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Exposure to perfluoroalkyl substances and associations with serum thyroid hormones in a remote population of Alaska Natives☆☆,☆

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ABSTRACT

Perfluoroalkyl substances (PFASs) are known to accumulate in traditional food animals of the Arctic, and arctic indigenous peoples may be exposed via consumption of subsistence-harvested animals. PFASs are suspected of disrupting thyroid hormone homeostasis in humans. The aim of this study is to assess the relationship between serum PFASs and thyroid function in a remote population of Alaska Natives.

Serum samples were collected from 85 individuals from St. Lawrence Island, Alaska. The concentrations of 13 PFASs, as well as free and total thyroxine (T_4), free and total triiodothyronine (T_3), and thyrotropin (TSH) were quantified in serum samples. The relationships between circulating concentrations of PFASs and thyroid hormones were assessed using multiple linear regression fit with generalized estimating equations.

Several PFASs, including perfluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA), were positively associated with TSH concentrations when modeled individually. PFOS and PFNA were significantly associated with free T_3 and PFNA was significantly associated with total T_3 in models with PFAS*sex interactive terms; these associations suggested negative associations in men and positive associations in women. PFASs were not significantly associated with concentrations of free or total T_4.

Serum PFASs are associated with circulating thyroid hormone concentrations in a remote population of Alaska Natives. The effects of PFAS exposure on thyroid hormone homeostasis may differ between sexes.

1. Background

Perfluoroalkyl substances (PFASs) are used as industrial surfactants and in the production of waterproof or stain proof surface coatings for a variety of commercial applications. The two most widely studied PFASs, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), have been voluntarily phased out of use in the United States due to concerns about toxicity, and PFOS is globally restricted under the Stockholm Convention on Persistent Organic Pollutants (UNEP, 2018). PFOA and perfluorohexane sulfonate (PFHxS) are currently undergoing evaluation for inclusion in the Convention and it was determined by the expert committee that these substances meet criteria for persistence, bioaccumulation, long-range transport, and toxicity (UNEP, 2018). PFASs are not efficiently removed from the body after exposure, and the biological half-lives of PFOA, PFHxS and PFOS are estimated to be several years (Li et al., 2018; Olsen et al., 2007).

Concentrations of PFOA and PFOS in humans are decreasing over time; the concentrations of long chain PFASs (≥8 carbons) tend to be more stable (Hurley et al., 2018; Olsen et al., 2017). Alternatives to PFASs, such as polyfluoroalkyl compounds and fluorotelomer alcohols, are known to degrade into recalcitrant PFASs, such as PFOA (Butt et al., 2014; Liu and Mejia Avendaño, 2013). Thus, long chain PFASs remain ubiquitous environmental contaminants, both due to historical releases, and continued production of precursors. Additionally, PFASs undergo atmospheric transport and deposition, as well as oceanic transport, to the Arctic (Armitage et al., 2009; Wania, 2007). Fluorotelomer alcohols are also known to undergo atmospheric transport to the Arctic, and can degrade to PFASs, specifically PFOA, perfluorononanoic acid (PFNA) and perfluoroundecanoic acid (PFUnA) (Stemmler and Lammel, 2010; Wallington et al., 2006; Young et al., 2007). Once in the Arctic, PFASs

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bioaccumulate in arctic biota (Butt et al., 2010; Kelly et al., 2009).

The St. Lawrence Island Yupik residents of St. Lawrence Island, Alaska rely heavily on a subsistence diet that includes many marine species including high trophic level and/or long lived marine mammals such as bowhead whale (*Balaena mysticetus*), Pacific walrus (*Odobenus rosmarus*), and bearded seal (*Erignathus barbatus*). Consumption of marine mammals is a source of exposure to persistent PFASs (Weihe et al., 2008). Consumption of caribou (*Rangifer tarandus*) is also a known source of PFAS exposure, specifically organs such as the liver (Ostertag et al., 2009). Residents of St. Lawrence Island have elevated serum concentrations of PFNA and PFUnA (Byrne et al., 2017), a pattern thought to occur due to atmospheric degradation of fluorotelomer alcohols, and subsequent bioaccumulation (Ellis et al., 2004; Rotander et al., 2012).

