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Perfluoroalkyl acids in pregnant women from Nunavik (Quebec, Canada): Trends in exposure and associations with country foods consumption

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ABSTRACT

Background: Perfluoroalkyl acids (PFAAs) are persistent and ubiquitous environmental contaminants that potentially disrupt endocrine system functions. While some PFAAs (perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA)) are regulated, currently used fluorotelomer alcohols (FTOHs) can be transported to the Arctic and are degraded in a number of PFAAs which biomagnify in Arctic wildlife (e.g. perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUdA)).

Objectives: From 2004 to 2017, 279 pregnant Inuit women were recruited as part of biomonitoring projects in Nunavik. Our goal was to evaluate: (i) time-trends in plasma/serum PFAAs levels in pregnant Nunavimmiut women between 2004 and 2017; (ii) compare plasma/serum PFAAs levels in Nunavimmiut women in 2016–2017 to those measured in women of childbearing age in the Canadian Health Measure Survey (CHMS); and (iii) evaluate the associations of PFAAs levels with the consumption of country foods and pregnancy and maternal characteristics during pregnancy in the 97 participants recruited in 2016–2017.

Methods: Individual blood sample were collected for serum or plasma PFAAs (PFOS, PFOA, pentafluorobenzoic acid (PFBA), perfluorohexanoic acid (PFHxA), perfluorobutanesulfonic acid (PFBS), perfluorohexane-1-sulfonic acid (PFHxS), PFNA, PFDA, PFUdA) analyses. Socio-demographic data, pregnancy and maternal characteristics and country foods consumption were documented using a questionnaire. Omega-3 and −6 polyunsaturated fatty acids (PUFA) were measured in red blood cell membranes and their ratio used as a biomarker of marine country foods consumption. Time-trends in PFAAs levels were evaluated using ANCOVA models adjusted for relevant co-variables. Serum/plasma levels of PFAAs in the 97 pregnant women aged 16 to 40 years old and recruited in 2016–2017 were compared to those measured in women aged 18 to 40 years old from the CHMS cycle 5 (2016–2017) using the geometric means (GM) and 95% confidence intervals (95% CI). Multivariate regression analyses were performed to examine associations between concentrations of PFAAs and country foods consumption data.

Results: Statistically-significant downward time trends were noted for concentrations of PFOS, PFOA and PFHxS in pregnant Nunavik women between 2004 and 2017. Conversely, between 2011 and 2016–2017, PFNA, PFDA and PFUdA maternal serum levels increased by 19, 13 and 21% respectively. Among participants in 2016–2017, mean concentrations for PFNA (GM: 2.4 μg/L), PFDA (0.53 μg/L) and PFUdA (0.61 μg/L) were higher than those measured in women aged 18–40 years old in the Cycle 5 (2016–2017) of the CHMS. PFOA (0.53 μg/L) and PFHxS (0.26 μg/L) were lower than in CHMS, whereas PFBA, PFHxA and PFBS were not detected in 2016–2017. Ratios of serum/plasma levels of PFNA/PFOA, PFNA/PFOS, PFNA/PFHxS and PFUdA/PFDA were significantly higher in the 97 pregnant women from Nunavik recruited in 2016–2017 compared to CHMS, highlighting their distinct

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exposure profile. In multivariate models, PFHxS, PFOS, PFNA, PFDA and PFUdA levels in 2016–2017 were strongly associated with the omega-3/omega-6 PUFA ratio, indicating a positive association between marine country foods consumption and higher exposure to PFAAs.
Conclusions: The exposure of pregnant women to long-chain PFAAs (PFNA, PFDA and PFUdA) increased from 2004 to 2017 in Nunavik. Associations noted between PFAAs levels and the omega-3/omega-6 ratio highlights the importance of implementing additional strict regulations on PFAAs and their precursors to protect the high nutritional quality and cultural importance of country foods in Nunavik.

1. Introduction

Per- and polyfluoroalkyl substances (PFASs) are a large family of synthetic compounds with various industrial, commercial and residential applications and used for their ability to repel both oil and water (Buck et al., 2011). Increasingly recognized for their human toxicity, these persistent and ubiquitous chemicals have multiple bioaccumulation pathways and a very large number of parent and degradation congeners. These characteristics make them some of the most complex contemporaneous industrial contaminants to study from analytical, toxicological, epidemiological and regulatory perspectives (Sunderland et al., 2019; Xiao, 2017).

Perfluoroalkyl acid (PFAAs) congeners are exceptionally stable and highly mobile in the environment, which leads to high concentrations in the Arctic (e.g. in air, snow, soil, water and sediments (AMAP 2017)) through long-range atmospheric and oceanic transport (Li et al., 2018; MacInnis et al., 2017; Wong et al., 2018). PFAAs chemicals accumulate in the food chain and have also been measured in many wildlife species consumed by Inuit populations living in the Arctic, such as marine mammals, fish, caribou and other species (AMAP, 2017; Muir et al., 2019). These congeners include perfluoroalkane sulfonates (PFSAs) such as perfluorooctane sulfonate (PFOS) and perfluorohexane sulfonate (PFHxS), as well as perfluoroalkyl carboxylic acids (PFCAs) including perfluorooctanoic acid (PFOA), and several long-chain PFAAs with 9 and more carbons such as perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA) and perfluoroundecanoic acid (PFUdA). Whereas PFOS is banned under the Stockholm Convention since 2009, PFOA was included in the Convention only recently (May 2019) and PFHxS is still under review for its inclusion (UN Environment Programme 2019). Nevertheless, the use of all these PFAAs has been restricted in North America (Government of Canada, 2018; Houde et al., 2006; Muir et al., 2019; Paul et al., 2009). However, increasing levels of long-chain PFCAs (e.g PFNA, PFDA, PFUdA) have been reported in Arctic terrestrial and marine wildlife in different circumpolar regions (Muir et al., 2019).

PFAAs are also degradation products of other more neutral PFASs such as fluorotelomer alcohols (FTOHs), which are still used as intermediates in many consumer and industrial products (e.g. paints, electronics, food packaging, waxes) (Dinglasan et al., 2004). FTOH are volatile, less persistent and detected ubiquitously in air (Stock et al., 2004). They are increasingly detected in the Arctic atmosphere, particularly 8:2 FTOH, but are not reported to accumulate in marine or terrestrial biota (Muir et al., 2019). Conversely, through environmental oxidation or biotransformation, FTOH are precursors of PFOA and also to a lesser extent to PFNA, PFDA, PFUnDA and others. For example, whereas 8:2 FTOH primarily metabolises into PFOA and PFNA (Martin et al., 2005), 10:2 FTOH metabolises into PFOA, PFDA and PFUnDA (Brandsma et al., 2011; Ellis et al., 2004; Martin et al., 2005). Thus, FTOHs have been indicated as an important additional source of PFCAs bioaccumulation in Arctic wildlife (Ahrens et al., 2011; Shoeib et al., 2006). The bioaccumulation potential of PFAAs is greater for PFOS and long-chain PFCAs with 9 and more carbons (D'Hollander, 2010a; Eriksson et al., 2016; Haukås et al., 2007; Müller et al., 2011; Xu et al., 2014). Interestingly, Byrne et al. (2017); Hu et al. (2018) recently reported that increasing serum concentration of PFOS and an elevated proportion of C9-C12 PFCAs in human serum was associated with marine food consumption in a Faroese community and Alaskan Natives communities.

