-Nuuk district data, and the subsequent data analysis was based on the comparison between Nuuk and pooled non-Nuuk district data. Normal distribution was assessed by Q-Q plots. Natural logarithm (ln)-transformed data improved the normality and homogeneity of variance and the statistical analyses were performed on the ln-transformed data. The data were treated as continuous variables.

Pearson correlation analysis was performed to assess the bivariate correlation between life-style factors and both PFAAs and legacy POPs. Previous studies reported a correlation between PFAA and both age and n-3/n-6 ratio (17,26,36). Therefore comparisons of means for PFAAs between the districts and genders were also performed by the general linear model procedure under adjustment of age and n-3/n-6. The following approaches were used: (1) Univariate regression analyses, where age and n-3/n-6 were included individually in the model; (2) Multi-variate regression analyses, in which PFOS, PFOA, sumPFSA sumPFCA, age and n-3/n-6 were included and thereby mutually adjusted. Multiple linear regression analysis was used to assess the relationship between serum PFAA levels and the serum level of legacy POPs under adjustment of age and n-3/n-6 ratio. Comparison of the biomarker of seafood intake (n-3/n-6 ratio) was also performed under adjustment of age since seafood intake is significantly correlated to age.

Time PFAA trend analyses were performed on 142 samples from Nuuk. Only time series with at least 4 years of data were included in the analysis. The analyses of temporal trends followed the procedures used in temporal trend assessments by the International Council for the Exploration of the Sea, a method that employs a robust, regression-based analysis to detect temporal trends (37). Annual geometric mean concentrations of PFAAs were used as the yearly contaminant index value. The total variation in the contaminant index values over time was divided into a linear and a non-linear component. Log-linear regression analysis was applied to describe the linear component, and a simple, 3-point running mean smoother was applied to describe the non-linear component. The linear and non-linear components were tested by means of an ANOVA. The time trend analysis was performed with PIA©, a statistic analytical tool developed for analysis of AMAP time trend data sets (38). Since PFAAs was reported to be related to age (26), age was also added as a covariate for the adjustment of age in the trend analysis.

Results

General characteristics of the study population

Table I shows the characteristics of the study population. The median age of the Green-landic Inuit in the study was 50 years, ranged from 18 to 73 years. The included Inuit living in Nuuk were older than those living in the pooled non-Nuuk districts, in terms of both the separate genders and pooled gender data. It should be noted that data for only 5 males were included in the Nuuk district data. No significant difference was found in the BMI and the seafood intake biomarker (n-3/n-6) between Nuuk and non-Nuuk Inuit. Most participants (68.9%) were smokers, but no difference was observed between districts. No gender differences were observed for age, BMI, n-3/n-6 and smoking status within Nuuk and pooled non-Nuuk districts ($p > 0.06$) (Table I).

District distribution of serum levels of PFAAs and legacy POPs

PFAA concentrations differed significantly between the studied Inuit from Nuuk and pooled non-Nuuk districts. Nuuk Inuit had significantly higher PFAA levels than pooled non-Nuuk Inuit, both for the separate gender data and pooled data. After adjustment for age and n-3/n-6, this significance persisted (Table II).

As for PFAAs, the levels of legacy POPs were generally higher for Nuuk Inuit compared to non-Nuuk Inuit. For the pooled gender data, levels of ΣPCBs, Σpesticides and Σlegacy POPs for Nuuk Inuit were significantly higher than for pooled non-Nuuk Inuit (Table II). However, after adjustment for age and n-3/n-6, ΣPCB levels were not significantly different between the Nuuk district and pooled non-Nuuk district for the separate genders, whereas Σpesticides differed between the 2 district groups for both genders.

Gender differences in serum PFAA levels and legacy POP levels

Serum PFAA levels in male Inuit were significantly higher than those in female Inuit both before and after adjustment for age and n-3/ n-6 within both Nuuk and pooled non-Nuuk districts (Figure 2A, 2B).

