Schlezinger *et al. Environmental Health* (2025) 24:10
https://doi.org/10.1186/s12940-025-01165-8

Environmental Health

RESEARCH Open Access

Per- and poly-fluoroalkyl substances (PFAS) in circulation in a Canadian population: their association with serum-liver enzyme biomarkers and piloting a novel method to reduce serum-PFAS

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Abstract

Extensive use of per- and polyfluoroalkyl substances (PFAS) has resulted in their ubiquitous presence in human blood. PFAS exposures have been associated with multiple adverse human health effects. Biomonitoring studies have focused on long-chain PFASs, but these are being replaced by short-chain PFASs or with alternate PFAS chemistries (or replacement chemistries such as GenX), resulting in changes in human exposures with time. Here, we take advantage of serum samples collected as part of a clinical trial testing the efficacy of a dietary fiber intervention to reduce serum cholesterol to investigate exposure to PFASs in Canadian participants. Serum samples were collected from 72 participants (adult males with elevated cholesterol) in 2019–2020 at baseline and after 4 weeks of the intervention and were analyzed for 17 PFASs. The highest geometric mean serum concentrations of PFAS measured at baseline corresponded to PFOSA (7.1 ng/ml), PFOS (4.2, ng/ml), PFOA (1.8 ng/ml) and PFHxS (1.3 ng/ml). Four long-chain PFASs (PFOA, PFOS, PFOSA and PFHxS) and two short-chain PFASs (PFBA, PFHxA) were detected in 100% of participants. GenX was detected in 71% of participants. Analyses of associations between serum-PFAS concentrations and biomarkers of adverse health outcomes showed the PFBA, PFHxA, PFDA and PFOSA were associated with higher serum gamma-glutamyl transferase concentrations but not with measures of serum-total or low-density lipoprotein cholesterol. Comparison of PFAS concentrations at baseline and after a 4-week follow-up showed that the total PFAS detected decreased in both the control and cholesterol intervention groups. However, the suite of long-chain PFASs of concern identified by the United States National Academies of Sciences, Engineering, and Medicine, significantly decreased only in the cholesterol intervention group. This observation suggests that a sustained dietary fiber intervention may reduce long-chain PFAS body burden, but future intervention studies need to control for PFAS exposure sources and extend the dietary supplement intake

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beyond 4 weeks. Overall, the results show that exposures to short-chain and replacement chemistry PFASs are common in this Canadian population.

Keywords Serum-PFAS, Oat β-glucan, PFAS intervention, PFOA, PFOS, PFOSA, Cholesterol, LDL-C, Dietary fiber

Introduction

Per- and polyfluoroalkyl substances (PFAS) are a large class of chemicals, many of which are persistent, mobile, and bioaccumulative chemicals. The general public is exposed to PFASs via ingestion of contaminated food and drinking water and use of consumer products that contain PFAS [1–3]. Long-chain perfluorocarboxylic acids with 7 or more fluorinated C atoms [e.g., perfluorooctanoic acid (PFOA)] and perfluorosulfonic acids with 6 or more fluorinated C atoms [e.g., perfluorooctane sulfonic acid (PFOS)] have been historically used in numerous commercial and industrial applications, including aqueous film forming foam (AFFF), processing aids in polymer manufacturing, and food contact materials [4]. The long-chain PFAS, also known as legacy PFAS, are commonly detected in drinking water, edible species, food packaging, air and other environmental media [5–7] It is estimated that 200 million people in the United States alone rely on tap water contaminated with PFAS [8]. Multiple PFAS are universally detected in the serum of human populations [9].

Biomonitoring efforts over the past decade have focused on assessing exposure to long-chain PFASs. Many long-chain PFAS have been phased out of production and have been replaced with short-chain PFAS or other PFAS chemistries (i.e., replacement chemistry PFAS). Short-chain perfluorocarboxylic acids have 6 or fewer fluorinated C atoms [e.g., perfluorobutanoic acid (PFBA)], and perfluorosulfonic acids have 5 or fewer fluorinated C atoms [e.g. perfluorobutane sulfonic acid (PFBS)]. Replacement chemistry PFAS include perfluoroalkyl ether carboxylic acids [e.g., hexafluoropropylene oxide-dimer acid (GenX)] and perfluoroalkyl ether sulfonic acids. Trends in PFAS production and use also have started to be reflected in human serum-PFAS concentrations worldwide, with serum concentrations of PFOA and PFOS decreasing while short-chain PFASs are increasing [10–13]. Focusing on studies conducted in North America, the Canadian Health Measures Survey (CHMS) of the general Canadian population began analyzing short-chain PFASs (PFBA, perfluorohexanoic acid (PFHxA) and PFBS) in Cycle 2 (2007–2009) but did not detect these PFASs in serum until sampling in Cycle 5 (2015 – 216) [14]. However, PFBA, PFHxA and PFBS were not detected in serum of First Nation populations in samples collected in 2016-17 [15–17]. In the 2013–2014 cycle of the United States National Health and Nutrition Examination Survey, small portions of the general population were found to have measurable levels of serum-PFBS and PFHpA (0.6% and 12.6%, respectively) [18]. In 2020, however, short-chain PFASs and ultra-short-chain PFASs (perfluorocarboxylic acids with 2–3 fluorinated carbons) were frequently detected in serum in samples collected in North America, reflecting changes in exposure profiles and possibly stemming from indoor sources [19]. Exposure to these shorter-chained PFASs in other populations and their potential health risks are not well understood.