Country foods are an integral part of Inuit culture and are crucial to sustain food security, nutrition, and healthy pregnancies and infants (Council of Canadian Academies, 2014). Indeed, they are rich in omega-3 polyunsaturated fatty acids, several proteins and vitamins, iron and selenium, and are well known to contribute to a higher dietary quality in Inuit communities (Kenny et al., 2018; Lemire et al., 2015). Therefore, it is essential to ensure that country foods can be safely consumed throughout life without increasing risk of exposure to potentially harmful contaminants.

A growing body of scientific literature highlights the potential health effects of prenatal PFAAs exposure. Indeed, exposure to these chemicals (e.g. PFHxS, PFOS, PFOA, PFNA) has been associated with alteration of thyroid hormone levels in adults, including pregnant women (Ballesteros et al., 2017; Blake et al., 2018; Ji et al., 2012; Lewis et al., 2015; Melzer et al., 2010; Shrestha et al., 2015; Wen et al., 2013; Winquist and Steenland, 2014), and children (Ballesteros et al., 2017; Caron-Beaudoin et al., 2019; Lin et al., 2013; Lopez-Espinosa et al., 2012). Prenatal exposure to PFHxS, PFOS, PFOA and PFNA has also been associated with suppressed immune responses during childhood (Dalsager et al., 2016; Pennings et al., 2016), and exposure to PFOA and PFNA *in utero* or during childhood has also been associated with some neurotoxic outcomes, including poorer executive function and behavior in boys (Vuong et al., 2018), and lower verbal IQ in children of both sexes (Wang et al., 2015). It is unclear if exposure to FTOH is associated with deleterious health effects, as these alcohols are rapidly metabolized to PFCAs (Nilsson et al., 2013).

Between 2004 and 2017, 279 pregnant Inuit women were recruited to participate in projects aiming to contribute to ongoing biomonitoring efforts in Nunavik and at the international level. Given the increasing levels of some PFAAs congeners in the Canadian Arctic (Muir et al., 2019), the bioaccumulation of PFAAs in wildlife consumed by communities in Nunavik (Byrne et al., 2017) and the potential health effects associated with exposure to these compounds during pregnancy (Ballesteros et al., 2017; Wang et al., 2014; Webster et al., 2014), it is paramount to assess the trends in exposure to these chemicals and their association with the country foods consumption. Therefore, the objective of the present study were: (i) to evaluate maternal PFAAs exposure time-trends since the first time they were measured in Nunavik (2004, 2007 or 2012, depending on the congener) in the context of international and national regulations; (ii) to compare plasma/serum PFAAs levels in Nunavimmiut women in 2016–2017 to those measured in women of childbearing age in the 5th cycle of the Canadian Health Measure Survey (CHMS); and (iii) to measure the associations of PFAAs levels with the consumption of country foods and pregnancy and maternal characteristics during pregnancy in the 97 participants recruited in 2016–2017. Only the participants recruited as part of the NQN study were included to measure the associations between country foods consumption and exposure to PFAAs because this study includes the most comprehensive data on exposure to PFAAs congeners and food frequency consumption.

2. Material and methods

2.1. Recruitment of participants in 2016–2017 and in previous biomonitoring studies

The *Nutaratsaliit qanuingisiarningit niqituinnanut* - Pregnancy Wellness with Country Foods (NQN) project is a cross-sectional study that was conducted between October 2016 and March 2017. The study population targeted all pregnant women at that time in the 14 communities of Nunavik (Fig. 1). Inuit pregnant women, aged 16 years old and older and living in Nunavik were eligible to participate. Recruitment was done on a voluntary basis (convenience sample) by a research nurse primarily based on the list of pregnant women that were provided by the Ungava Tulattavik Health Centre & Inuulitsivik Health centre based in Kuujjuaq and Puvirnituq respectively. The NQN project, in collaboration with the Nunavik Regional Board of Health and Social Services (NRBHSS) and midwifes, nurses and physicians from Tulattavik and Inuulitsivik hospitals, maternity centres and local health clinics, was approved by the Nunavik Nutrition and Health Committee (NNHC). Ethical approval was obtained from the Research Ethics Board of the CHU de Québec – Université Laval (no. 2017–3176). To be granted the right to access the Tulattavik and Inuulitsivik hospitals list of pregnant women and medical records, an authorization form was signed by the research team. Confidentiality agreements were also signed by the research team and the interpreters engaged in fieldwork activities. All pregnant women who agreed to participate signed an informed consent form.

Previous biomonitoring projects involving pregnant women in Nunavik were also realised in 2004 (n = 31, plasma samples, study: Qanuippitaa? Nunavik Inuit Health Survey) (Anctil et al., 2008; Valera et al., 2009), 2007 (n = 40, plasma samples, study: Monitoring Spatial and Temporal Trends of Environmental Pollutants in Maternal Blood in Nunavik) and 2011–2012 (n = 111, serum samples, study: Monitoring Spatial and Temporal Trends of Environmental Pollutants in Maternal Blood in Nunavik) (Adamou et al., 2020). PFAAs congeners were measured in individual plasma/serum samples collected as part of these biomonitoring projects. A database was created from these individual analyses. This database enables temporal trends assessment of PFAAs serum/plasma concentrations over 2 to 4 time points, covering a period of 13 years for PFOS (2004 to 2016–2017), of 10 years for PFOA and PFHxS (2007 to 2016–2017) and of 5 years for long-chain PFAAs (PFNA, PFDA and PFUdA) as well as PFBS, PFHxA and PFBA (2011–2012 and 2016–2017). Using this database, the geometric means and 95% confidence intervals were calculated by year for each PFAAs congeners. All studies were designed by the same research team at CHU de Québec Research Centre – Université Laval, followed the same research protocol, data collection methods and all contaminant analyses were conducted in the same laboratory. More details are provided elsewhere (Adamou et al., 2020).

