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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.