The United States National Academies of Sciences, Engineering, and Medicine (NASEM) recently provided clinical guidance for follow up with patients exposed to seven specific PFAS compounds. NASEM PFASs include PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorohexane sulfonic acid (PFHxS), PFOS and N-methylperfluro-1-octanesulfonamido-acetic acid (MeFOSSA). The consensus report recommends that individuals with summed serum concentrations of NASEM PFASs ≥ 20 ng/ml should undergo clinical follow-up for thyroid function (age 18 or older); kidney function and cancer (age 45 or older); and ulcerative colitis and testicular cancer (age 15 or older) [20]. Individuals with the sum of the same PFASs ≥ 2 ng/ml should be prioritized for screening for dyslipidemia, hypertensive disorders of pregnancy, and breast cancer (at specified intervals). The association between serum-PFAS concentrations and increased total cholesterol and non-high density lipoprotein cholesterol (HDL-C) in people is supported by strong epidemiological evidence (as reviewed in [21]. Further, a recent meta-analysis of observational human studies reports a significant association between PFASs and markers of liver function [22].

Despite the growing concerns about the toxicity of PFAS, specific interventions to reduce PFAS levels in the body are limited. Recent epidemiological studies suggest one potential strategy. Investigation of dietary patterns and PFAS body burdens show that the consumption of fruits or vegetables and fiber-rich diets are associated with lower serum-PFAS concentrations in both adults and children [23–28]. Further, life-style changes designed to reduce serum cholesterol via increasing dietary fiber were shown to be associated with reductions in serum-PFAS [29]. One explanation for this association is that dietary fibers may impede the absorption or reabsorption of PFAS by cells lining the gut. In fact, gel forming, soluble dietary fibers decrease the absorption of bile acids leading to increased bile acid elimination in feces [30]. Oat β-glucan is one such dietary fiber that has been shown to reduce serum cholesterol by enhancing bile

acid elimination [31]. Bile acids are chemically similar to long-chain PFAS in that both are amphipathic, are charged at pH's above 5, have molecular weights in the 400–500 g/mol range, and are moved into gut epithelial cells via active transport [32, 33]. Thus, gel-forming dietary fibers may enhance elimination of PFAS as they do bile acids.

Here, we take advantage of serum samples collected as part of a clinical trial in 2019–2020 testing the efficacy of an oat β-glucan intervention to reduce serum cholesterol, to investigate body burden of long-chain, short-chain and replacement chemistry PFASs in a Canadian population. In addition, we used clinical data on liver function biomarkers and serum lipid concentrations to examine associations between PFASs and these clinically relevant biomarkers. Last, given that bile acids and PFAS are biochemically similar as amphiphilic compounds, we examined whether the fiber intervention, which was designed to reduce cholesterol by trapping bile acids in the gut lumen, might reduce PFAS concentrations in serum.

Methods

Human serum samples

Serum samples were obtained from a previously conducted clinical trial (NCT03911427) that was conducted with the goal of reducing cholesterol through oat β-glucan (OBG) supplementation in adults 18-65y with elevated low density lipoprotein cholesterol (LDL-C) at baseline. Participants in the original study (224 in total) were recruited from Toronto, Ontario, Canada and the surrounding area from April 2019-February 2020 (Wolever et al., 2021). In the randomized, double-blind, placebo-controlled, parallel-arm design clinical trial, participants consumed sachets of OBG (1 g β-glucan, 1.9 g fiber per sachet; intervention group) or brown rice powder (0 g β-glucan, 0.3 g fiber per sachet; control group) mixed with 8 oz water three times per day separated by ≥ 3 h and preferably immediately before or within 10 min of each main meal (breakfast, lunch, and dinner)(Wolever et al., 2021). Detailed subject recruitment, study protocols and Institutional Review Board compliance for human subjects research are described elsewhere (Wolever et al., 2021). Fasting serum samples were collected at baseline and after 4 weeks of intervention (Wolever et al., 2021). Deidentified serum samples were transported on temperature monitored dry ice and blinded before PFAS analyses. Serum samples from the participants were analyzed for seventeen PFAS at baseline and after 4 weeks of the intervention. As determined by the Boston University Institutional Review Board, secondary analysis of previously collected, deidentified samples described herein does not constitute human subjects research.