2.2. Samples and questionnaires in 2016–2017

During a visit at the local community center, a research nurse collected a blood sample from each participant and administered a questionnaire covering pregnancy details, sociodemographic data,

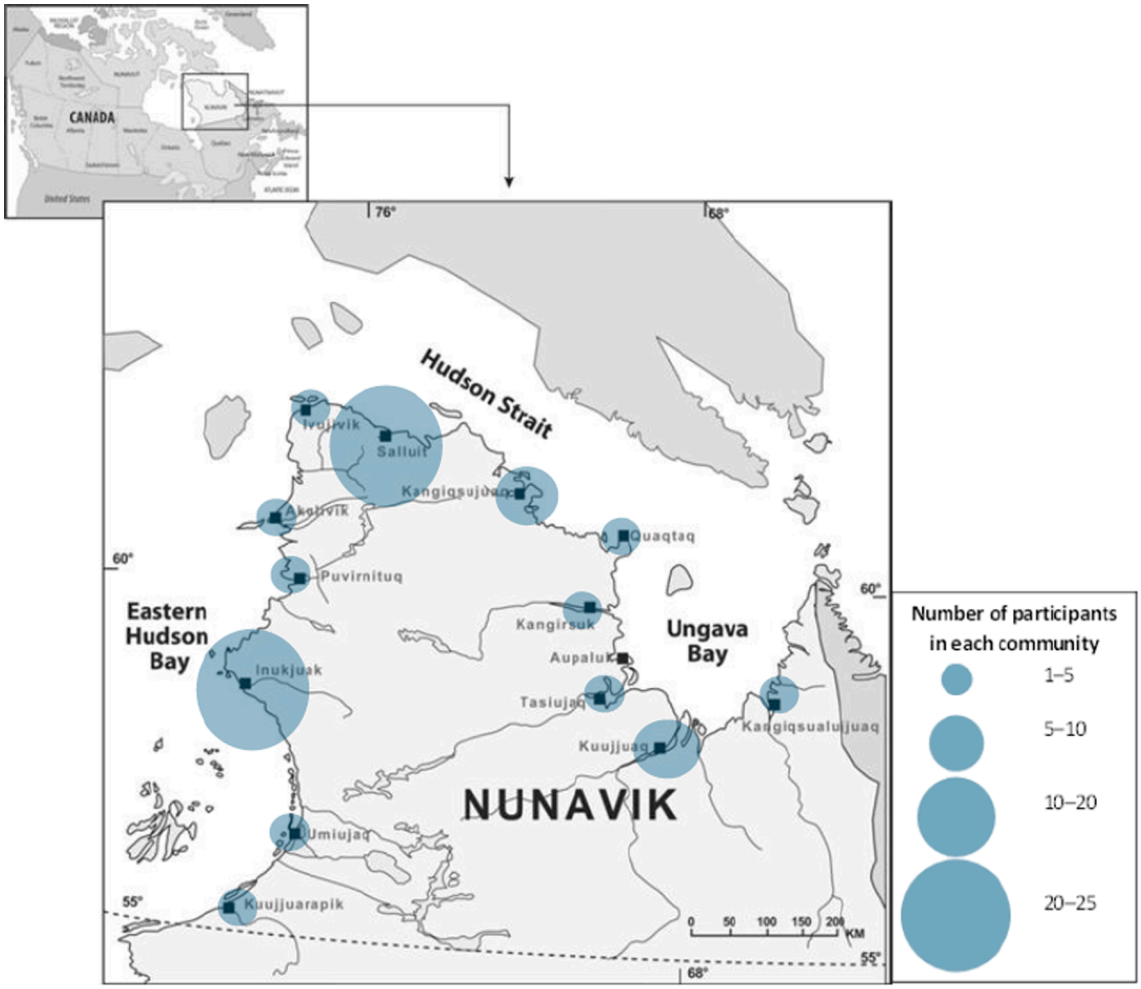

Fig. 1. Map of Nunavik displaying the number of participants in each community in 2016–2017. Derived from Lemire et al. (2015).

lifestyle habits and the season-specific frequency of country foods consumption. Blood samples were collected from an antecubital vein in a 10 mL plastic vacutainer tube (red cap silicone-coated interior tube with a clot activator, BD Medical; Mississauga, Canada). Blood tubes were then kept at room temperature for a minimum of 30 min and a maximum of one hour, before being centrifuged at 6000 rpm for 15 min at room temperature. The serum was transferred into 2 mL Sarstedt vials, kept temporarily in the freezer (at −20° C), and sent to the *Centre de toxicologie du Québec* (CTQ) of the *Institut National de Santé Publique du Québec* (INSPQ) in Quebec City for PFAAs analysis.

The study design and questionnaires were developed based on previous pregnant women biomonitoring projects and Inuit Health Surveys in Nunavik (Gautier et al., 2016; Rochette and Blanchet, 2007). An electronic version of the questionnaire was developed using Qualtrics® survey software. The food frequency questionnaire included pictures and asked participants to report the frequency of having eaten each country food by season (winter, spring, summer and fall) over the past 12 months. Medical records were reviewed to collect additional information with respect to maternal and pregnancy details.

2.3. Chemical analysis in 2016–2017 blood samples

2.3.1. PFAAs in serum

The analyses for a total of 9 PFAAs (PFBA (C4), PFBS (C4), PFHxA (C6), PFHxS (C6), PFOS (C8), PFOA (C8), PFNA (C9), PFDA (C10), PFUdA (C11)) were performed as follows: serum samples (100 μL) were enriched with isotopically-labeled internal standards and were acidified with a 50% formic acid solution. Thereafter, the samples were extracted using a solid phase extraction (SPE) with a Strata-X AW 96 well plate 30 mg (33 μm) (Phenomenex; Torrance, CA, USA). The 96 well plate was washed first with NH_4OH 5% in methanol to remove contaminants and conditioned with methanol and water prior to processing the samples. The resin was washed with a 2% formic acid solution and methanol and analytes were eluted by 980 μL of NH_4OH 5% in methanol. The extracts were evaporated to dryness and dissolved in 900 μL of ammonium acetate 5 mM in methanol 40%.