There is evidence that some PFASs disrupt thyroid hormone homeostasis in humans; however, the results of epidemiological studies are inconsistent with regard to strength and direction of associations. Although animal studies suggest several plausible mechanisms of these effects, their clinical significance in humans remains unclear. Among an adult Inuit population in Canada, PFOS was associated with reduced thyrotropin (TSH) and total triiodothyronine (T_3), and increased free thyroxine (T_4). In the same population, PFOS was negatively associated with thyroid binding globulin (Dallaire et al., 2009). In a heavily exposed population in the Ohio River Valley, PFOA and PFOS were positively associated total T_4 concentrations (Knox et al., 2011). In the US general population, higher exposure to PFASs has been associated with current thyroid disease (Melzer et al., 2010). However, in addition to the significant associations noted above, these studies also reported null associations between PFASs and other measures of thyroid function assessed in the study.

Due to inconsistent epidemiological associations between PFASs and measures of thyroid function, the public health significance of these compounds remains unclear. Despite a well understood dietary exposure pathway (Haug et al., 2010; Ostertag et al., 2009), Alaska Natives are poorly studied with regard to health effects of PFASs. This study aims to evaluate the associations between serum PFAS concentrations and circulating thyroid hormones in a remote population of Alaska Natives. Additionally, we address the potential for sex to modify the association between PFAS and thyroid hormones.

2. Methods

As part of a long-term study of contamination of St. Lawrence Island, Alaska (Miller et al., 2013; von Hippel et al., 2018) participants were recruited from two native villages on St. Lawrence Island, Gambell and Savoonga, during the years 2013–2014. Participants were recruited through flyers posted in public spaces, or directly by bilingual (Yupik-English) community health researchers. Inclusion criteria included being reproductive aged (18–45 years). An attempt was made to recruit a participant of the opposite sex from the same home. A total of 85 individuals from 49 homes were recruited for the study. There are a total of 36 male-female pairs from a single home, and an additional 11 unpaired women and 2 unpaired men. Structured interviews were conducted by bilingual community health researchers to collect data on participant characteristics and potential confounders. Approximately 20 ml fasting blood samples were drawn into sterile vacutainers (Becton Dickinson, Franklin Lakes, NJ), and allowed to clot at room temperature for one hour, then centrifuged for 15 min before serum was collected.

Approximately 2 ml serum aliquots were frozen in the field at − 18 °C and shipped overnight to Labcorp (Seattle, Washington) for analysis of thyroid hormones. TSH, total T_3, free T_3 (fT_3), and free T_4 (fT_4) were quantified using an Electro-chemiluminescence immunoassay (ECLIA). Precision was not determined for the samples under study; however, method precision is reported as maximum observed coefficients of variation (CV) in human serum reported by Labcorp. TSH had a maximum CV 7.1%, cross reactivity < 0.04%, and an LOD of 0.005 μIU/ml. Total T_3 had a maximum CV of 5.4%, cross reactivity of < 1% for other thyroid hormones, and a limit of detection (LOD) of 0.195 ng/ml. Free T_3 had a maximum CV of 8.2%, cross reactivity of < 0.01% for other thyroid hormones, and a LOD of 0.06 ng/dl. Free T_4 had a maximum CV of 7.6%, cross reactivity of ≤ 0.005% for other thyroid hormones, and a LOD of 0.101 ng/dL. Total T_4 was quantified using a cloned enzyme donor immunoassay (CEDIA) with a maximum CV of 9.2%, cross reactivity of < 0.1% for other thyroid hormones, and a LOD of 0.5–20 μg/dL. Laboratory reference intervals were 0.45–4.5 μIU/ml for TSH, 4.5–12 μg/dl for total T_4, 0.82–1.77 ng/dl for fT_4, 71–180 ng/dl for total T_3, and 2–4.4 pg/ml for fT_3. Serum for PFASs analyses was frozen at − 20 °C in pre-cleaned polypropylene falcon tubes (Becton Dickinson, Franklin Lakes, NJ) and shipped overnight to AXYS Analytical (Sydney, British Columbia, Canada). Thirteen PFASs were quantified using reverse-phase high-performance liquid chromatography/mass spectrometry (HPLC-MS) using a triple quadrupole mass spectrometer (AXYS Analytical Services Ltd., 2014). Target analytes included perfluorobutanoic acid (PFBA), perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoA), perfluorobutane sulfonate (PFBS), perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), and perfluorooctane sulfonamide (PFOSA). Isotopically labelled surrogate standards were used, and a blank and matrix spike were included in each analytical batch of approximately 13 samples. Matrix spike recoveries were typically between 90% and 110%, and never outside of 80–120%. The limit of detection ranged from 0.5 to 1 ng/ml. If blanks contained quantifiable concentrations of analytes, this concentration was subtracted from the other samples in the analytical batch.