Based on serum-PFAS levels observed in the general North American (Canada and US) population, males have been reported to have greater concentrations of total long-chain PFASs than females [14, 35–37]. Using this information, we selected serum samples from male participants and restricted the sample pool to only those males who followed protocol (per protocol, PP) according to Wolever et al. 2021. Of the 224 original study participants, 74 were male, among which 72 were identified as "per protocol " (PP; 42 PP in the OBG intervention group; 30 PP in the rice control group).

Biomarker analyses

Fasting serum samples were analyzed for total- and high density lipoprotein cholesterol, triglycerides, calculated LDL-C, aspartate aminotransaminase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) as described in the original study (Wolever et al., 2021).

Serum-PFAS analyses

The analytical method targeted 17 PFASs consisting of PFBA, PFHxA, PFHxS, PFHpA, PFOA, PFOS, perfluorooctanesulfonamide (PFOSA), PFNA, PFDA, PFUdA, GenX, 1 H,1 H,2 H,2 H-Perfluorooctanesulfonate (6:2 FTS), MeFOSSA, N-ethylperfluro-1-octanesulfonamidoacetic acid (Et-FOSAA), perfluoropentylsulfonate (L-PFPeS), PFDoA, and perfluro-4ethylcyclohexanesulfonate (PFECHS). Information on materials and samples preparation are provided in the Supplemental Material.

Serum samples (200 µL) were spiked with the internal standard (IS) cocktail (Table S1)(nominal 1–10 ng/ml each; IS mix cocktail obtained from Wellington Labs LLC, Wilmington, DE), followed by the addition of 1 ml of 1% acetic acid in distilled water to denature protein and centrifugation at 12,500× G for 5 min. The supernatant was loaded into a prewashed and preconditioned solid phase extraction cartridge (Strata X-AW 33 µm; 6 mg/3 ml; Phenomenex Inc, Torrance CA) for sample cleanup and concentration. The final eluate containing PFAS (2 × 1 ml 1% ammonium hydroxide in methanol) was evaporated to dryness under a gentle stream of nitrogen, reconstituted in 200 µL methanol, and analyzed for PFASs.

PFASs were identified and quantified by liquid chromatography– negative electrospray ionization - tandem-mass spectrometry (LC-ESI$^-$ - MS/MS) in an Applied Biosystems API4000 triple quadrupole mass spectrometer using the isotope dilution method. Chromatographic separation was accomplished on a Shimadzu LC20 series stack using a Luna C18, 3 µm, 100 × 4.6 mm analytical column (Phenomenex). Mobile phases were 10mM ammonium acetate in deionized water (A) and 10mM ammonium acetate in methanol (B). Chromatographic

gradient was 10% B the first min, to 65% B at 2 min, to 99% B at 15 min, hold 99% B to 20 min, followed by 5 min post-column equilibration. Sample injection volume was 10µL. Background PFAS contamination was eliminated using an online delay column (Phenomenex Luna C18, 50 × 4.6 mm, 3 µm). A diverter valve was used (VICI, Valco Instrument Co. Inc.) to divert the front and back-end of the chromatographic run to waste.

The scheduled MRM mode (Table S2) was used for data acquisition of the target set of PFASs. 20% of samples were analyzed as true blind duplicates. Analyte recoveries, derived from internal standard recovery rates, were in the 95–102% range at serum concentrations of 0.5-5 ng/ml (< 7% relative standard deviation), with calibration curve coefficients of $R > 0.999$ for all analytes. Limits of detection ranged from 1 to 50 pg/ml, equivalent to 10–500 fg injection on the column (Table S3). Tested and certified PFAS-free labware was used throughout the chain of sample acquisition, processing, and analysis. Quality control included laboratory blanks, blind sample duplicates, random blanks to check for carryover or cross-contamination, and a well-characterized aqueous film forming foam sample.

Statistical analyses

Demographic data were examined for underlying distributions using the Shapiro-Wilks statistical test, and ln-transformed values were applied to normalize the distribution and subsequent statistical analysis (unpaired t-tests) performed with Prism 10.2.3 (GraphPad Inc. Boston, MA). Concentrations of individual PFAS in serum samples were examined for underlying distributions using the Shapiro-Wilks statistical test, and ln-transformed serum values were used to normalize the skewed values in subsequent statistical analysis performed with SAS 9.4 (SAS Institute Inc. Cary, NC). Descriptive statistics including geometric means (GM) and geometric standard deviations (GSD) were calculated for 11 individual PFAS detected at baseline and after 4 weeks of intervention in 70% or more of participants, stratified by intervention (OBG vs. rice group). Concentrations of PFASs for samples below LOD were substituted with the LOD /√2 (Zeghnoun et al., 2007). The GM ratios of serum concentrations between baseline and week 4 of intervention were calculated as the difference in logged values of the paired data for each individual PFAS. Paired t-tests on the ln-transformed data were conducted to examine the difference between serum-PFAS concentrations at baseline and week 4 within each group. Multivariable linear regression was used to test the associations between serum-PFAS and clinical biomarkers (liver enzymes and cholesterol values) at baseline adjusting for age and BMI.