The samples were analyzed by Ultra Performance Liquid Chromatography (UPLC Waters Acquity) with a tandem mass spectrometer (MS/MS Waters Xevo TQ-S) (Waters, Milford, MA, USA) in the multiple reaction monitoring mode with an electrospray ion source in the negative mode. The column used was an ACE EXCEL C_{18}-PFP 50 mm × 2.1 mm, 2.0 μm (ACE; Aberdeen, Scotland). The mobile phase consisted of a gradient of (30:70) methanol: H_2O (both containing 5 mM ammonium acetate) to 100% methanolover 14.6 min and a constant flow rate of 0.5 mL/minute. The limits of detection (LOD) for PFOS, PFOA, PFHxS, PFNA, PFDA and PFUdA were 0.2, 0.03, 0.04, 0.07, 0.07 and 0.05 μg/L, respectively (See supplemental Material Table S1 for the LODs in the three previous biomonitoring studies, CHMS cycle 5 and MIREC). LODs were determined by first estimating concentrations of analytes yielding a signal to noise ratio of 3. A plasma/serum sample spiked with analytes in concentrations ranging from 4 to 10 times the estimated LODs was analyzed (10 replicates) and standard deviations were multiplied by three to obtain the LODs. The intra-day precision varied between 3.3 and 8.1 and the inter-day precision varied between 4.2 and 13 % depending on the analytes. The calibration curve was made in bovine serum and was linear with a weighting of 1/x between 0.15 and 50 μg/L for PFNA, PFOA, PFHxS and between 0.6 and 200 μg/L for PFOS. Two laboratory blanks constituted with demineralized water were inserted in each analysis sequence. They underwent the same treatment as the samples during the extraction.

The internal reference materials used for quality control were the standard reference material SRM-1958 from the National Institute of Standards and Technology (NIST; Gaithersburg, MD) and in-house quality controls (QCs) for PFAAs. The overall quality and accuracy for the analytical method was monitored through participation in the AMAP External Quality Assessment Scheme (CTQ, INSPQ, Québec, Canada) for the analytes PFOA, PFNA, PFHxS and PFOS as well as the German External Quality Assessment Scheme (G-EQUAS; Erlangen, Germany) for the analytes PFOA and PFOS. It is to note that PFAAs concentrations measured in serum are perfectly comparable to those measured in plasma samples, as in CHMS Cycle 5.

2.3.2. Fatty acid composition

Fatty acid composition was determined in red blood cell membranes. A 600 μL aliquot of lysed red blood cells was thawed at room temperature, centrifuged at 3000 g for 5 min, and washed 3 times with a 0.9% saline solution. Lipids were extracted from red blood cell membranes with a chloroform/methanol solution (2:1, by volume). Then, extracted lipids were methylated with methanol/benzene 4:1 (v/v) and 200 μL acetyl chloride. The fatty acid profile of red blood cell membranes was determined by gas chromatography using a HP 5890 gas chromatograph equipped with an automated injector 7673A and coupled to a flame ionization detector (Hewlett Packard, Toronto, Canada). Red blood cell membranes PUFA analyses were carried out at the Lipid Research Centre of the CHU de Québec Research Centre – Université Laval. The detailed procedure is described elsewhere (Rochette and Blanchet, 2007).

2.4. Statistical analysis

2.4.1. PFAAs serum concentrations and time trends

PFAAs concentrations were compared between NQN (2016–2017 participants), Maternal-Infant Research on Environmental Chemicals (MIREC) Study and Canadian Health Measure Survey (CHMS) - Cycle 5 (2016–2017). For these comparisons between independent populations, when 95% confidence intervals for the geometric means (GM) did not overlap, the two population exposure levels were judged with confidence to be significantly different. To evaluate the temporal trends in PFAAs serum/plasma concentrations, the database consisting of biomonitoring data from pregnant women who participated in PFAAs biomonitoring projects in Nunavik since 2004 was used. For each chemical, ½ LOD value was attributed to individual sample concentrations below the LOD. If more than 40% of the individual samples were below the LOD, then the contaminant was considered not detected sufficiently. PFAAs concentrations were log transformed given the skewedness of pollutant concentration distributions. ANCOVA analyses with year of sampling treated as a categorical factor were adjusted for age, smoking status (smoking vs non-smoker), trimester of pregnancy at the time of blood sampling and number of previous pregnancies according to existing literature on PFAAs. These analyses were performed using a generalized linear model with a normal distribution and an identity link in the SAS GENMOD procedure. Changes in log transformed concentrations across the years of sampling were evaluated using contrasts. The statistical significance of the contrasts was assessed using the likelihood ratio tests. When only 2 years were compared, the contrast tested the equality between the 2 time points. When more than 2 years were compared, the contrast tested the linear trend using linear contrast coefficients for unequally spaced time points. The mean estimates obtained from the model for each time point were transformed back to the original scale to obtain an adjusted GM. Results are presented as percentage of change comparing the GM for 2016–2017 with the GM for 2004, 2007 and/or 2011–2012. These percentages were calculated as the difference between the most recent year and the prior one, divided by the prior one.

2.4.2. Profile of exposure to PFAAs

To investigate the proportion of exposure to PFAAs from country food consumption versus from consumer goods in pregnant women from Nunavik, the ratios of PFNA/PFOA, PFNA/PFOS, PFNA/PFHxS and PFUdA/PFDA were calculated using the geometric means of serum concentrations and compared to CHMS cycle 5. Shorter carbon chain length congeners such as PFOS and PFOA are generally associated with exposure through consumer goods (Xie et al., 2013), while a higher

proportion of longer carbon chain length congeners (e.g. PFNA, PFDA) would be indicative of exposure to these congeners through their bioaccumulation in the food chain and the metabolism of FTOHs (D'Hollander, 2010a; Eriksson et al., 2016; Haukås et al., 2007; Müller et al., 2011; Xu et al., 2014). As serum concentrations of PFUdA in the CHMS study cycle 5 were detected in <40% of the samples, we used the limit of detection divided by 2 to calculate the PFUdA/PFDA ratio. Such PFAAs congener profiling approaches have previously been used for Arctic biota (Martin et al., 2004), Arctic ice (Pickard et al., 2018) and drinking water (Guelfo and Adamson, 2018).

2.4.3. Country foods consumption

The consumption of marine country foods was estimated using the omega-3/omega-6 PUFA ratio in red blood cell membranes (Deutch et al., 2004; Proust et al., 2014). Moreover, the overall consumption of country foods and by categories of country foods (marine mammals' meat and organs, fish, mollusks, seaweeds, land mammals, wild birds and wild berries) for the season at which the recruitment took place were assessed using data from the food frequency questionnaire, through which the consumption's frequency of each country foods item (number of times per week) was asked by season. Marine mammal blubber consumption was not considered in the analyses as PFASs are not reported to significantly accumulate in lipophilic tissues (Conder et al., 2008). A detailed list of food items in each country food category is available in Table S2 (Supplemental Material). Correlations between the omega-3/omega-6 PUFA ratio and the frequencies of consumption of country foods by categories were tested using Pearson's correlation test.

2.4.4. Explanatory models of PFAAs serum concentrations

Multiple linear regression models were used to determine if pregnancy and maternal characteristics and the consumption of country foods could explain the serum concentrations of PFAAs (individual congeners and sum of PFAAs) among pregnant women in 2016–2017. The sum of PFAAs was calculated for each participant individually by summing up urinary concentrations of the individual PFAAs congeners. Potential covariables were chosen *a priori* based on previous literature and included age, number of previous pregnancies, smoking status at recruitment and trimester of current pregnancy (Brantsaeter et al., 2013; Kato et al., 2014). Three categories of models were conducted based on the different tools used to evaluate the consumption of country foods: 1) Omega-3/omega-6 PUFA ratio for marine country food consumption; 2) total country foods consumption frequency and; 3) country foods consumption frequency by categories. For the latter, only the country foods frequencies by categories with medians over 0 times/week were used in the models.