PFASs were natural log transformed in order to better fit a normal distribution. TSH was also natural log transformed. Spearman's rank correlations were used to assess unadjusted relationships among PFASs, and between PFASs and thyroid function measures. Multiple linear regression estimated with generalized estimating equations (GEE) was used to determine the influence of PFASs on circulating thyroid hormone concentrations. Several models were constructed to assess relationships between PFASs and thyroid hormone measures. Each of 4 PFASs with a detection frequency above 70% (PFOS, PFOA, PFNA, and PFUnA) were considered as the independent variable in five models, using total T_3, fT_3, total T_4, fT_4 or TSH as the dependent variables, adjusted for age, sex, and smoking habits (Bertelsen and Hegedüs, 1994; Bremner et al., 2012; Kamijo et al., 1981; Suzuki et al., 2012). Confounders were identified using directed acyclic graphs (Greenland et al., 1999). Additionally, a model was constructed using PFOS, PFOA, and PFNA as covariates in a single model, for each of five thyroid measures. When the concentration of a PFAS was below the LOD, the data point was imputed as LOD/√2 for regression analysis (Hornung and Reed, 1990), because machine read values were unavailable. A sensitivity analysis was conducted in which PFASs were also modeled with data < LOD imputed as the mean of observed values, a method which produces minimally biased conservative estimates (Schisterman et al., 2006). Influential observations were identified using DFBETAS which is a standardized measure of the impact of a single observation on the regression coefficient; in the event a DFBETAS was > 1 the observation was removed from the regression, and the regression was re-run. Statistical analysis was conducted in SAS 9.4 (SAS Institute, Cary, NC.). Potential effect modification by sex was assessed by adding a product term of sex (female = 1, male = 0), and the individual PFAS under study in the model along with the main effects. This study was approved by the Alaska Area IRB (Indian Health Service IRB00000636) and the Research Ethics Review Board of the Norton Sound Health Corporation.

Table 1
Descriptive statistics for study participants.

	Men (n = 38)			Women (n = 47)		Laboratory reference range
	Median	**Range**		**Median**	**Range**	
TSH (μIU/ml)	1.28	0.323–4.65		0.957	0.051–4.47	0.45–4.5
Total T4 (μg/dL)	9.05	4.8–13.8		8.1	4.3–11.8	4.5–12
fT4 (ng/dL)	1.3	0.95–1.71		1.23	0.94–1.67	0.82–1.77
Total T3 (pg/ml)	143.5	109–176		137	92–197	71–180
fT3 (ng/dL)	3.6	2.8–4.4		3.2	2.2–4.5	2–4.4
Age (yr)	29	19–45		28	18–45	
Smoke[a] n(%)	5 (13%)			8 (17%)		
PFASs (ng/ml)	**Median**	**Range**	**% detect**	**Median**	**Range**	**% detect**
PFOA	1.47	0.51–2.9	100	0.772	nd-0.44	85
PFNA	2.74	0.73–10.8	100	2.13	nd-12.1	98
PFUnA	0.969	nd-3.74	68	0.719	nd-1.73	74
PFOS	6.81	nd-16	100	3.35	nd-9.69	98