Table 1 Demographic and biomarker characteristics between men with oat β-glucan intervention versus control group[a] at baseline

	Total	OBG	Rice	*p*-value[b]
n	72	42	30	
Age (years)	41 ± 1.3	42.0 ± 1.3	41 ± 1.2	0.72
Smoker (Y: N)	4:68	3:39	1:29	
Wt (kg)	82.1 ± 1.2	82.6 ± 1.2	81.3 ± 1.2	0.71
BMI (kg/m^2)	27.2 ± 1.1	27.1 ± 1.2	27.3 ± 1.2	0.77
Triglycerides (mmol/L)	1.5 ± 1.6	1.6 ± 1.6	1.4 ± 1.6	0.30
T-Chol (mmol/L)	5.6 ± 1.1	5.6 ± 1.1	5.5 ± 1.1	0.55
HDL-C (mmol/L)	1.2 ± 1.2	1.2 ± 1.3	1.2 ± 1.2	0.63
LDL-C (mmol/L)	3.6 ± 1.1	3.6 ± 1.2	3.6 ± 1.1	0.84
GGT (U/L)	24.0 ± 2.0	26.0 ± 2	27.0 ± 2	0.22
ALT (U/L)	26.0 ± 2.0	25.0 ± 2	24.0 ± 1	0.45
AST (U/L)	24.0 ± 1.0	23.0 ± 1	24.0 ± 1	0.34

[a]Values are geometric means ± geometric standard deviations or *n*

[b]Unpaired t-tests were performed on ln-transformed data

Results

Demographics and clinical biomarker values of study participants at baseline

The demographic data and clinical serum biomarker characteristics of the participants at baseline are presented in Table 1. These characteristics were similar between the two groups.

PFAS distribution in serum at baseline

In serum samples collected at baseline, 11 of 17 PFASs were detected in >70% of participants (GenX, PFBA, PFHpA, PFHxA, PFHxS, PFOA, PFOS, PFOSA PFNA, PFDA, PFUdA) while five of them (6:2 FTS, Me-FOSAA, Et-FOSAA, L-PFPeS, PFDoA, PFECHS), were below the method limit of detection (LOD, Table S3). Of the PFASs detected above the LOD, PFBA, PFHxA, PFOA, PFHxS, PFOS and PFOSA were quantified in 100% of the samples. Five PFAS (GenX, PFHpA, PFNA, PFDA, PFUdA) were measured in 71-97% of samples (Table 2). The highest PFAS concentrations measured at baseline correspond to PFOSA (GM=7.1; GSD=1.8 ng/ml), PFOS (4.2; 1.9 ng/ml), PFOA (1.8;1.6 ng/ml) and PFHxS (1.3; 2.4 ng/ml) and the lowest levels correspond to PFDA and PFUnDA (Table 2). We compared the serum-PFAS concentrations of participants from Ontario, Canada to those observed in cycle 6 of CHMS (2018-2019) [14]. Compared to concentrations reported in CHMS, serum concentrations of PFBA and PFHxA were at least 7-10x higher (Table 2). GenX and PFOSA, which were not measured in the CHMS study, were detectable in the majority of participants. The long-chain PFASs had similar concentrations in both studies (Table 2).

Table 2 Comparison of serum-PFAS concentrations (ng/ml) between the Canadian health measures survey (CHMS) study and the current study

	CHMS Cycle 6	Current Study Baseline (*n*=72)		
PFAS	**Geometric Mean (range)** [c]	**LOD**	**% Detection**	**GM (GSD)**
PFBA	< 0.08 [d]	0.014	100	0.77 (1.55)
PFHxA	<0.08 [d]	0.008	100	0.59 (2.32)
PFHpA	NA [e]	0.008	90	0.44 (4.08)
PFOA	1.4 (1.2-1.6)	0.008	100	1.79 (1.69)
PFNA	0.48 (0.44–0.53)	0.010	97	0.84 (2.54)
PFDA	0.13 (0.11–0.15)	0.007	88	0.11 (2.92)
PFUdA	0.38 [f]	0.011	71	0.16 (4.11)
PFHxS	1.2 (1.0–1.4)	0.007	100	1.27 (2.42)
PFOS	3.6 (3.3–4.0)	0.012	100	4.16 (1.88)
GenX[a]	NA	0.014	71	0.45 (8.66)
PFOSA	NA	0.017	100	7.06 (1.79)
Total PFAS				21.51 (1.72)
NASEM PFASs[b]				9.19 (1.63)

[a]Two samples had GenX concentrations 57 and 62 ng/ml (2-fold higher than the next highest concentration). 75th percentile = 1.25 ng/ml. 95th percentile = 16.76 ng/ml

[b]NASEM PFASs include PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFOS. Me-FOSAA