Sensitivity analyses were performed by including 1) the participant's education; 2) housing crowding condition and; 3) housing need of repair. The latest covariable was included in the sensitivity analyses to tentatively assess for the contribution of housing furniture and consumer goods to overall PFAAs exposure (Bost et al., 2016). Although diet seems to be the primary exposure pathway to PFAA, these congeners have been measured in house dust (D'Hollander et al., 2010b). Participants reported the number of people living in their residence and the number of bedrooms. As described in Perreault et al., (2020), we added two additional rooms (kitchen and living room) to the number of bedrooms. We defined the participant's household as "crowded" if the number of people living in the participant's home divided by the number of rooms (PPR) was greater than 1. For multiple regression models, PFAAs concentrations were also log transformed. The normal distribution of the residuals of the regression models and the multicollinearity (using the variance inflation factor (VIF)) were verified. Statistical significance was established at p-value < 0.05, while non-statistically significant tendencies were established at p-value between 0.05 and 0.1. Analyses were performed using SPSS 24 and SAS software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Characteristics of the NQN participants

In 2016–2017, 97 pregnant women were recruited within the context of the NQN study, representing about 42% of the total pregnant women population at that time in Nunavik. The number of participants per Nunavik village is illustrated in Fig. 1. The study population is presented in Table 1. The median age was 24 years old and most women were recruited during their second trimester of pregnancy. The majority of the participants were daily smokers (74%) or occasional smokers (9%). Thirthy-nine percent of participants reported living in crowded conditions (PPR greater than 1) and 10% in dwellings where major repairs were needed.

3.2. Current exposure to PFAAs and temporal trends

Similarly to CHMS cycle 5, PFBA, PFHxA and PFBS were not detected in any of the NQN participants. Serum concentrations of PFHxS, PFOS, PFOA, PFNA, PFDA and PFUdA in NQN participants are presented in Table 2. Mean concentrations for PFOS and PFNA were the highest, followed by PFDA and PFUdA. PFOS, PFNA, PFDA and PFUdA serum concentrations in the NQN participants were significantly higher than those measured in women aged 18–40 years old in the Cycle 5 of CHMS, which was conducted during the same period as NQN (2016–2017). Indeed, PFOS, PFNA and PFDA in the NQN participants were respectively 1.8, 6.3 and 3.3 times higher than in CHMS. Conversely, PFOA and PFHxS were significantly lower than in CHMS. As illustrated in the graphical abstract, overall PFAAs concentration found in NQN is 2 times the level reported in women from the Canadian general population (CHMS) during the same period. PFOS, PFOA and PFHxS were also measured in the MIREC study in 2008–2011 (Fisher et al., 2016). Median serum concentration of PFOS in NQN participants was 1.9 times higher than that reported in the MIREC participants, while PFOA and PFHxS were respectively 8.7 and 4.2 times lower than in MIREC.

Since they were first measured in pregnant women from Nunavik in 2004 or 2007, serum concentrations of PFOS, PFOA and PFHxS have significantly declined by 66, 44 and 49%, respectively (Table 3). To the contrary, PFNA serum concentrations significantly increased by 19% since 2011. As shown in Table 4, the relative proportion of PFNA over PFOA, PFNA over PFOS, PFNA over PFHxS and PFUdA over PFDA in NQN participants were respectively, 10, 3.5, 10.7 and 3 times higher compared to women in CHMS.

3.3. Country foods consumption by NQN participants

Median, 25th and 75th percentiles for the frequencies of country foods consumption by NQN participants at the season of recruitment are presented in Table 5. Eight participants were recruited in the fall and 89 participants were recruited in the winter. Land mammals (primarily caribou meat (frozen, raw or cooked) and caribou *nikku* (air-dried meat)) were the most frequently consumed, followed by fish (primarily Arctic char, lake trout and *pitsik* (air-dried fish), followed by, brook trout, whitefish and sculpin), marine mammals (primarily beluga *mattaaq* (skin and blubber), beluga *nikku* (air-dried meat), beluga meat (frozen, raw or cooked) and seal meat, and in few cases seal liver and walrus meat) and wild birds (primarily ptarmigan). Mollusks (primarily blue mussels), seaweeds and wild berries were not often consumed during this period. The ratio of omega-3/omega-6 PUFA was significantly positively correlated with the consumption frequency of marine mammals (Pearson = 0.271), fish (Pearson = 0.217) and mollusks (Pearson = 0.344).

Table 1
Characteristics of the NQN participants in 2016–2017.

Characteristic	Participants (n=97) n (%)	Median (min-max)
Age (years)		24 (16-40)
Pregnancy trimester		
1	32 (33)	
2	40 (41)	
3	25 (25)	
Number of previous pregnancies		3 (1-12)
Marital status		
Single	17 (18)	
Married	5 (5)	
Common law relationship	74 (76)	
Separated	1 (1)	
Divorced	0 (0)	
Widowed	0 (0)	
Region		
Hudson Bay	38 (39)	
Hudson Strait	37 (38)	
Ungava Bay	22 (23)	
Highest grade completed		
Grade 5	1 (1)	
Grade 6	4 (4)	
Grade 7	17 (18)	
Grade 8	18 (19)	
Grade 9	18 (19)	
Grade 10	12 (12)	
Grade 11	18 (19)	
CEGEP/College, not graduated	6 (6)	
CEGEP/College, graduated	1 (1)	
University, not graduated	0 (0)	
University, graduated	0 (0)	
Doesn't know	2 (2)	
Work status		
Full-time	18 (19)	
Part-time	10 (10)	
Occasionally	8 (8)	
Housework	23 (24)	
Employment insurance	3 (3)	
Maternity leave	22 (23)	
Income support	2 (2)	
Student	7 (7)	
Other	4 (4)	
Smoking status at time of recruitment		
Smoker	72 (74)	
Occasional smoker	9 (9)	
Non-smoker	16 (17)	
Crowding (number of people living in home/number of rooms > 1) [a]		
Yes	37 (39)	
No	58 (61)	
Dwellings in need of major repair [b]		
Yes	10 (10)	
No	84 (90)	
Red blood cells Omega-3/Omega-6 PUFA ratio		0.44 (0.12-0.49)

Pregnancy Wellness with Country Foods (NQN) project is a cross-sectional study that was conducted between October 2016 and March 2017.
[a] Data on number of rooms missing for two participants.
[b] Data on need of repair missing for three participants.

