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Decreases in serum PFAS are associated with decreases in serum lipids: A longitudinal study on a highly exposed population

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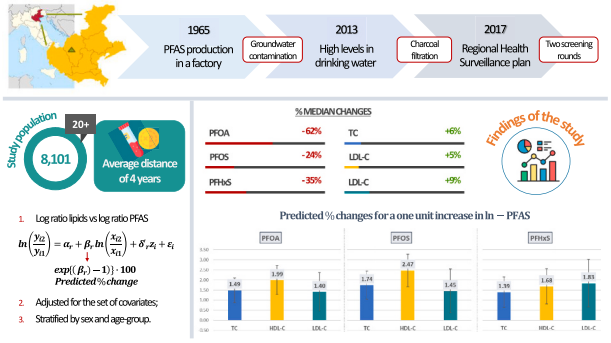
HIGHLIGHTS

- Groundwater of a wide area in the Veneto Region was found to be contaminated by PFAS.
- Several cross-sectional studies have found PFAS exposure to be associated with increased cholesterol levels.
- Few studies conducted longitudinal investigations using more than one measurement of both PFAS and lipid.
- The aim of this study was to investigate the association between within-individual changes in PFAS and changes in lipids.
- Significant longitudinal associations were found, supporting the reversibility of the cross-sectional associations.

GRAPHICAL ABSTRACT



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ABSTRACT

Introduction: Perfluoroalkyl substances (PFAS) are widely used, ubiquitous and highly persistent man-made chemicals. Previous cross-sectional studies have consistently linked PFAS exposure to alterations in lipid profiles. However, longitudinal investigations are preferred to mitigate issues related to reverse causation and confounding. Hence, we aimed to investigate the association between changes in serum PFAS and changes in serum lipids, while shedding light on potential modifiers of the examined relationships.
Methods: We used data from a health surveillance program offered to residents of a vast area of the Veneto Region (North-Eastern Italy), who had been exposed to PFAS via contaminated drinking water until 2013. We included subjects aged ≥20 years who provided two blood samples over an average 4-year interval (n = 8101). We examined the relationships between changes in PFOA, PFOS and PFHxS and changes in total cholesterol (TC), high-density lipoprotein cholesterol (HDL—C) and low-density lipoprotein cholesterol (LDL-C). Linear models were fitted for change in the natural logarithm (ln) of each lipid in relation to the change in the ln of PFAS. From

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the estimated regression coefficients, we calculated the predicted percentage change in the response for a ln-decrease in PFAS serum concentrations.
Results: Overall concentrations of PFOA, PFOS, PFHxS fell by 62.1 %, 24.4 % and 35.4 % from baseline, while small increases in lipids were observed. Declines in PFAS concentrations were associated with decreases in all lipids. For a ln-decrease in PFOA HDL-C decreased by 1.99 % (95 % CI: 1.28, 2.70), TC by 1.49 % (95 % CI: 0.88, 2.10), and LDL-C by 1.40 % (95 % CI: 0.45, 2.37).
Conclusions: We found a positive association between changes in PFAS concentrations and changes in cholesterol levels, observing the most marked contrasts across sexes and age groups. Our findings support the reversibility of the associations identified in cross-sectional analyses, emphasizing the importance of water treatment measures in mitigating adverse health effects.

1. Introduction

Perfluoroalkyl substances (PFAS) are a group of widely used, ubiquitous, and highly persistent man-made chemicals (Glüge et al., 2020). Despite phasing out some long-chain PFAS from industrial processes, their bioaccumulative potential remains a major concern, because prolonged exposure to PFAS is associated with a variety of adverse health effects, including increased cholesterol levels, immune system dysregulation and toxicity, liver and kidney disease, thyroid hormone disruption, child developmental effects, and reproductive outcomes (Committee on the Guidance on PFAS Testing and Health Outcomes et al., 2022; Fenton et al., 2021; Sunderland et al., 2019). Considerable existing evidence, including our previous works (Batzella, 2022; Canova et al., 2020), conducted in both high- and background-exposed populations, has shown that PFASs exposure is associated with altered lipid profiles; however, since these cross-sectional studies might be vulnerable to reverse causation and/or confounding, longitudinal studies are preferable.