Significantly higher levels of Σlegacy POPs for males were found in the pooled non-Nuuk districts only, and a statistically insignificant tendency of higher legacy POPs in Nuuk males was observed, although the small sample

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Table I. Characteristics of Greenlandic Inuit participants

Parameters		Male				Female				Male + Female			
		All	Nuuk	Non-Nuuk	p-value*	All	Nuuk	Non-Nuuk	p-value*	All	Nuuk	Non-Nuuk	p-value*
Age (year)	n	74	5	69	<0.0001	190	127	63	<0.0001	264	132	132	<0.0001
	Median	37.5	65.0	37.0		53.0	56.0	34.0		50.0	56.0	36.0	
	Min	18.0	43.0	18.0		18.0	34.0	18.0		18.0	34.0	18.0	
	Max	73.0	73.0	67.0		66.0	66.0	62.0		73.0	73.0	67.0	
	p-value (m vs. f in Nuuk)	ns											
	p-value (m vs. f in non-Nuuk)	ns											
BMI (kg/m^2)	n	50	5	45	ns	187	127	60	ns	237	132	105	ns
	Median	26.4	24.9	27.0		25.8	25.9	25.1		25.9	25.9	25.4	
	Min	17.6	23.1	17.6		16.6	16.6	18.2		16.6	16.6	17.6	
	Max	37.0	26.1	37.0		43.4	43.4	37.5		43.4	43.4	37.5	
	p-value (m vs. f in Nuuk)	ns											
	p-value (m vs. f in non-Nuuk)	ns											
n-3/n-6	n	69	5	64	ns	190	127	63	ns	260	132	128	ns
	Median	0.3	0.5	0.3		0.5	0.6	0.4		0.4	0.6	0.3	
	Min	0.1	0.2	0.1		0.1	0.1	0.2		0.1	0.1	0.1	
	Max	1.5	1.2	1.5		2.2	2.2	1.4		2.2	2.2	1.5	
	p-value (m vs. f in Nuuk)	ns											
	p-value (m vs. f in non-Nuuk)	ns											
Smoking	n	74	5	69	ns	190	127	63	ns	264	132	132	ns
	Yes (%)	48 (64.9%)	4 (80%)	44 (63.8%)		134 (70.5%)	91 (71.7%)	43 (68.3%)		182 (68.9%)	95 (72%)	87 (65.9%)	
	No (%)	26 (35.1%)	1 (20%)	25 (36.2%)		56 (29.5%)	36 (28.3%)	20 (31.7%)		82 (31.1%)	37 (28%)	45 (34.1%)	
	p-value (m vs. f in Nuuk)	ns											
	p-value (m vs. f in non-Nuuk)	ns											

*Nuuk vs. non-Nuuk; [a]adjusted for age. m = male, f = female. ns = not significant ($p > 0.05$).

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Table II. Serum levels of PFAAs and legacy POPs of Greenlandic Inuit participants