Table 2
Serum/plasma concentrations of PFAAs (μg/L) in participants from NQN in 2016–2017, compared to women aged 18 to 40 years old in the general Canadian population (CHMS cycle 5, 2016–2017) and the Maternal-Infant Research on Environmental Chemicals (MIREC 2008–2011).

Population description	NQN 2016–2017	CHMS cycle 5 2016–2017	MIREC 2008–2011
PFAAs	**Pregnant women (n = 97)**	**Women 18–40 yo (n = 243)**	**Pregnant women, first trimester (n = 1723)**
	GM 95% CI, (median, min–max)	**GM** 95% CI, (median, 10th – 95th percentiles)	(median, 25th – 75th percentiles)
PFHxS 6 carbons	**0.27** 0.23 – 0.31 (0.24, 0.06–1.20)	**0.44** 0.36–0.54 (0.43, 0.18–2.30)	(1.00, 0.66–1.60)
PFOS 8 carbons	**3.3** 2.8 – 3.9 (3.2, 0.7–19.0)	**1.80** 1.70–2.00 (1.70, 0.91–4.10)	(1.70, 1.10–2.40)
PFOA 8 carbons	**0.54** 0.49 – 0.58 (0.53, 0.16–1.40)	**0.84** 0.77–0.91 (0.84, 0.42–1.90)	(4.60, 3.30–6.80)
PFNA 9 carbons	**2.3** 2.1 – 2.7 (2.5, 0.8–10.0)	**0.38** 0.32–0.45 (0.41, 0.19–0.89) **(n = 220)**	
PFDA 10 carbons	**0.51** 0.46 – 0.61 (0.52, 0.10–3.10)	**0.16** 0.13–0.19 (0.16, <LOD-0.60) **(n = 222)**	
PFUdA 11 carbons	**0.54** 0.43 – 0.6 (0.61, 0.09–3.80)	**NA** (<LOD, <LOD-0.33) **(n = 241)**	
Sum PFAAs	**8.0** 7.0–9.0 (7.7, 2.0–35.8)		

yo = years old.
GM = geometric mean.
CI = confidence interval.
PFAAs ((μg/L) in MIREC: (Ashley-Martin et al., 2016)

3.4. Associations between the consumption of country foods and exposure to PFAAs

In adjusted models, strong significant positive associations were found between the omega-3/omega-6 PUFA ratio and serum concentrations of PFHxS, PFOS, PFNA, PFDA, PFUdA and the sum of PFAAs (Table 6). A positive tendency was observed with PFOA. The participant's age, parity, smoking status and trimester of pregnancy were not significantly associated with any serum PFAAs concentrations in the adjusted models. Moreover, the models of the associations between the

Table 3
Time-trends in serum/plasma concentrations of PFAAs (μg/L) in pregnant women from Nunavik since 2004, 2007 and/or 2011–2012.

Biomonitoring studies	2004 (n = 31)		2007 (n = 40)		2012 (n = 111)		NQN 2016–2017 (n = 97)		% of Change since 2004[a] or 2007[b]	% of Change between 2011 and 2012 and 2016–2017
	%> LOD	GM 95% CI	%> LOD	GM 95% CI	%> LOD	GM 95% CI	%> LOD	GM 95% CI		
PFHxS			60	0.53	91.6	0.35	100	0.27	−49.2[b] ***	−22.8
6 carbons				0.41–0.67		0.3–0.41		0.23–0.31		
PFOS	100	9.8	100	5.3	100	3.8	100	3.3	−66.1[a] ***	−13.7
8 carbons		7.4–12.8		4.3–6.6		3.3–4.5		2.8–3.9		
PFOA			100	0.97	100	0.67	100	0.54	−43.8[b] ***	−19.3
8 carbons				0.82–1.14		0.6–0.75		0.49–0.58		
PFNA					100	2.0	100	2.3		19.0*
9 carbons						1.7–2.3		2.1–2.7		
PFDA					98.1	0.45	100	0.51		13.1
10 carbons						0.37–0.54		0.46–0.61		
PFUdA					91.8	0.44	100	0.54		20.9
11 carbons						0.35–0.56		0.43–0.6		

Grey cells: specific PFAA congener not measured during that biomonitoring study
PFNA, PFDA and PFUdA were measured for the first time in pregnant women from Nunavik in 2011–2012
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$p-value of time trends analysis adjusted for age, smoking, trimester of pregnancy and number of previous pregnancies.
[a] PFOS was measured for the first time in pregnant women from Nunavik in 2004
[b] PFHxS and PFOA were measured for the first time in pregnant women from Nunavik in 2007

Table 4
Ratio of serum GM concentrations of PFAA congeners (μg/L) in participants from NQN in 2016–2017, compared to the general Canadian population (CHMS cycle 5, 2016–2017, women age 18–40 yo).

	NQN 2016–2017	CHMS cycle 5 2016–2017
PFNA/PFOA ratio	4.53	0.45
PFNA/PFOS ratio	0.73	0.21
PFNA/PFHxS ratio	9.23	0.86
PFUdA/PFDAratio	1.15	0.38

Table 5
Frequencies of country foods consumption by categories in participants from NQN in 2016–2017.

Country foods category	Frequency at the season of recruitment (times/week) n = 96 Median 25th–75th percentiles
Marine mammals [a]	0.49
	0.00–0.98
Fish	0.98
	0.49–1.96
Mollusks	0.00
	0.00–0.00
Seaweeds	0.00
	0.00–0.00
Land mammals	1.47
	0.61–4.97
Wild birds	0.49
	0.00–0.98
Wild berries	0.00
	0.00–0.00
Total	4.97
	2.45–10.89

The list of specific food items for each category is available in Table S2.
[a] Marine mammals: Contrary to other POPs, as PFAAs do not accumulate in the blubber, only marine mammal meat and organs were included here.

serum PFAAs concentrations and the omega-3/omega-6 ratio remained similar following the inclusion of the participant's education, household crowding condition or need of repair into the models, which were also not associated to PFAAs exposure levels.

In adjusted models, non-statistically significant positive tendencies ($p \leq 0.1$) were found between the total frequency of country foods consumption and serum concentrations of PFHxS, PFOS, PFNA, PFDA, PFUdA and the sum of PFAAs (Table 6). Conversely, no significant associations were found with PFOA. The participant's age, parity and smoking status were not significantly associated with serum concentrations of PFAAs in the adjusted models, although the trimester of pregnancy was negatively associated with the serum concentrations of PFHxS and PFOA in the adjusted models.