[c]Canadian Health Measures Survey (CHMS) study (2018-2019). Measured in males 12-79 years of age (PFBA, PFHxA, PFNA, PFDA, PFUdA) or 20-79 years of age (PFOA, PFHxS, PFOS). Health Canada, 2021

[d]LOD (limit of detection) for the specified analyte in the CHMS

[e]NA, Not analyzed

[f]A GM was not reported for PFUdA because of a low detection rate (39%). Here we report the 90th percentile value

Testing for associations of liver damage biomarkers with serum-PFAS levels

Liver is a major target organ of PFAS, with PFAS inducing hepatomegaly and lipid accumulation in rodent models (e.g., [38]). Therefore, we tested associations between PFAS serum levels and serum markers of liver damage GGT, AST and ALT. A number of PFASs, including PFBA, PFHxA, PFDA and PFOSA, were associated with higher GGT concentrations, while PFHxA and PFHxS were associated with higher ALT concentrations (Table 3, Table S4). We observed no associations between PFASs analyzed in serum and AST concentrations.

Testing for associations of serum-lipids with serum-PFAS levels

Increased total cholesterol and non-HDL-C are well-supported health endpoints linked to PFAS exposure in humans [21]; therefore, we assessed the relationship between PFAS and blood lipid levels. Only PFHxA and PFHpA were significantly associated with serum-cholesterol concentrations, and they were associated with higher concentrations of HDL-C (Table 4, Table S5).

Assessing the impact of a dietary fiber intervention on serum-PFAS levels

The original study, from which the samples were collected, was designed to test the efficacy of an oat β-glucan beverage in reducing serum-cholesterol levels (Wolever et al., 2021). Total dietary fiber intake was the same at baseline for participants that consumed the oat β-glucan beverage versus a rice beverage (Wolever et al., 2021). Dietary fiber intake overall increased in the oat β-glucan group versus baseline and versus the rice group (Wolever et al., 2021). Given that PFAS can share biochemical

Table 3 Association between liver function biomarkers and serum- PFAS (adjusted for age and BMI), *n*=72

	GGT		AST		ALT	
PFAS	**β**[a]	***p*-value**[b]	**β**	***p*-value**	**β**	***p*-value**
PFBA	**1.377**	**0.009**	0.965	0.649	1.200	0.152
PFHxA	**1.129**	**0.054**	1.055	0.171	**1.133**	**0.051**
PFHpA	0.978	0.558	1.008	0.735	1.022	0.579
PFOA	1.127	0.281	1.094	0.193	1.117	0.331
PFNA	1.066	0.279	0.993	0.853	0.973	0.654
PFDA	**1.099**	**0.062**	0.976	0.445	0.963	0.463
PFUdA	0.994	0.880	0.970	0.217	0.943	0.146
PFHxS	0.968	0.605	1.045	0.259	**1.163**	**0.017**
PFOS	1.019	0.841	0.989	0.849	0.999	0.99
GenX	0.979	0.43	0.981	0.245	0.956	0.087
PFOSA	**1.203**	**0.059**	1.070	0.266	1.160	0.141
Total PFAS	1.079	0.489	1.034	0.627	1.050	0.66
NASEM PFASs[c]	1.064	0.614	1.027	0.720	1.100	0.448

[a]β = Change in U/L of serum liver biomarker per ng/ml PFAS increase in serum

[b]Multivariable linear regression

[c]NASEM PFASs include PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFOS. Me-FOSAA concentrations were below the LOD

Table 4 Associations between measures of serum-cholesterol and PFAS exposure (adjusted for age and BMI). *n* = 72

	Total cholesterol		LDL-C		HDL-C	
PFAS	**β**[a]	***p*-value**[b]	**β**	***p*-value**	**β**	***p*-value**
PFBA	0.015	0.731	0.017	0.755	-0.059	0.395
PFHxA	0.031	0.15	0.015	0.582	0.073	**0.035**
PFHpA	0.002	0.879	-0.006	0.712	0.053	**0.009**
PFOA	-0.007	0.848	-0.004	0.935	-0.026	0.674
PFNA	0.019	0.342	0.018	0.483	0.031	0.345
PFDA	-0.006	0.726	-0.005	0.823	-0.021	0.452
PFUdA	0.006	0.668	0.017	0.302	-0.031	0.157
PFHxS	-0.014	0.53	-0.025	0.35	0.036	0.301
PFOS	-0.006	0.847	0.017	0.67	-0.061	0.237
GenX	-0.003	0.779	0.003	0.796	-0.018	0.208
PFOSA	0.011	0.744	0.004	0.916	0.034	0.536
Total PFAS	-0.005	0.892	-0.002	0.971	-0.001	0.993
NASEM PFASs[c]	-0.004	0.924	0.021	0.686	-0.052	0.444

[a]β = change in mmol of cholesterol biomarker per ln-ng PFAS increase in serum

[b]Multivariable linear regression

NASEM PFASs include PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFOS. Me-FOSAA concentrations were below the LOD