		Male				Female				Male + Female			
Parameters		All	Nuuk	Non-Nuuk	p-value* (#)	All	Nuuk	Non-Nuuk	p-value* (#)	All	Nuuk	Non-Nuuk	p-value* (#)
PFOS (ng/ml)	n	74	5	69	<0.0001	209	137	72	<0.0001	284	142	142	<0.0001
	Median	14.9	74.5	13.0	(0.003)	19.5	28.5	10.5	(0.001)	18.5	29.9	12.2	(0.006)
	Min	3.96	54.7	4.0		1.5	3.70	1.53		1.53	3.70	1.5	
	Max	213	213	103.0		172	172	83.1		213	213	103.0	
PFOA (ng/ml)	n	74	5	69	<0.0001	209	137	72	<0.0001	284	142	142	<0.0001
	Median	0.94	7.2	0.9	(<0.0001)	1.7	2.57	0.52	(<0.0001)	1.45	2.6	0.9	(<0.0001)
	Min	0.20	4.4	0.2		0.2	0.36	0.20		0.20	0.4	0.2	
	Max	10.8	10.8	8.6		7.8	7.79	4.10		10.8	10.8	8.6	
ΣPFSAs	n	74	5	69	<0.0001	209	137	72	<0.0001	284	142	142	<0.0001
(ng/ml)	Median	16.6	81.9	15.1	(0.002)	23.1	31.5	11.6	(<0.0001)	21.6	32.7	13.6	(0.005)
	Min	4.5	63.7	4.5		2.0	4.70	2.0		2.0	4.7	2.0	
	Max	229.0	229.0	113.0		184.0	184	90.1		229	229.0	113.0	
ΣPFCAs	n	74	5	69	<0.0001	209	137	72	<0.0001	284	142	142	<0.0001
(ng/ml)	Median	2.8	24.0	2.8	(<0.0001)	4.5	6.06	2.35	(<0.0001)	3.84	6.2	2.6	(<0.0001)
	Min	1.3	13.4	1.3		1.0	1.63	0.96		0.96	1.63	1.0	
	Max	43.0	43.0	16.9		28.1	28.1	16.3		43.0	43.0	16.9	
ΣPCBs	n	74	5	69	0.38	189	126	63	<0.0001	264	131	133	<0.0001
(μg/kg lipid)	Median	1630.5	3927.9	1550.8	(0.36)	1752.7	1990.6	1015.1	(0.21)	1739.1	1995.2	1350.6	(0.002)
	Min	201.6	560.8	201.6		92.7	207.8	92.7		92.7	207.8	92.7	
	Max	16827.5	4600.5	16827.5		11275.3	5640.2	11275.3		16827.5	5640.2	16827.5	
ΣPesticides	n	74	5	69	0.45	189	126	63	<0.0001	264	131	133	0.01
(μg/kg lipid)	Median	2857.8	4111.7	2685.7	(0.04)	2644.0	2764.0	1366.0	(0.01)	2666.6	2795.8	2123.7	(<0.0001)
	Min	203.0	916.2	203.0		92.5	175.3	92.5		92.5	175.3	92.5	
	Max	15610.4	7417.9	15610.4		10939.3	9284.5	10939.3		15610.3	9284.8	15610.4	
Σlegacy POPs	n	74	5	69	0.43	189	126	63	<0.0001	264	131	133	0.003
(μg/kg lipid)	Median	5075.5	8324.9	4366.1	(0.10)	4433.4	4592.8	2557.3	(0.04)	4433.9	4618.2	3627.1	(<0.0001)
	Min	473.3	1477.0	473.3		187.8	383.2	187.8		187.8	383.2	187.8	
	Max	25681.1	11345.7	25681.1		20073.3	13950.4	20073.3		25681.1	13950.4	25681.1	

*Nuuk vs. non-Nuuk; (#) p-value of Nuuk vs. non-Nuuk after adjustment for age and n-3/n-6; Σlegacy POPs is the summation of PCBs and pesticides (ΣPCBs + ΣPesticides). Two subjects from Upernavik district had relatively high values of PFAAs (PFOS: 91.8 and 74.9 ng/ml; PFOA: 8.6 and 4.0 ng/ml; ΣPFSA: 101 and 83.5 ng/ml; ΣPFCA:12.8 and 9.85ng/ml). However, similar results were obtained upon including and excluding these 2 subjects. ns = not significant ($p > 0.05$).