Although there is some existing evidence of association between PFAS levels and lipids from longitudinal studies, most had only one measurement of PFAS and follow-up of lipids levels alone/solely (Lin et al., 2019; Winquist and Steenland, 2014). Only a few studies have examined this relationship using more than one measurement of both PFAS and lipid levels (Dunder et al., 2022; Fitz-Simon et al., 2013; Sakr et al., 2007), showing significant associations between declines in PFAS levels and decreases in multiple lipid parameters. However, these studies were conducted on small samples (Fitz-Simon et al., 2013; Sakr et al., 2007) or populations with background levels of exposure (Dunder et al., 2022), limiting the generalizability of their findings to high-exposure settings.

We used data from the health surveillance program of the Veneto Region (North-Eastern Italy), where a large area's groundwater was found to be contaminated by PFAS from a manufacturing plant that had been active since the late 1960s. Consequently, residents were exposed to high levels of PFAS, particularly perfluoro-octanoic acid (PFOA) (median of 319 ng/L in water samples), through their drinking water until the pollution was detected by authorities in 2013, after which contaminated waterworks were provided with charcoal filtration (Pitter et al., 2020). The effectiveness of water treatment continued to improve, and by 2017 only a few drinking water samples detected PFOA (at low levels), and by 2018 and subsequent years, nearly all samples were below detection for all PFAS congeners. The regional health surveillance program was established in 2017, and included the invitation of residents to provide measurements at two time points over an average 4-year period (Pitter et al., 2020).

Hence, the main objective of the present study is to investigate the association between within-individual changes in serum PFAS, namely PFOA, perfluoro-octane sulfonic acid (PFOS) and perfluoro-hexane sulfonic acid (PFHxS) and changes in serum lipid concentrations over a time span of approximately 4 years. Such analyses address whether the association is reversible and are less vulnerable to confounding than cross-sectional analyses. Furthermore, as this is the largest such study, we aimed to investigate effect modification, in particular the role of sex, age, smoking and alcohol habits in the examined relationships, since there is no existing evidence on how these factors may affect the associations.

2. Materials and methods

2.1. Participants and study design

From January 2017, the regional health service offered a free population-based health surveillance program, to residents of 30 the municipalities in the "Red Area" who had been exposed to PFAS through contaminated drinking water for several decades (for more information please see (Pitter et al., 2020). Recruitment for the first screening round (baseline) began on January 1, 2017, targeting all residents in the contaminated area born between 1951 and 2014 (for whom enrolment has been completed with a participation rate of approximately 60 %, given an eligible population of more than one hundred thousand subjects). A follow-up screening round, which was offered to all participants adhering to the baseline examination, started in 2020 and is still ongoing. During each screening, participants completed an interview questionnaire on socio-demographic characteristics, personal health history, and lifestyle habits. Non-fasting blood samples were collected when the participants visited the clinic and sent to the Local Health Unit laboratory for analysing clinical biomarkers, while additional blood samples were sent to the centralized ARPAV laboratory to measure 12 PFAS. The laboratory responsible for analysing clinical biomarkers remained unchanged and adhered to the same external quality assurance program throughout the study duration.

The study population is a subset of the surveillance program's target group, consisting of subjects who provided blood samples for both the baseline and follow-up examinations (n = 11,594). Baseline blood samples were collected between January 2017 and February 2020, while follow-up blood samples between September 2020 and April 2023. Only participants above 20 years of age were included in the present analyses (n = 8895), since children and adolescents are known to have differences in dilution and excretion pattern resulting from ongoing growth. 8101 subjects were analysed after excluding pregnant women (n = 145, n = 92 at 1st round, n = 60 at 2nd round, n = 7 at both), users of cholesterol-lowering medications (n = 575: n = 235 at 1st round, n = 525 at 2nd round, n = 185 at both) or with missing information on the selected covariates (n = 164) in one of the two sampling time (Fig. S1).