a = active smoking in home; nd = non-detect

3. Results

Men and women had comparable age ranges, with a median age of 29 and range of 19–45 in men, and median age of 28 and range of 18–45 in women (Table 1). Based on data from our questionnaire, smoking or environmental tobacco smoke exposure was slightly more prevalent in women (17%) than men (13%); however, this is likely underreported given that prevalence of smoking is as high as 39% in the region (Alaska Department of Health and Human Services, 2012). PFOS, PFNA and PFOA were the most frequently detected PFASs and present at the highest concentrations. PFHxS and PFDA were detected in less than half of participants (Supplemental data). There were moderate to strong statistical correlations among serum PFASs (Supplemental data). Men tended to have higher concentrations of PFASs than women (Table 1). No individuals reported current or former thyroid disease, or current thyroid medication. One individual had a TSH concentration above the reference range. Eight individuals had TSH concentrations below the reference range. One individual had both total T_3 and fT_3 concentrations above the reference ranges. Two individuals had total T_4 concentrations above the reference range, and one had total T_4 concentration below the reference range. Unless specified all other hormones in these individuals were within the reference ranges.

Table 2 presents the results for models of individual PFASs and thyroid hormones, not controlling for the presence of other PFASs. PFOA, PFNA, and PFUnA were all positively and significantly associated with TSH, indicating higher TSH concentrations were present in more exposed individuals. Table 3 presents the results of individual PFAS regression models including a $PFAS_i$ *female sex product term. The table includes the effects of the $PFAS_i$ in men, as well as the joint effect of the $PFAS_i$ and female sex. Sex stratified models were unstable due to small sample size and so joint effects, the combined effect of female sex and exposure to $PFAS_i$ due to interaction, are reported. There was a significant interaction between female sex and PFNA for the effect on fT_3; the effect of PFNA on fT_3 in men was negative, and the joint effect of female sex and PFNA was positive. Another significant interaction was present between sex and PFOS for the effect on fT_3; the effect of PFOS in men was negative and the joint effect in women was positive. The interaction between PFNA and sex was significant ($p = 0.048$) for total T_3, with a negative association for men and a positive association for the joint effect of PFNA and female sex.

Table 4 presents a single model including multiple PFASs as predictors (PFOS, PFOA and PFNA), controlling for age, sex and smoking. Only PFOA remains positively associated with TSH in the combined model. Both PFNA and PFOA were correlated with total T_3 in the combined model, and interestingly the effects were in different directions; however, these associations were not statistically significant.

4. Discussion

In the current study of adult Alaska Natives, the blood serum concentrations of multiple PFASs were positively associated with TSH concentrations. PFOA, PFNA, and PFUnA were all significantly positively associated with TSH. When PFOA, PFOS and PFNA were simultaneously modeled as predictors, only PFOA remained as having a significant positive association with TSH. This may suggest that the inter-correlation of PFASs (Supplemental data) precludes parsing the effects of individual PFASs on thyroid status with the limited sample size.

Positive associations between PFASs and TSH have been observed in PFOS-treated cynomolgus monkeys, although this was hypothesized to be a response to a decrease in T_3 (Seacat et al., 2002). Several epidemiological studies have also reported positive associations between PFASs and TSH in humans. A study of the Korean general population found that perfluorotridecanoic acid (PFTrDA) was positively associated with serum TSH, and the association was stronger for females

Table 2
Log-unit effects of individual PFASs on thyroid hormones controlling for age, sex, and smoking status.