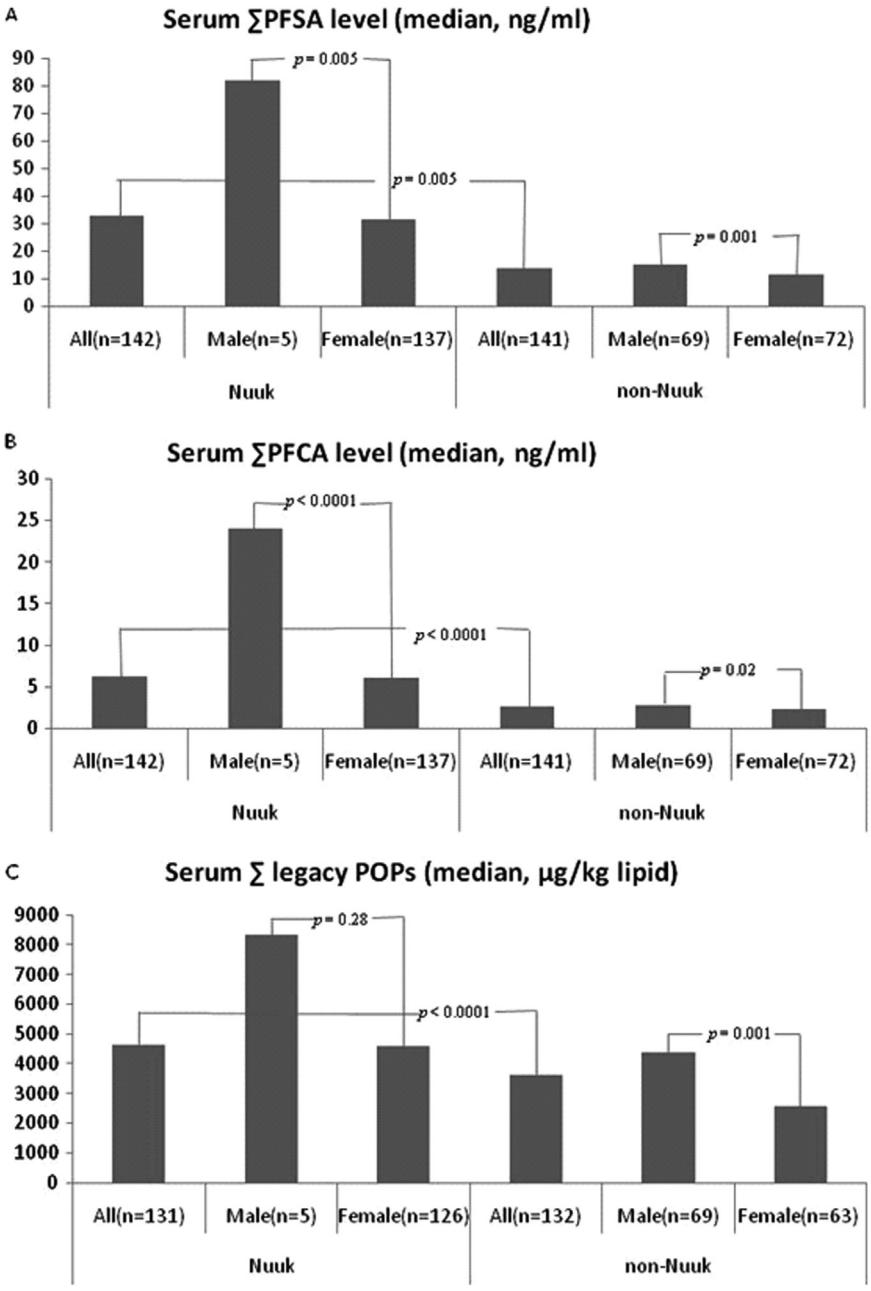

Fig. 2. Serum levels of PFAAs and legacy POPs of Greenlandic Inuit. A) ΣPFSAs (PFOS + PFHxS + PFOSA); B) ΣPFCAs (PFHpA + PFOA + PFNA + PFDA + PFUnA + PFDoA + PFTrA); C) Σlegacy POPs (ΣPCBs + Σpesticides). P-values were adjusted for age and n-3/n-6.

size of Nuuk males must be taken intoconsideration (Figure 2C).

Correlation between serum lifestyle factors and PFAAs, legacy POPs

A significant but weakly positive correlation between age and serum PFAA levels ($r \leq 0.29$, $p \leq 0.001$) was observed in non-Nuuk Inuit. For the Nuuk Inuit, in general, PFAAs were not significantly correlated to age (Supplementary Table I a, www.ijch.fi). A relatively weak correlation between serum concentrations of ΣPFSAs and ΣPFCAs and n-3/n-6 ($r < 0.27$, $p < 0.05$) was observed for both Nuuk and non-Nuuk Inuit (Supplementary Table I a, www.ijch.fi). Legacy POPs significantly correlated with age ($r > 0.42$, $p < 0.0001$) and n-3/n-6 ($r > 0.60$, $p < 0.0001$) (Supplementary Table I a, www.ijch.fi).

Positive correlations among PFAA levels with both age and seafood intake were also observed for both genders. In general, the correlations found in female Inuit were higher than those in male Inuit, while the correlations

between age, n-3/n-6 and legacy POPs between genders were similar (Supplementary Table I b, www.ijch.fi). For male Inuit, the correlation between n-3/n-6 and PFAAs was weaker than that between legacy POPs and n-3/n-6 (Supplementary Table I b, www.ijch.fi).