2.2. Outcome assessment

Several plasma lipid parameters were assessed, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL—C), and low-density lipoprotein cholesterol (LDL-C). TC and HDL-C were measured using a direct enzymatic colorimetric test, and recorded in mg/dL. LDL-C levels were calculated using the Friedewald equation when triglycerides were below 400 mg/dL.

2.3. PFAS exposure

Serum concentrations of twelve PFAS were quantified using high-

performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS) [Prominence UFLC XR 20 (Shimadzu) coupled to API 4000TM LC-MS/MS System (Sciex)]: perfluorooctanoic acid (PFOA), perfluorooctanesulfonate (PFOS), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDeA), perfluoroheptanoic acid (PFHpA), perfluorobutanesulfonic acid (PFBS), perfluorobutanoic acid (PFBA), perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroundecanoic acid (PFUnA), and perfluorododecanoic acid (PFDoA). Method performances allow analytes to be detected as low as 0.1 ng/mL level of detection (LOD) and to be quantified above 0.5 ng/mL level of quantification (LOQ). Concentrations below the LOQ were indeed assigned the LOQ/$\sqrt{2}$ at both rounds. Detailed information regarding PFAS measurement and the analytical method is provided elsewhere (Pitter et al., 2020). Three of the twelve measured PFAS were detected in >90 % of participants: PFOA (99.94 %), PFOS (99.74 %) and PFHxS (97.59 %). For each PFAS we limited our analysis to subjects having detectable concentrations above the limit of quantification (LOQ) at baseline. Hence, each PFAS specific analysis had slightly different sample sizes: $n = 8096$ for PFOA, $n = 8080$ for PFOS and $n = 7906$ for PFHxS.

2.4. Covariates

Data on socio-demographic and medical history were collected via structured computer-assisted questionnaires during in-person interviews conducted at both examinations. Covariates included as potential confounders or effect modifiers were selected from available variables and through the construction of a Directed Acyclic Graph (DAG) (Fig. S2), based on existing literature on pharmacokinetics and factors associated with PFAS serum concentrations or with serum lipids/cholesterol levels, i.e. age, sex, educational level, country of birth, smoking habits, alcohol consumption, and Body mass index (BMI, calculated using self-reported weight and height).

Education level was categorized as low (middle school or lower), medium (high school) or high (university degree or higher); smoking status was classified as current smokers or non-smokers, and alcohol consumption was categorized as 0, 1–3, 3+ alcohol units (AU) per week. Countries of birth were grouped into Italy with other Highly Developed Countries (HDC) defined (Western Europe, North America, Oceania, Israel and Japan), and High Migratory Pressure Countries (HMPC) (Central-Eastern Europe, North Africa, Sub-Saharan Africa, Asia and Central and South America).

2.5. Statistical analyses

Continuous variables, including PFAS serum concentrations and serum lipid levels, were summarized using arithmetic means, standard deviations (SD), and percentiles. Categorical variables were described using absolute and relative frequencies (percentages). To assess the pairwise correlations between PFAS, cholesterol levels, and their respective ratios, Spearman's rank correlation coefficient was employed.

To investigate the relationships between changes in PFOA, PFOS and PFHxS, and changes in serum lipids, we employed generalized additive models (GAMs) for the natural logarithm (ln) of ratio change in each serum lipid measurement in relation to the natural logarithm of ratio change in PFAS, separately. This method is equivalent to modelling the difference between baseline and follow-up ln(lipids) as a linear function of the difference in ln(PFAS) (Fitz-Simon et al., 2013). The change-versus-change model is defined as follow

$$ln\left(y_{i2}/y_{i1}\right) = \alpha_r + \beta_r ln\left(x_{i2}/x_{i1}\right) + \delta_r' z_i + \varepsilon_i.$$

In this model, y_{ij} and x_{ij} represent the serum concentrations of lipids and PFAS for individual i at time j = 1 (baseline) and j = 2 (follow-up). The parameters α_r, β_r, δ_r are the model coefficients, z_i includes covariates (all measured at baseline) that may influence PFAS, lipids, or both, and ε_i denotes the error term.