	(ln)TSH				**Total T4**					**fT4**			
	β (95% CI)			**p-value**		**β (95% CI)**			**p-value**		**β (95% CI)**			**p-value**
PFOA	**0.630**	**0.228**	**1.031**	**< 0.005**	**PFOA**	− 0.128	− 1.524	1.268	0.86	**PFOA**	− 0.036	− 0.138	0.066	0.49
PFOS	0.251	− 0.132	0.634	0.20	**PFOS**	− 0.348	− 0.977	0.282	0.28	**PFOS**	0.004	− 0.056	0.064	0.89
PFNA	**0.245**	**0.047**	**0.442**	**0.02**	**PFNA**	− 0.094	− 0.712	0.524	0.77	**PFNA**	− 0.007	− 0.052	0.037	0.75
PFUnA	**0.324**	**0.075**	**0.573**	**0.01**	**PFUnA**	0.354	− 0.331	1.039	0.31	**PFUnA**	0.005	− 0.056	0.066	0.88
	Total T3				**fT3**									
	β (95% CI)			**p-value**		**β (95% CI)**			**p-value**					
PFOA	− 7.669	− 18.609	3.272	0.17	**PFOA**	− 0.038	− 0.271	0.196	0.75					
PFOS	− 4.968	− 13.311	3.376	0.24	**PFOS**	− 0.057	− 0.224	0.109	0.50					
PFNA	0.662	− 5.763	7.086	0.84	**PFNA**	0.017	− 0.105	0.138	0.79					
PFUnA	− 2.809	− 9.104	3.486	0.38	**PFUnA**	− 0.098	− 0.217	0.020	0.10					

Table 3
Effect of PFASs in men, and the joint effect of PFASs-female sex interaction on thyroid hormones.

	Men				Joint effect in women			
	β	95% CI		p-value	β	95% CI		ǂp-value
				TSH				
PFOA	0.302	− 0.247	0.851	0.28	0.531	− 0.263	1.324	0.19
PFOS	− 0.055	− 0.618	0.508	0.85	0.439	− 0.182	1.061	0.17
PFNA	0.213	− 0.102	0.528	0.19	0.054	− 0.387	0.495	0.81
PFUnA	0.140	− 0.214	0.495	0.44	0.436	− 0.103	0.974	0.11
				Total T4				
PFOA	− 0.621	− 2.461	1.219	0.51	0.803	− 0.841	2.448	0.34
PFOS	0.201	− 1.096	1.499	0.76	− 0.797	− 2.525	0.930	0.37
PFNA	0.164	− 0.737	1.066	0.72	− 0.424	− 1.481	0.633	0.43
PFUnA	0.448	− 0.433	1.330	0.32	− 0.250	− 1.285	0.785	0.64
				fT4				
PFOA	− 0.010	− 0.142	0.122	0.88	− 0.043	− 0.185	0.100	0.56
PFOS	0.054	− 0.036	0.145	0.24	− 0.072	− 0.207	0.063	0.30
PFNA	0.005	− 0.059	0.068	0.89	− 0.020	− 0.103	0.063	0.64
PFUnA	0.033	− 0.038	0.104	0.37	− 0.072	− 0.172	0.029	0.16
				Total T3				
PFOA	− 14.241	− 26.241	− 2.240	0.02	11.292	− 5.246	27.829	0.18
PFOS	− 10.542	− 22.284	1.199	0.08	8.084	− 8.587	24.754	0.34
PFNA	− 5.648	− 11.937	0.641	0.08	**10.930**	**0.074**	**21.786**	**< 0.05**
PFUnA	− 6.702	− 13.033	− 0.371	0.04	9.783	− 3.539	23.104	0.15
				fT3				
PFOA	− 0.219	− 0.506	0.068	0.14	0.299	− 0.073	0.671	0.11
PFOS	− 0.302	− 0.529	− 0.074	0.01	**0.352**	**0.050**	**0.653**	**0.02**
PFNA	− 0.139	− 0.283	0.005	0.06	**0.265**	**0.062**	**0.467**	**0.01**
PFUnA	− 0.174	− 0.302	− 0.047	0.01	0.192	− 0.057	0.441	0.13