Correlation between PFAAs and legacy POPs

To explore whether the sources for the body burden of PFAAs and legacy POPs in Green-landic Inuit were identical, we analysed the correlation between serum PFAAs and legacy POPs. For the Nuuk Inuit, positive correlations between serum PFOS, ΣPFSAs, ΣPFCAs and Σ legacy POPs were observed. But after adjustment for age and seafood intake (n-3/n-6), the significant correlations of PFOS and ΣPFSAs with Σlegacy POPs disappeared (Table III). For the non-Nuuk Inuit, significant correlations between serum PFAAs and legacy POPs were observed both before and after adjustments for age and n-3/n-6 (Table III). The correlation between PFAAs and legacy POPs was also different between genders. For the male Nuuk Inuit no correlations were observed, possibly because of the low number of males in the study (n = 5). For non-Nuuk males the significant correlation between PFAAS and legacy POPs disappeared after adjustment for age and n-3/ n-6. For non-Nuuk female Inuit and for female Inuit in general, serum PFAAs significantly correlated to legacy POPs both before and after adjustment for age and n-3/n-6, whereas for Nuuk females alone the significance disappeared upon adjustment (Table III).

Time trend of serum PFAAs levels for Nuuk Inuit

Temporal trend analysis was performed for the district of Nuuk, where a sufficient number of samples were available for the period 1998–2005. As shown in Table IV, PFOS level and ΣPFCA level showed 2.2% and 7.1% yearly increasing trends, respectively, for female Inuit. For the pooled gender data, 28%, 28%, 10%, 13% and

Table III. Association between serum PFCs and serum legacy POPs

			PFOS		PFOA		ΣPFSA		ΣPFCA	
Gender	District		raw	adjusted	raw	adjusted	raw	adjusted	raw	adjusted
Male + female	Nuuk	n	131	131	131	131	131	131	131	131
		$\beta_{\Sigma legacyPOPs}$	0.39	0.32	0.03	0.09	0.38	0.31	0.45	0.32
		p	0.004	0.08	0.82	0.54	0.005	0.08	<0.0001	0.04
	non-Nuuk	n	131	125	131	125	131	125	131	125
		$\beta_{\Sigma legacyPOPs}$	0.49	0.55	0.20	0.34	0.47	0.54	0.29	0.26
		P	<0.0001	<0.0001	0.01	0.001	<0.0001	<0.0001	<0.0001	<0.0001
	Nuuk + non-Nuuk	N	262	256	262	256	262	256	262	256
		$\beta_{\Sigma legacyPOPs}$	0.54	0.38	0.28	0.09	0.52	0.36	0.42	0.16
		P	<0.0001	<0.0001	<0.0001	0.29	<0.0001	<0.0001	<0.0001	0.02
Male	Nuuk	n	5	5	5	5	5	5	5	5
		$\beta_{\Sigma legacyPOPs}$	0.14	−0.25	−0.01	−0.38	0.15	−0.21	0.31	−0.35
		P	ns	ns	ns	ns	ns	ns	ns	ns
	non-Nuuk	n	68	63	68	63	68	63	68	63
		$\beta_{\Sigma legacyPOPs}$	0.33	0.27	−0.08	−0.04	0.32	0.27	0.22	0.11
		p	0.002	ns	ns	ns	0.003	ns	0.01	ns
	Nuuk + non-Nuuk	n	73	68	73	68	73	68	73	68
		$\beta_{\Sigma legacyPOPs}$	0.37	0.13	−0.30	−0.19	0.35	0.14	0.27	−0.03
		P	0.002	ns	ns	ns	0.002	ns	0.01	ns
Female	Nuuk	n	126	126	126	126	126	126	126	126
		$\beta_{\Sigma legacyPOPs}$	0.38	0.31	−0.01	0.07	0.36	0.30	0.42	0.30
		p	0.007	ns	ns	ns	0.009	ns	<0.0001	0.05
	non-Nuuk	n	62	62	62	62	62	62	62	62
		$\beta_{\Sigma legacyPOPs}$	0.56	0.65	0.30	0.40	0.53	0.63	0.31	0.31
		p	<0.0001	<0.0001	0.001	0.001	<0.0001	<0.0001	<0.0001	0.002
	Nuuk + non-Nuuk	n	188	188	188	188	188	188	188	188
		$\beta_{\Sigma legacyPOPs}$	0.65	0.46	0.45	0.19	0.62	0.44	0.51	0.24
		p	<0.0001	<0.0001	<0.0001	ns	<0.0001	<0.0001	<0.0001	0.009

$\beta_{\Sigma legacy\ POP}$ is the regression coefficient of PFAAs to Σlegacy POPs. Σlegacy POPs is the summation of PCBs and pesticides (ΣPCBs + ΣPesticides). Adjusted data was adjusted for age and n-3/n-6. ns = not significant ($p > 0.05$).