First, the models employed thin plate spline smooth terms for the continuous covariates. To explore the shape of the associations between changes in PFAS concentrations and changes in lipid levels, we also applied these smooth terms to the ln PFAS ratio, and plotted the predicted outcomes against exposure levels. The Estimated Degree of Freedom (EDF) in the GAMs reflects how much a polynomial function is needed to fit the data compared to using splines. An EDF of 1 suggests a nearly linear relationship, and the associated *p*-value indicates the significance of the exposure variable's effect. Secondly, the changes in exposure were included as ln-linear predictor. These models were first adjusted for sex, age at baseline (continuous variable), and continuous time between measurements. Then, we calculated the parameter estimates after adjusting for smoking habit, alcohol consumption, country of birth and educational level. Interaction terms between the ln PFAS ratio and sex, age-group (categorized in [20–39], [≥40] years old), smoking habit and alcohol consumption (one at a time) were included in a separate set of models. A likelihood ratio test was used to test the significance of each possible interaction. We decided to stratify the main analysis by sex (a priori) and for characteristics showing a significant interaction with PFAS changes.

As sensitivity analyses, models were further adjusted for baseline BMI, which was not included in the main set of confounders since it was not identified as a determinant of PFAS excretion rates in our previous analysis (Batzella et al., 2024). Similarly, BMI change between rounds was also adjusted for, although it was not included in the main set of confounders as it may be on the causal pathway between PFAS and lipids.

Furthermore, to investigate how menopausal status could impact the examined relationships, a separate analysis was conducted in women aged ≥40 who had not undergone hysterectomies (2211 out of 2254). In this sensitivity analysis, additional adjustment was made for menopausal status, categorized as: no (57.35 %); yes, before the 1st round (27.27 %); yes, between rounds (14.88 %).

From the estimated regression coefficients, we calculated the predicted percentage decreases and 95 % confidence interval (95 % CI) per ln unit decrease in PFOA, PFOS or PFHxS serum concentrations, using $\left[e^{\beta} - 1\right]x100$, with β representing the estimated coefficient in its original scale (Stock and Watson, 2003).

Finally, we fitted cross-sectional models for the natural logarithm of the cholesterol levels in relation to the natural logarithm of PFAS for both baseline and follow-up examinations, adjusting for the confounders measured at each respective round. Estimates were converted into predicted percentage increases in each serum lipid per ln-unit increase of PFAS using the same formula as for the longitudinal coefficients. Cross-sectional analyses were conducted for comparison with previous studies and to gain further insight in the association between PFAS and lipids, given that individuals included in this study represent a subpopulation of those analysed in our previous works.

3. Results

The analysed population consisted of 8101 adults (53.1 % of which were women), with a median age of 40 years at baseline (ranging from 20 to 58 years), and a median distance between the two measurements of nearly 4 years (Table 1).

Spearman's rank correlation (ρ) was calculated to evaluate pair-wise correlations between the PFASs and the lipid parameters (Table S1). The correlation between PFOA and PFHxS was the strongest, both at baseline and at follow-up (ρ = 0.90 and ρ = 0.88, respectively), whereas that between PFOS and the other PFASs was weaker (ρ = 0.66 and ρ = 0.72 with PFHxS; ρ = 0.62 and ρ = 0.65 with PFOA). All three PFAS were positively correlated with LDL-C levels and negatively correlated with

Table 1
Descriptive statistics at baseline in the study population stratified by sex (n = 8101). Veneto Region, Italy (2017–2023).