Table 5 Effect of fiber beverage intervention on serum-PFAS concentrations

	OBG (*n*=42)				Rice (*n*=30)			
	Baseline	**4 weeks**	**GM Ratio**[a]	***p*-value**[b]	**Baseline**	**4 weeks**	**GM Ratio**[a]	***p*-value**[b]
PFAS	GM (GSD)	GM (GSD)	B/W4		GM (GSD)	GM (GSD)	B/W4	
PFBA	0.80 (1.6)	0.66 (1.6)	1.2	**<0.01**	0.73 (1.5)	0.58 (1.6)	1.3	**0.01**
PFHxA	0.59 (2.4)	0.51 (2.2)	1.2	**0.06**	0.58 (2.2)	0.45 (1.9)	1.3	**0.02**
PFHpA	0.37 (4.5)	0.30 (4.4)	1.2	**<0.01**	0.56 (3.4)	0.38 (2.9)	1.5	**0.01**
PFOA	1.74 (1.7)	1.61 (1.8)	1.1	0.14	1.87 (1.6)	1.85 (1.8)	1	0.8
PFNA	0.70 (3.1)	0.66 (3.1)	1.1	0.14	1.07 (1.7)	1.07 (1.7)	1	0.98
PFDA	0.10 (3.2)	0.10 (3.2)	1	0.84	0.13 (2.5)	0.14 (2.5)	0.9	0.4
PFUdA	0.13 (4.4)	0.13 (4.3)	1	0.8	0.20 (3.7)	0.20 (3.7)	1	0.89
PFHxS	1.09 (2.6)	1.00 (2.5)	1.1	**0.07**	1.56 (2.2)	1.53 (1.8)	1	0.88
PFOS	3.91 (1.8)	3.59 (2.0)	1.1	0.12	4.50 (2.0)	4.31 (2.1)	1	0.35
GenX	0.29 (6.4)	0.28 (6.7)	1	0.77	0.83 (11.0)	0.66 (8.1)	1.3	0.29
PFOSA	6.91 (1.8)	6.55 (1.8)	1.1	0.5	7.27 (1.8)	7.35 (1.8)	1	0.78
Total PFAS	19.2 (1.5)	17.7 (1.6)	1.1	**0.08**	24.9 (1.9)	21.6 (1.6)	1.2	**0.05**
NASEM PFASs[d]	8.6 (1.6)	7.9 (1.7)	1.1	**0.03**	10.1 (1.6)	9.7 (1.7)	1	0.27

[a]GM ratios were calculated as the difference in ln-serum concentrations at baseline (B) and week 4 (W4) of the intervention of the paired data for each specific PFAS, NASEM PFASs and total sum

[b]GM concentrations are reported in ng/ml

[c]Paired t-tests were performed on ln-transformed data to compare PFAS concentrations at baseline vs. week 4

[d]NASEM PFASs include PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFOS. Me-FOSAA concentrations were below the LOD in all samples

characteristics with bile acids, we examined the data to determine if serum-PFAS concentrations were reduced to a greater extent in participants that consumed the oat β-glucan beverage versus a rice beverage. Total PFAS concentrations decreased in both groups; however, there was no difference in the magnitude of decrease between the OBG and Rice groups (Table 5). Of the individual PFAS, PFBA, PFHxA and PFHpA decreased significantly in concentration in both groups over the 4-week study period (Table 5). However, NASEM PFASs significantly decreased in concentration only in the OBG group over the study period, potentially driven by combined decreases in PFOA and PFOS (Table 5).

Discussion

Targeting a broader and more diverse list of PFAS analytes than in most previously published studies, we aimed to characterize long-chain, short-chain and replacement chemistry PFAS in previously collected serum from Canadian participants from a published clinical trial. Also, using the available liver and lipid homeostasis biomarker data, we tested the associations of PFASs with these biomarkers. Finally, we took the opportunity

to pilot test a novel hypothesis, that consumption of gel-forming dietary fibers can decrease PFAS body burdens in people.

Serum concentrations of long-chain PFASs in this study were largely typical of those found in the general population of Canada. Overall, the participants in this study had serum-PFAS concentrations consistent with typical food/water borne exposure and not with occupational exposures or exposures associated with living in a community heavily contaminated with PFASs [39–41]. Regardless, all of the participants had NASEM PFAS serum concentrations ≥ 2 ng/ml, the exposure level at which NASEM clinical guidance recommends decreasing exposure and further medical follow-up (screening for dyslipidemia, hypertensive disorders of pregnancy and breast cancers). 7% of participants had NASEM PFAS serum concentrations ≥ 20 ng/ml. Per NASEM guidelines, these individuals should undergo clinical follow-up for thyroid function (age 18 or older); kidney function and cancer (age 45 or older); and ulcerative colitis and testicular cancer (age 15 or older)([20].