ǂ p for interaction.

than males (Ji et al., 2012). Unfortunately, PFTrDA was not measured in the current study. However, PFTrDA has been detected in numerous high trophic level arctic species at concentrations comparable to PFOA (Rotander et al., 2012; Routti et al., 2017). Future studies should assess exposure to long chain PFASs in the Arctic. Among adults in the 2007–2008 NHANES study, PFOA was positively associated with TSH concentrations (Jain, 2013). PFOS has also been positively associated with TSH in pregnant women; however, it is unclear whether these results are generalizable to non-pregnant women (Berg et al., 2017; Wang et al., 2013).

4.1. Effect modification by sex

Published literature suggests differential effects of PFASs on thyroid hormones based on sex. Among adult participants of the C8 study, participant sex significantly modified the associations between PFOS and T_4 (Knox et al., 2011). Among the Korean general population, total T_4 exhibited a significant negative association with PFTrDA, while TSH concentrations were positively associated with PFTrDA. When stratified by sex, the relationships between PFTrDA and thyroid hormones were only significant in women (Ji et al., 2012). Among participants of the 2007–2010 NHANES study, Wen et al. (2013) reported significant effects in sex stratified models. Positive associations in women were reported between PFOA and T_3, PFHxS and T_3, and PFHxS and T_4, while a negative association was reported between PFHxS and fT4 in men (Wen et al., 2013).

In the current study, a significant interaction was found between sex and individual PFASs (Table 3). The sex of the participant significantly modified the effect of both PFOS and PFNA on fT_3. PFOS and PFNA were positively associated with fT_3 in women and negatively associated with fT_3 in men. The association between PFNA and total T_3 was also significantly modified by sex. The interaction term suggests a positive association in women and a negative association in men. Small sample sizes resulted in unstable estimates for stratified models, and these results are not reported. This could be addressed in studies with larger sample sizes.

Additionally, the significant $PFAS_i$*female sex product term often produced significant associations for the effect estimates in men. Effect estimates in men and women tended to be in opposite directions regardless of the hormone or PFAS under study. While this trend was only significant in select PFASs, it may be indicative of fundamental differences in how PFASs influence thyroid function in men and women.

Table 4
Log-unit effects of PFOA, PFNA, and PFOS on thyroid hormones controlling for age, sex, smoking status, and other PFASs.

(ln)TSH					Total T4					fT4				
β (95% CI)				**p-value**	**β (95% CI)**			**p-value**		**β (95% CI)**				**p-value**
PFOS	− 0.073	− 0.495	0.350	0.74	**PFOS**	− 0.425	− 1.389	0.538	0.39	**PFOS**	0.028	− 0.041	0.096	0.43
PFOA	**0.555**	**0.067**	**1.043**	**0.03**	**PFOA**	0.114	− 1.619	1.847	0.90	**PFOA**	− 0.051	− 0.176	0.075	0.43
PFNA	0.128	− 0.113	0.370	0.30	**PFNA**	0.049	− 0.705	0.803	0.90	**PFNA**	− 0.004	− 0.060	0.051	0.88
Total T3					**fT3**									
β (95% CI)				**p-value**	**β (95% CI)**			**p-value**						
PFOS	− 5.476	− 12.278	1.326	0.11	**PFOS**	− 0.091	− 0.250	0.069	0.27					
PFOA	− 10.291	− 21.322	0.740	0.07	**PFOA**	− 0.045	− 0.313	0.223	0.74					
PFNA	5.299	− 0.364	10.961	0.07	**PFNA**	0.063	− 0.063	0.190	0.33					