When looking at the associations by country food categories, non-statistically significant positive tendencies ($p \leq 0.1$) were observed between the consumption frequency of marine mammals' meat and organs, and the serum concentrations of PFHxS, PFOS, PFOA, PFNA, PFDA and the sum of PFAAs (Table 6). Again, the models of these associations were similar following the inclusion of the participant's education household crowding condition or need of repair into the models.

4. Discussion

Exposure during pregnancy to regulated PFAAs (PFOS, PFOA and PFHxS) is declining in Nunavik, while long-chain PFCAs exposure is on the rise. PFNA serum concentrations of pregnant women from Nunavik in 2016–2017 was among the highest compared to other recently reported PFNA concentrations in the circumpolar region (Byrne et al., 2017; Hanssen et al., 2013; Jørgensen et al., 2014; Glynn, 2017). PFOS, PFNA, PFDA and PFuDA exposure levels in pregnant women from Nunavik were also higher than in women of childbearing age from CHMS cycle 5 (2016–2017), whereas the exposure to PFOA and PFHxS was lower than in women from CHMS cycle 5. To our knowledge, the present study represents the only PFAAs time-trend data and the most recent exposure data across the Canadian Arctic since the Qanuippitaa Health Survey conducted in Nunavik in 2004 and the Inuit Health Survey conducted in 2007–2009. Our study is also aligned with the findings of Dallaire et al. (2009), showing that marine country foods consumption is associated with higher exposure to PFOS in Nunavik. Interestingly, the unique PFAAs exposure profile found in Nunavik reflects the high bioaccumulative properties of PFOS and long-chain PFCAs in Arctic wildlife (D'Hollander, 2010a; Eriksson et al., 2016; Haukås et al., 2007; Müller et al., 2011; Xu et al., 2014). Moreover, while most PFAAs are now regulated, the high PFNA exposure level in Nunavik during pregnancy supports ecological findings showing that FTOHs, and particularly 8:2 FTOH, are important contributors to exposure to long-chain

Table 6
Associations between serum concentrations of PFAAs and omega-3/omega-6 ratio, total frequency of country foods consumption and categories of country foods consumption in multiple regression analyses in NQN participants (n = 96).

Country food consumption	PFHxS	PFOS	PFOA	PFNA	PFDA	PFUdA	Sum PFAAs
	Adjusted ß [95% CI]	Adjusted ß [95% CI]	Adjusted ß [95% CI]	Adjusted ß [95% CI]	Adjusted ß [95% CI]	Adjusted ß [95% CI]	Adjusted ß [95% CI]
Omega-3/omega-6 PUFA ratio	0.487 ** [0.30 to 0.67]	0.546 ** [0.36 to 0.73]	0.189 † [−0.02 to 0.39]	0.332 * [0.13 to 0.53]	0.596 ** [0.42 to 0.78]	0.587 ** [0.41 to 0.77]	0.517 ** [0.33 to 0.70]
Total country foods frequency	0.152 † [−0.05 to 0.36]	0.179 † [−0.003 to 0.39]	0.090 [−0.11 to 0.28]	0.156 † [−0.05 to 0.37]	0.182 † [−0.003 to 0.39]	0.163 † [−0.05 to 0.37]	0.187 † [−0.002 to 0.40]
Country foods frequency by category							
Marine mammals[a]	0.185 † [−0.02 to 0.39]	0.190 † [−0.02 to 0.40]	0.180 † [−0.02 to 0.38]	0.199 † [−0.01 to 0.40]	0.157 † [−0.04 to 0.37]	0.149 [−0.06 to 0.36]	0.202 † [−0.01 to 0.41]
Fish	0.130 [−0.08 to 0.22]	0.119 [−0.09 to 0.33]	0.106 [−0.10 to 0.31]	0.058 [−0.16 to 0.27]	0.130 [−0.09 to 0.35]	0.140 [−0.08 to 0.36]	0.114 [−0.10 to 0.33]
Land mammals	0.065 [−0.14 to 0.27]	0.113 [−0.09 to 0.32]	−0.014 [−0.21 to 0.18]	0.128 [−0.08 to 0.33]	0.128 [−0.08 to 0.34]	0.102 [−0.11 to 0.32]	0.128 [−0.08 to 0.34]
Wild birds	−0.08 [−0.28 to 0.23]	−0.05 [−0.19 to 0.22]	0.046 [−0.16 to 0.25]	−0.021 [−0.23 to 0.19]	−0.010 [−0.22 to 0.20]	−0.060 [−0.27 to 0.15]	−0.035 [−0.25 to 0.18]

[A]Contrary to other POPs, as PFAAs do not accumulate in the blubber, only marine mammal meat and organs were included.
Adjusted for pregnant women's age, number of previous pregnancies, smoking status and the trimester of pregnancy.
Data for the food frequency questionnaire missing for 1 participant.
Data for omega-3/omega-6 ratio missing for 1 participant.
† $p \leq 0.10$; *$p < 0.05$; **$p < 0.001$

PFCAs in the Arctic (Ahrens et al., 2011; Shoeib et al., 2006, Muir et al., 2019). Some studies found that smokers and passive smokers had higher concentrations of PFAAs (Park et al., 2019; Tsai et al., 2018). However, because cigarettes do not contain PFAAs, smoking status may capture other factors associated with exposure to PFAAs (Park et al., 2019).

Similarly to what we observed from 2004 to 2017 in pregnant women from Nunavik, concentrations of older PFAAs (e.g. PFOS, PFOA, PFHxS) are declining in various human populations, including in women from the general population in Canada (Health Canada, 2019; Health Canada, 2010), United States (Hurley et al., 2017) and Denmark (Bjerregaard-Olesen et al., 2016) due to the regulation of these compounds. Similar declining trends for these PFAAs are also observed among circumpolar populations. In children from the Faroe Islands, PFOS concentrations peaked around 2000 and have declined significantly, while longer carbon-chain congeners such as PFNA and PFDA have remained at constant concentrations between 2000 and 2012 (Dassuncao et al., 2018). Similar serum PFAAs concentrations profiles and time trends were observed in men from Northern Norway between 1979 and 2007 (Nøst et al., 2014), and in primiparous women from Sweden between 1996 and 2016 (Glynn, 2017). Conversely, exposure to long-chain PFCAs is on the rise in Nunavik and circumpolar regions, and this reflect trends reported in Arctic wildlife (Muir et al., 2019; Muir and de Wit, 2010). Interestingly, serum composition of PFAAs in pregnant women from Nunavik was similar to what was reported in childbearing age women from Alaska Natives communities in 2013–2014 (Byrne et al., 2018). In pregnant women from Greenland between 2010 and 2015, median serum PFOS concentration was higher than what we reported in pregnant women from Nunavik, but median PFNA serum concentration for all regions in Greenland was lower than exposure levels in Nunavik (9.0 μg/L and 1.2 μg/L, respectively), whereas it was higher in the Eastern part of Greenland (Hjermitslev et al., 2020). Different serum composition of PFAAs may reflect different consumption patterns of marine foods and/or different circumpolar distribution of PFAAs, knowing that industrial fluoropolymers production sites have shifted from North America, Europe and Japan to emerging Asian economies (Muir et al., 2019).