Long-chain precursors (e.g., PFOSA, a precursor to PFOS), short-chain PFASs and replacement chemistry PFASs (e.g., GenX) were commonly detected in baseline serum samples. One previous study attempted to quantify PFOSA in Canadians in samples taken in 2002, yet all samples were below the LOD of 1.5 ng/ml [42]. In our study, PFOSA was detectable in all baseline samples and had the highest geometric mean serum concentration of any PFAS measured (7.1 ng/ml). This is the first study to report GenX exposure in a Canadian population; we detected GenX in 71% of baseline serum samples. Of note, we detected short-chain PFBA and PFHxA in nearly 100% of baseline serum samples, not previously detectable in CHMS Cycle 6. We detected PFHpA in 90% of serum samples, a higher frequency of detection than was observed in samples of pregnant Canadians taken in 2009-12 (67% [43]) or 2004–2005 (< 5% [44]). The lower LODs in our study likely has played a role in the higher detection frequencies relative to the earlier studies. However, higher exposure concentrations (GM and median for example) likely reflect increasing use of these PFASs in consumer products and with them exposures to the general population [19].

Several adverse health effects have been linked to PFAS and are well-supported by epidemiological data in humans [45]. Here, we were specifically interested in testing the associations of serum-PFAS concentrations with biomarkers of liver toxicity and dyslipidemia, as they are likely mechanistically linked [46]. A recent meta-analysis reported associations between PFOA, PFNA, PFOS, and PFHxS and higher serum-ALT levels, with PFOA also being associated with higher GGT levels [22]. Here, we observed that PFHxS also was associated with higher serum-ALT and multiple PFASs (PFBA, PFHxA, PFDA, and PFOSA) were associated with higher GGT concentrations. This is in line with another recent study of Canadian participants that showed that GGT was the liver function biomarker most commonly associated with multiple PFASs [11]. Overall, however, the GGT geometric mean levels in the participants (24 U/L) is within the normal range for men 30–50 years of age who do not consume alcohol (mean: 30 ± 22 U/L, range: 9–72 U/L) [47]. The normal reference range value for GGT in men is 55 U/L. For comparison, in 30–50 year old men who moderately consume alcohol (1 to 21 standard drinks per week, 1–40 g ethanol per day), the mean GGT was 34 ± 24 U/L (range: 10–86 U/L) [47]. In 30–50 year old men and women who are heavy drinkers (40–540 g ethanol per day), the mean GGT was 183 ± 341 U/L [47].

We expected to observe positive associations between total cholesterol and low density lipoprotein cholesterol measures and serum-PFAS concentrations, as the epidemiological data supporting these associations are robust [21] and they have been reported in Canadians [11]. However, the only associations that reached significance were for higher levels of HDL-c associated with PFHpA and PFHxA, possibly due to the relatively small sample size in this study compared to Cakmak et al. 2022 (72 participants vs. 6768 participants). There are multiple reasons why we detected associations between serum-PFAS concentrations and biomarkers of liver injury and not serum-cholesterol. Since perturbation of lipid metabolism is likely to occur downstream of liver injury, changes in serum-cholesterol may not have had sufficient time to develop. Additionally, differences in precision of the analyses may allow for greater sensitivity to detect differences in biomarkers of liver injury than changes in serum-cholesterol.

Many PFASs are ionized at physiological pH and thus are transported from the gut contents into the body by cells that line the intestines [48], leading to efficient initial absorption following ingestion of PFASs [49] and reabsorption after excretion of PFASs in bile [50]. Together with low levels of urinary excretion of PFASs in humans [51], the cycle of excretion in bile and reuptake by gut lining cells via enterohepatic recirculation is an important factor contributing to the long half-life of long-chain PFASs in humans [52]. As such, reducing enterohepatic recirculation is anticipated to reduce body burdens of PFASs. Numerous studies have shown that consumption of gel-forming dietary fibers (e.g., β-glucan found in oats and barley) [31] leads to reductions in LDL-C in the blood because these fibers "trap" bile acids, which are formed from cholesterol in the liver. Trapping of bile acids in the gut lumen thereby decreases bioaccessibility and the potential for enterohepatic recirculation, enhancing their fecal excretion [30]. Consistent with chemical

similarities between bile acids and long-chain PFAS (i.e., both are amphipathic, are charged at pH's above 5, have molecular weights in the 400–500 g/mol range), decreased serum-PFAS concentrations have been associated with increased fiber intake [26].

Taking advantage of the original clinical study design, which was designed to test the ability of an oat β-glucan beverage to reduce serum-cholesterol concentrations, a pilot analysis of the effect of consumption of a gel-forming fiber on serum-PFAS concentrations was conducted. Serum concentrations of the sum of 11 PFASs decreased overall in both study groups. Significant reductions in some PFASs in both groups may reflect shorter human half-lives of short-chain PFAS (e.g., 62 days for PFHpA [53]. Interestingly, only the oat β-glucan group saw significant reductions in the NASEM PFAS concentration, which appeared to have been driven by combined reductions in PFOA and PFOS. It is not necessarily surprising that differences in effect across PFAS types are seen, given that the ratio of urinary to biliary PFAS excretion depends upon PFAS structure [54].