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Table IV. Time trend of serum concentrations (ng/ml) of PFAAs in Greenlandic Inuit from Nuuk in the period 1998–2005

		PFOS	PFOA	PFNA	PFDA	PFDoA	PFTrA	ΣPFSAs	ΣPFCAs
Raw	n	**137**	137	137	137	137	137	137	**137**
(female only)	Slope (%)	**2.2**	0.16	20	20	3.3	4.6	2.1	**7.1**
	95% CI	**1.2,3.1**	−20,20	−15,55	−9.8,50	−13,20	−13,22	−2.9,7.0	**2.4,12**
	p-value	**<0.02**	ns	ns	ns	ns	ns	ns	**<0.03**
Adjust age	n	137	137	137	137	137	137	137	137
(female only)	Slope (%)	−1.3	−0.57	3.0	2.8	−0.89	−0.79	−1.5	0.97
	95% CI	−29,27	−27,26	−42,48	−54,59	−33,31	−48,47	−30,27	−42,44
	p-value	ns	ns	ns	ns	ns	ns	ns	ns
Raw	n	142	142	**142**	**142**	**142**	**142**	142	**142**
(male + female)	Slope	9.8	5.7	**28**	**28**	**10**	**13**	9.2	**15**
	95% CI	−6.2,26	−24,36	**4.4,5.2**	**8.9,47**	**5.7,15**	**11,15**	−9.4,28	**4.5,25**
	p-value	ns	ns	**<0.05**	**<0.03**	**<0.02**	**<0.009**	ns	**<0.03**
Adjust age	n	142	142	142	142	142	142	142	142
(male + female)	Slope	0.96	1.4	4.1	4.3	0.42	−0.51	0.85	2.7
	95% CI	−40,42	−42,45	−60,69	−55,63	−42,43	−50, 49	−42,43	−51,56
	p-value	ns	ns	ns	ns	ns	ns	ns	ns

Slope: yearly difference; values in bold indicate that the trend is statistically significant.
ΣPFSAs: PFOS + PFHxS + PFOSA; ΣPFCAs: PFHpA + PFOA + PFNA + PFDA + PFUnA + PFDoA + PFTrA.
Time trend analysis was not performed for the male Inuit because there were only 5 males studied in Nuuk.
For other test PFAAs, no time trend was observed. ns = not significant ($p > 0.05$).

15% yearly increasing trends were found for PFNA, PFDA, PFDoA, PFTrA and ΣPFCAs, respectively. The trends were statistically significant ($p < 0.05$). However, after adjustment for age, the significant trend disappeared (Table IV). No significant time trend was observed for the serum level of PFOA and ΣPFSA before and after adjustment for age (Table IV), and neither for PFHxS, PFOSA, PFHpA or PFUnA (data not shown).

Discussion

The range observed for serum PFOS and PFOA in all the Greenlandic districts in the present study corresponded to the range observed in European biomonitoring studies of general populations (14) although the PFOA was found slightly lower in Inuit (11,14). The serum PFOS level of Nuuk Inuit were comparable to those observed in Europeans from Sweden and from Northern Bavaria, Germany, while non-Nuuk Inuit had a lower level of PFOS – similar to that of Europeans in Southern Bavaria, Germany, and in Tarragona, Spain (14). The median serum PFOS and PFOA concentrations in male Greenlandic Inuit were lower than the plasma levels of PFOS and PFOA in Danish men (39).

Very few data are available for PFAA serum concentrations from other Arctic locations; the literature data that are available are summarized in Table V. The range of mean concentrations of PFOS and PFOA in the other Arctic studies were 9.3–36.9 ng/ml and 1.0–3.4 ng/ml, respectively, while the mean concentrations of PFOS and PFOA of Green-landic Inuit reported in the present study were 33.3 ng/ml and 2.3 ng/ml, respectively (Table V). The size of our data set is larger than most of the other Arctic data. Moreover, both male and female samples were included in the present study, thus avoiding the bias that could be generated by only including serum samples from one gender. The PFOS mean concentration (33.3 ng/ml) of the Greenlandic Inuit in this study was slightly higher than the value (25.7 ng/ml) reported by Chateau-Degat et al., which also included male and female Inuit (40). PFOS concentrations reported in other Arctic studies including relatively few female subjects were generally lower than the PFOS levels of Greenlandic Inuit observed in the present study (Table V). However, the mean PFOA level of the pooled Greenlandic Inuit in our study was comparable to the other reported Arctic studies (Table V).