Interestingly, women tended to have lower concentrations of PFASs than men in the study population, suggesting they may be more susceptible to PFAS induced thyroid disruption. Several sex hormones, including estrogen and human chorionic gonadotropin, can influence thyroid homeostasis, including increasing TSH expression, increasing production of thyroid hormones, as well as inhibition or induction of iodine absorption by the thyroid (D'Angelo and Fisher, 1969; Kraiem et al., 1994; Zingg and Perry, 1953). The effects of PFOS on T_3 may differ in women currently undergoing hormone replacement therapy (Shrestha et al., 2015), suggesting that estrogen or other sex hormones may play a role in the effect modification. In a study of 2011–2012 NHANES participants, PFOA and PFOS were also positively associated with T_3, and PFOA was positively associated with fT_3 among women aged 60–80, however not in women 20–40 years of age (Lewis et al., 2015), which may suggest different mechanisms of effect pre- and post-menopause. While PFASs are not thought to be estrogenic, they are capable of promoting estrogen dependent gene expression (Sonthithai et al., 2016) and altering concentrations of both estrogen and androgens in toxicological studies (Oakes et al., 2005; Seacat et al., 2002). The specific causes of the apparent effect modification by sex have not been determined.

4.2. Modeling exposure to multiple PFASs

Typically, epidemiological studies have reported effect estimates for individual PFASs without controlling for the effects of other PFASs (Melzer et al., 2010). When PFOS, PFOA and PFNA were simultaneously modeled, only PFOA remained significantly associated with TSH. Both PFOA and PFNA tended to associate with total T_3; however, the directions of the effects differed. PFNA was positively correlated with total T_3, while PFOA was negatively correlated with total T_3. Unfortunately, the high mutual correlation in the multiple PFAS models makes interpretation difficult. The model suggests that individual PFASs may have differential effects on thyroid function, and that controlling for confounding by other PFASs would be ideal given a large enough sample size. In assays of T_3 dependent cell growth, different PFASs demonstrated differential activity, and a non-monotonic dose response curve was observed for PFHxS (Long et al., 2013). High statistical correlation among PFASs, but different biological effects may in part explain the inconsistent associations in the literature.

4.3. Role of PFASs in thyroid disruption

Toxicological studies have reported numerous mechanisms by which PFASs may alter thyroid hormone homeostasis. Select PFASs are thyroid receptor agonists, with longer chain PFASs exhibiting greater binding affinity (Ren et al., 2014). Several PFASs are known to bind with thyroid transport proteins (Jones et al., 2003; Liu et al., 2011). PFOS may increase excretion of T_4 by upregulating β-glucuronidase expression in the liver. PFOS may influence type one deiodinase concentrations, which may increase conversion of T_4 to T_3 (Weiss et al., 2009; Yu et al., 2009). Additionally, PFOS is known to upregulate OATp and MRP2 expression, which may increase active transport of thyroid hormones into cells. Additionally, the response to PFAS exposure differs by species, making extrapolation from toxicological data difficult. For example, PFOS exposure in rodents is typically associated with hypothyroxinemia (Chang et al., 2008), while in fish it has been associated with increases in T_3 (Du et al., 2009; Shi et al., 2009). Furthermore, the net impact of these various mechanisms is difficult to predict. Despite similar exposure pathways, and high correlation of serum PFASs, evidence exists for differential biological effects (Jantzen et al., 2016).

Some studies suggest there are understudied modifiers and/or mediators of the relationship between PFASs and thyroid health. An analysis of 2007–2008 NHANES data suggests that the effect of PFAS exposure on thyroid measures may be modified by autoimmune status (TPO-ab) and iodine sufficiency (Webster et al., 2016). PFASs are also capable of altering sex hormone concentrations and sex hormone dependent gene expression (Liu et al., 2007; Oakes et al., 2005), which may indirectly impact thyroid health. While the overall weight of evidence indicates a relationship between PFASs and thyroid health, the inconsistency of the results suggests that the full complexity of this relationship is not yet understood.