There are several likely reasons why a stronger effect of the intervention was not observed. Samples used in the current study were from a previously conducted study that was not designed as an intervention to reduce serum-PFAS concentrations; thus, there was no information collected on potential sources of PFAS exposure prior to or during the study and no attempt to control for differences in ongoing exposures between intervention and control groups. Further, the time of the intervention was short, only 4 weeks. Many long-chain PFASs have half-lives on the order of 2–7 years [55–59], thus a one-month intervention may be insufficient to strongly influence serum-PFAS concentrations with ongoing exposure. Along these lines, a recent cholestyramine intervention study in which the ability of the anion resin to trap PFASs in the gut lumen was tested, showed that a 12-week intervention induced notable reductions in serum-PFAS concentrations [60]. A meta-analysis of barley β-glucan showed that consumption of a minimum of 6.5–6.9 g β-glucan per day was necessary to reduce serum-cholesterol [61], which is higher than the 3 g oat β-glucan consumed daily in the current study. Thus, a higher consumption of β-glucan is possible and may also improve PFAS reductions.

Conclusions

The types of PFASs to which humans are being exposed are evolving, yet the bulk of exposure assessment has focused on long-chain PFASs. As such, broader biomonitoring is needed to capture changing PFAS exposures in humans. Here, we show that short-chain and replacement chemistry PFAS are measurable in Canadians, along with the PFOS-precursor PFOSA. Given that this is the first time some of these PFASs have been measured in Canadians, follow-up studies are needed to define exposure trends, sources, and differences in PFAS species between different populations. For a subset of participants, we observed serum-PFAS concentrations that exceeded NASEM guidelines of 20 ng/ml, who are considered at high risk for cancer and other disorders and require clinical follow-up and PFAS-reduction interventions. Despite the limited sample size and cross-sectional nature of the biomarker analysis, we found positive associations between PFBA and PFHxA and biomarkers of liver toxicity, suggesting potential health impacts for short-chained PFASs that warrant further investigation. Current clinical treatments to reduce PFAS body burden are minimal. Results from this pilot analysis suggest a potentially practical and feasible intervention that may reduce human body burdens for some PFASs. However, studies utilizing a larger sample with a broader range of serum concentrations, longer intervention period, and clinically relevant fiber intakes are needed to determine the efficacy of using gel-forming dietary fibers to increase PFAS excretion.

Abbreviations

6:2 FTS	1H,1H,2H,2H-Perfluorooctanesulfonate
CHMS	Canadian Health Measures Survey
Et-FOSAA	N-Ethylperfluro-1-octanesulfonamidoacetic acid
GenX	Hexafluoropropylene oxide-dimer acid
GM	Geometric mean
GSD	Geometric standard deviation
HDL-C	High density lipoprotein cholesterol
LDL-C	Low density lipoprotein cholesterol
LOD	Limit of detection
L-PFPeS	Perfluoropentylsulfonate
Me-FOSAA	N-Methylperfluro-1-octanesulfonamidoacetic acid
NASEM	United States National Academies of Sciences, Engineering and Medicine
OBG	Oat β-glucan
PFAS	Per and polyfluoroalkyl substances
PFBS	Perfluorobutane sulfonic acid
PFBA	Perfluorobutanonic Acid
PFCA	Perfluoroalkyl carboxylic acid
PFDA	Perfluorodecanoic acid
PFDoA	Perfluorododecanoic acid
PFECHS	Perfluro-4-ethylcyclohexanesulfonate
PFHpA	Perfluoroheptanoic acid
PFHxA	Perfluorohexanoic Acid
PFHxS	Perfluorohexane sulfonic acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PFOSA	Perfluorooctanesulfonamide
PFSA	Perfluoroalkyl sulfonic acid
PFUdA	Perfluoroundecanoic acid
PP	Per protocol

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-025-01165-8.

Supplementary Material 1

Author contributions
J.S. conceived of the idea and wrote the main manuscript.T.W. conducted the original study and provided the samples.E.P. and W.H.-B. developed the sampling strategy.D.B. and K.B conducted the PFAS analyses.A.B, K.M., and P.P. conducted the statistical analyses and data review.All authors reviewed the manuscript.

Funding
The study was made possible in part by a seed grant from the University of Massachusetts Lowell and support from the National Institutes of Health (R21 ES032882, JJS) and FEMA EMW-2020-FP-00078 (AB, DB).

Data availability
Data is provided within the manuscript and supplementary materials files.

Declarations

Competing interests
TMSW is an employee of INQUIS, Inc.; neither he nor INQUIS own any intellectual property related to the study product or study results and have no financial interest in any food companies with which INQUIS does, has done or may do business.

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Received: 9 August 2024 / Accepted: 26 February 2025
Published online: 15 March 2025

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