We did observe gender differences in PFAA levels; Greenlandic Inuit within the same district tended to be in accordance with the majority of studies on gender dependency of PFOS serum concentrations (14), with higher levels in male donors. This gender difference has been partially explained by increased excretion through menstrual flow (41), transplacental transfer of PFOS and other PFAAs to the developing foetus and transfer via milk during breastfeeding in females of younger ages (42). Other explanations of lower levels in women rely on higher renal clearance of PFAAs in women and longer half-lives in males, based on studies of laboratory rodents (14). But the last assumption might not be completely true, as better renal clearance in females was not observed in other species (dogs, rabbits and mice) (14), and no sex

Table V. Summary of PFOS and PFOA serum concentrations reported for Arctic populations. Concentrations are given in ng/ml

Location	Population	Sampling period	Gender (number of samples)	Mean age (min–max)	PFOS mean concentration (min–max)	PFOA mean concentration (min–max)	Reference
Greenland (10 districts)	Inuit	1997–2006	Male + Female (284*)	46.0 (18.0–73.0)	33.3 (1.5–213)	2.3 (0.20–10.8)	Present study
			Male (74)	39.0 (18.0–73.0)	32.9 (4.0–213)	2.3 (0.20–10.8)	
			Female (209)	49.0 (18.0–66.0)	33.5 (1.5–172)	2.3 (0.20–7.8)	
Northwest and Nunavut Territories (Canada)		1994–2001	Female (10 pooled maternal blood)		36.9 (2.8–57.9)	2.20 (0.5–5.5)	Tittlemier et al. (27)
Nunavik (Canada)	Inuit	2004	Male + Female (723)	36.9 (18.0–74.0)	25.7	-	Chatean-Degat et al. (40)
			Male (325)	36.6	28.2		
			Female (395)	37.0	23.1	-	
Yup'ik (Alaska, USA)		2004–2006	Female (180-202)	26.0	7.40 (<0.2–28.0)	1.0 (<0.1–4.3)	AMAP (20)
Bodø (Norway)		2004	Female (12)	39.0 (29.0–48.0)	16.0 (9.0–29.0)	2.3 (1.7–7.0)	AMAP (20)
Kiruna (Sweden)		2006	Female (25)	27.0 (22.0–33.0)	8.10 (1.2–22.0)	1.6 (<LOD–3.6)	AMAP (20)
Taimyr (Russia)		2002	Female (12)	26.0 (20.0–35.0)	9.30 (5.1–14.0)	2.2 (1.2–5.7)	AMAP (20)
Naryan Mar (Russia)		2002	Female (12)	30.0 (22.0–35.0)	16.0 (5.0–49.0)	1.7 (0.8–5.2)	AMAP (20)
Faroe Islands		2000–2001	Female (12)	pregnant**	25.5 (16.4–38.3)	2.6 (0.1–4.0)	Weihe et al. (28)

*One sample had no gender information.
**Age of the pregnant women was unknown.

difference was found in the renal clearance of humans (41). Moreover, our data do not support the hypothesis that the higher PFAA levels in males were due to a higher intake of traditional marine food, because males and females had similar seafood intake (n-3/n-6). Moreover, after adjustment for age and n-3/n-6, the PFAA differences between genders were still statistically significant. We suggest that other sources must contribute to the higher levels of PFAAs in male Greenlandic Inuit.

Since PFAAs are very persistent, the body burden of PFAAs may increase with age. Studies investigating the dependency of PFAA serum concentrations on age have given inconsistent results, with some studies reporting statistically significant correlations (17,36), and others not observing any correlations (16,43). In this study, no correlation was observed between PFAAs and age for Nuuk Inuit, while significant correlation was found for non-Nuuk Inuit. Because the median age of non-Nuuk Inuit was lower than that of Nuuk Inuit in this study, this discrepancy may be related to the fact that the lifestyle of younger individuals could pose a higher chance of exposure to PFAAs (via clothing or consumption of food items that have been in close contact with packaging containing PFCs) (26,44).