Because no participants reported clinical disease, and circulating hormones did not suggest clinical thyroid disruption in any participants, the study does not support inferences about PFAS exposure and thyroid disease. However, sub-clinical thyroid disruption is associated with morbidity. Osteoporosis and changes in cardiac anatomy and physiology are more common among individuals with sub-clinical hyperthyroidism (Biondi et al., 2005), while subclinical hypothyroidism is associated with overweight and obesity (Biondi, 2010), adverse cardiovascular outcomes (Imaizumi et al., 2004; Rodondi et al., 2005), and impaired cognitive function (Osterweil et al., 1992).

4.4. Limitations

These data are cross-sectional and therefore the temporal relationship between PFASs and thyroid hormones cannot be assessed. Additionally, this was a convenience sample and therefore may not be representative of the study population. However, there is no reason to suspect that participants would have *a priori* knowledge of serum PFAS concentrations or thyroid status, making the source of bias small for these associations. The small sample size limits the number of covariates that can be simultaneously modeled while preserving power to detect associations (i.e., the study has low statistical power). It additionally complicates interpretation, as a lack of significance may not represent a lack of effect, and regression estimates may not represent population level parameters. This study presents multiple statistical tests, which could increase the probability finding false positive associations. More information on thyroid health, such as measurements of thyroid transport proteins, thyroperoxidase antibodies, and iodine sufficiency would provide a clearer picture of this complex association. Bias from competitive binding in thyroid hormone assays has been reported but is not thought be an issue at concentrations present in human serum (Lopez-Espinosa et al., 2012).

In most cases, effects estimates from models using the mean of the observed for data < LOD produced similar, but more conservative estimates of effect. Larger percentages of missing data often resulted in greater disagreement between models. Given relatively small percentages of missing data, simple imputation can produce minimally biased effect estimates (Schisterman et al., 2006); however, a poor approximation of the variance will affect estimates of the standard error. Underestimating the standard error may artificially reduce p-values. The empirical (i.e., robust/sandwich) estimator used by GEE, based on actual within cluster variation, provides a reasonable estimate of covariance given an unknown covariance structure, but may underestimate the true standard error (Hanley et al., 2003).

Residents of St. Lawrence Island are exposed to a wide range of persistent halogenated organic compounds, many of which are known or suspected to disrupt thyroid hormone homeostasis (Byrne et al., 2015, 2018; Carpenter et al., 2005). PFASs tend to be poorly correlated with lipophilic chemicals such as polychlorinated biphenyls; this limits the potential confounding by these chemicals, but uncharacterized interactions are possible (Grandjean et al., 2012). Several PFASs, such as PFTrDA, have been associated with thyroid disruption (Ji et al., 2012), but were not measured as part of this study. Residual confounding by unmeasured PFASs is possible. This study did not measure body mass index (BMI), which may be an uncontrolled confounding variable. While other studies have reported effect modification by sex while controlling for BMI, it is possible that BMI impacted the interaction between PFAS and sex in this study.

5. Conclusion

The results of this study suggest an association between select PFASs and disruption of thyroid homeostasis. The causal relationship between PFASs and human thyroid disruption, and the clinical relevance of this relationship, remain unclear. Statistically significant relationships were present despite the lack of clinical thyroid disease in the study population. The results of this study suggest differential effects in men and women; effect modification by sex should be assessed in larger studies of PFASs and thyroid function. Associations between PFNA and thyroid function measures in this population are notable because PFNA is one of the most frequently detected PFASs in the Arctic (Muller et al., 2011). When multiple PFASs are simultaneously modeled, the strength and direction of effect estimates can be dissimilar to those of individually modeled PFASs. This study suggests a complex relationship between PFASs and thyroid homeostasis involving multiple PFASs and modified by the sex of the individual.

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Conflicts of interest

The authors declare they have no actual or potential competing financial interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2018.06.014.

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