8:2 FTOH is known to be among the highest PFASs in the Canadian Arctic atmosphere (Muir et al., 2019). The long-range transport in the Arctic of currently-used FTOHs substances (Wong et al., 2018), the biotransformation of 8:2 FTOH into primarily PFOA and PFNA (Martin et al., 2005) and the higher bioaccumulation potential of C9-C14 PFAAs such as PFNA compared to PFOA (D'Hollander, 2010a; Eriksson et al., 2016; Haukås et al., 2007; Müller et al., 2011; Xu et al., 2014) could lead to high accumulation of PFNA in Arctic wildlife and may explain the unique PFAAs serum signature measured in these pregnant women from Nunavik (Brandsma et al., 2011; Ellis et al., 2004; Martin et al., 2005). As shown in the graphical abstract, the overall sum of mean serum concentrations of PFHxS, PFOS, PFOA, PFNA, PFDA and PFUdA was 2 times higher in Nunavik pregnant women (7.6 μg/L) compared to women who participated in the CHMS study cycle 5 (3.7 μg/L), and importantly, the contribution of long-chain bioaccumulative PFAAs such as PFNA, PFDA and PFUdA in the total PFAAs serum concentrations was 5.9 times higher in Nunavik compared to CHMS study cycle 5.

Interestingly, exposure to PFOA and PFHxS in Nunavik was lower than in the Canadian general population, suggesting that the contribution of local consumer goods or other local sources to overall PFAAs exposure is low. Because of the phase-out in legacy PFAAs (PFOS and PFOA) that were directly used in consumer goods (e.g. carpet, leather, textiles, paper, food packaging) (Xie et al., 2013), the importance of this route of exposure is declining (Sunderland et al., 2019). In the general population, PFOS and PFOA exposure typically predominates due to the plethora of exposure sources including drinking water and products whereas the longer chain PFCAs are less prevalent mainly due to the relatively low trophic level occupied by most humans who consume an omnivorous diet consisting of farm-raised livestock, poultry and fish (Domingo et al., 2012; Manzano-Salgado et al., 2016; Tittlemier et al., 2007), which is quite different from the marine food diet in Nunavik.

A few studies have shown that the highest PFAAs concentrations in Arctic wildlife occur in marine mammals due to the pronounced trophic magnification potential for PFOS and long-chain PFCAs in Arctic marine food webs (Gebbink et al., 2016; Haukås et al., 2007; Kelly et al., 2009). PFAAs are not entirely lipophilic (Conder et al., 2008), as is the case for older persistent organic pollutants like polychlorinated bisphenyls (PCBs). Contrary to other organic chemicals, biomagnification of PFAAs also occurs in freshwater and terrestrial food webs (Müller et al., 2011; Xu et al., 2014). With increasing trophic level, a distinct odd-even PFAAs congener pair ratio is presented in wildlife wherein PFNA > PFOA, PFNA > PFHxS and PFUdA > PFDA (Martin et al., 2005). Interestingly, in pregnant women from Nunavik, these three ratios were respectively 10, 11 and 3 times higher than in the general Canadian population

(Table 4). These higher ratios also support existing findings that elevated C9-C14 PFAAs in serum is indicative of marine food consumption (Hu et al., 2018) and highlight that pregnant women in Nunavik are disproportionally exposed to PFAAs congeners that tend to bioaccumulate and biomagnify in Arctic wildlife, which is still a staple of the local diet. Indeed, in the present study, we found significant positive associations between exposure to PFHxS, PFOS, PFNA, PFDA, PFUdA and the sum of PFAAs, and the consumption of marine country foods estimated by the omega-3/omega-6 PUFA ratio. We also found modest, non-statistically significant associations between the total country foods, marine mammal meat and organs consumption frequencies and the serum concentrations of PFHxS, PFOS, PFNA, PFDA, PFuDA and the sum of PFAAs. Therefore, it is most likely that marine mammal consumption was the greatest contributor to elevated PFAAs exposure. Further studies are needed in order to better assess PFASs levels in country food consumed in Nunavik.

These findings must be interpreted with caution. The small sample size and the use of a convenience sample are significant limitations of the study. However, it must be emphasized there are approximately only 340 pregnancies per year in Nunavik (based on the number of live births per year during the period from 2013 to 2017 in Nunavik), but spread out between 14 villages across a vast territory only accessible by plane. Still, between October 2016 and March 2017, up to 42% of the pregnant women in Nunavik were recruited, making our sample size an important portion of the total population of pregnant women in Nunavik at that time. Despite the small sample size, the results of the trend analysis are considered reliable. Indeed, the coefficients of variation for the geometric means at each time points were between 4.5% amd 9.3%, except for one at 15.3%.

5. Conclusions

Although exposure to PFOS seems to be declining, serum concentrations of this congener in pregnant women from Nunavik remains elevated compared to CHMS. Moreover, Nunavik pregnant women exposure to long-chain PFAAs (PFNA, PFDA and PFUdA) are on the rise since they were first measured in 2011–2012, and PFNA exposure is the among the highest reported to date in the Arctic and elsewhere. The higher ratios of PFNA/PFOA, PFNA/PFOS, PFNA/PFHxS and PFUdA/PFDA in the NQN participants compared to the general Canadian population, and the associations between the omega-3/omega-6 ratio and serum concentrations of several PFAAs show that exposure to these compounds occur through their bioaccumulation in marine country foods, which originates most likely through the degradation of more recent fluorotelomer alcohols currently found in great concentrations the Arctic. Overall, these results highlight the importance of implementing additional strict regulations on PFAAs and their precursors in North America and elsewhere to protect the high nutritional quality and cultural importance of country foods in Nunavik.

CRediT authorship contribution statement

Élyse Caron-Beaudoin: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Pierre Ayotte:** Conceptualization, Methodology, Formal analysis, Data curation, Investigation, Resources, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Caty Blanchette:** Methodology, Software, Validation, Formal analysis, Data curation, Investigation, Resources, Writing - original draft, Writing - review & editing. **Gina Muckle:** Conceptualization, Resources, Writing - review & editing. **Ellen Avard:** Conceptualization, Resources, Writing - review & editing. **Sylvie Ricard:** Conceptualization, Resources, Writing - review & editing. **Mélanie Lemire:** Conceptualization, Methodology, Formal analysis, Data curation, Investigation, Resources, Writing - original draft, Writing - review & editing, Supervision, Visualization, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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