Dallaire et al. also observed an age dependency of PFOS plasma concentrations, with older individuals having higher concentrations (26). This was partially explained by the fact that marine food intake also increases with age. Consumption of traditional food has been suggested to be an important source of PFAA exposure for Indigenous Arctic populations (28,45). Dallaire et al. indicated that consumption of fish and marine mammals, male gender and age were the strongest predictors of PFOS plasma concentrations in the investigated Inuit population. However, diet, gender and age could account for only 28% of the variation in PFOS concentrations (26). In the present study, we observed that the correlation between PFAAs and seafood intake was weaker than the correlation between legacy POPs and seafood intake, suggesting that seafood intake might be the main source for legacy POPs and to a lesser degree for PFAAs. Thus other factors may contribute to PFAA exposure in the Inuit populations, such as consumer products (e.g., impregnation spray for outdoor clothing) and different indoor sources (e.g., house dust in carpeted houses). Moreover, our data are supported by the study of Tittlemier and co-workers, which suggested that a diet based on traditional foods does not contribute to higher body burdens of PFAAs to the same degree as has been observed for legacy POPs (27).

Similarly to the data reported by Fromme and co-workers (36), the correlation between PFAAs and marine food intake observed for male Inuit in the present study was weaker than that observed for female Inuit, suggesting that sources other than n-3/n-6 might also contribute to the higher PFAA levels in male Inuit. Moderately positive correlations were observed between legacy POPs and age as well as n-3/n-6, similar to previous reports (21,35,46). In male Inuit, the correlation between legacy POPs and n-3/n-6 was stronger than the correlation between PFAAs and n-3/n-6, further suggesting that other sources might play a more important role than seafood intake in the higher body levels of PFAAs in Greenlandic male Inuit as observed in the present study.

The correlation between PFAAs and legacy POPs differed between districts. For Nuuk Inuit, no significant association was observed between PFAAs and legacy POPs, suggesting that sources of serum PFAAs and legacy POPs in Nuuk Inuit might vary. For non-Nuuk Inuit, significant correlations between serum PFAAs and legacy POPs were observed both before and after adjustments for age and n-3/n-6, suggesting that there might be common sources for the body burden of PFAAs and legacy POPs in non-Nuuk Inuit. The correlation between PFAAs and legacy POPs was also different between genders; no correlation was found for male Inuit and a significant correlation was observed for females, further suggesting that sources other than seafood intake played an important role in the body burden of PFAAs and legacy POPs for male Greenlandic Inuit.

Overall, our data indicate that the sources contributing to the body burden of PFAAs and legacy POPs might be different for Nuuk Inuit when compared to non-Nuuk Inuit. These sources seem to be something other than seafood intake. Further studies are needed to clarify the PFAA and legacy POP exposure routes of Green-landic Inuit.

For female Nuuk Inuit, we observed an age-dependent, increasing trend of PFOS and ΣPFCAs. We also observed increasing, age-dependent trends for PFNA, PFDA, PFDoA and PFTrA in all Nuuk Inuit during the period between 1998 and 2005. However, we cannot conclude that there was an increasing trend of PFAAs in Nuuk Inuit during 1998–2005, since the significant trend disappeared upon adjustment forage and only 4 years of data series were used in the present study. However, neither did we observe an obvious decreasing trend for PFAAs in Nuuk Inuit. Further research including more time series is needed to study the time trend of PFAAs in Greenlandic Inuit.

In conclusion, the levels of PFOS and PFOA of Greenlandic Inuit were comparable to those found in European populations and were similar to, or slightly higher than, those of other Arctic populations. The PFAA serum levels differed between the 2 district groups, with higher levels found in the Nuuk district than the pooled non-Nuuk districts. Within the districts, higher PFAA levels were found for males. Sources for the body burden of PFAAs and legacy POPs in Greenlandic Inuit

might differ and sources other than seafood intake should be taken into consideration when assessing the body levels of PFAAs in Greenlandic Inuit, especially for male Inuit. An age-dependent, but no obvious increasing trend of serum PFAAs in Nuuk was observed during 1998–2005.

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None to declare

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