Characteristics		Total		Males (n = 3802)		Females (n = 4299)	
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Age (years)		38.96 (9.94)	40 (31–47)	38.65 (10.02)	39 (30.25–47)	39.24 (9.87)	40 (32–47)
BMI (kg/m^2)		24.47 (4.37)	23.83 (21.37–26.67)	25.36 (3.91)	24.77 (22.84–27.17)	23.68 (4.61)	22.68 (20.41–25.78)
T_1-T_0 (months)*		46.83 (6.1)	47 (42–52)	46.76 (6.07)	47 (42.25–52)	46.89 (6.13)	47 (42–52)
Time-lag (months)**		59.48 (9.03)	57 (52–67)	59.22 (9)	57 (52–67)	59.71 (9.06)	57 (53–68)
		n	**%**	**n**	**%**	**n**	**%**
Age-group	*[20–39]*	3948	48.74 %	1903	50.05 %	2045	47.57 %
	≥40	4153	51.26 %	1899	49.95 %	2254	52.43 %
BMI	*normalweight*	5010	61.84 %	1994	52.45 %	3016	70.16 %
	overweight	3091	38.16 %	1808	47.55 %	1283	29.84 %
Smoke	*No*	5169	63.81 %	2092	55.02 %	3077	71.57 %
	Yes	1703	21.02 %	993	26.12 %	710	16.52 %
	Ex-smoker	1226	15.13 %	714	18.78 %	512	11.91 %
Alcohol (AU per week)	*None*	2291	28.28 %	538	14.15 %	1753	40.78 %
	[1–3]	2620	32.34 %	1019	26.80 %	1601	37.24 %
	3+	3190	39.38 %	2245	59.05 %	945	21.98 %
Country of birth	*HDC*	7475	92.27 %	3564	93.74 %	3911	90.97 %
	HMPC	626	7.73 %	238	6.26 %	388	9.03 %
Educational level	*elementary/middle*	2102	25.95 %	1009	26.54 %	1093	25.42 %
	high school	4243	52.38 %	2067	54.37 %	2176	50.62 %
	university/higher	1756	21.68 %	726	19.10 %	1030	23.96 %

* distance between the two measurements.
** distance between the 1st measurement and 1/8/2013.

HDL-C levels, both at baseline and during follow-up examinations. The strongest positive correlations were observed between PFOS and LDL-C ($\rho = 0.13$ at baseline and $\rho = 0.18$ at follow-up), while the strongest negative correlations were noted between PFHxS and HDL-C ($\rho = -0.19$ at baseline and $\rho = -0.21$ at follow-up) (Table S1).

Spearman's rank correlations were also assessed for the PFAS and lipids ratios (follow-up/baseline), showing a similar magnitude as observed in pair-wise correlations, with the strongest relationship found between PFOA and PFHxS, followed by that of PFOS with PFHxS, and finally that of PFOA with PFOS (Table S2).

The serum concentrations of lipids and PFAS at baseline and follow-up are summarized in Table 2, in all subjects and in males and females separately. Median baseline serum PFOA concentration were higher compared to those detected in the general population (45.6 ng/mL compared to 1.64 ng/mL), while PFOS and PFHxS median concentrations were quite similar to those measured at background level (4.5 ng/mL and 4.8 ng/mL compared to 5.84 ng/mL and 2.49 ng/mL, respectively) (Ingelido et al., 2018), and were substantially higher in males than females. The median serum PFOA, PFOS and PFHxS decreased between baseline and follow-up of 62.06 %, 24.44 % and 35.42 %, respectively. On the other hand, small increases in serum lipids concentrations were observed, of 6.08 % in TC, 5.36 % in HDL—C, and 8.65 % in LDL-C.

The adjusted concentration-response curves between changes in serum lipid concentrations and changes in PFAS are shown in Fig. 1 through the plot of predicted values, and Fig. S3 stratified by sex (EDF

Table 2
Descriptive statistics on serum lipid levels (mg/dL) and PFAS serum levels (ng/mL) (considering only PFAS > LOD at 1st round) at baseline and follow-up, stratified by sex. Veneto Region, Italy (2017–2023).

Characteristics		Total			Males			Females		
		Mean (SD)	Median (IQR)	Median % change	Mean (SD)	Median (IQR)	Median % change	Mean (SD)	Median (IQR)	Median % change
TC	Baseline	183.86 (33.35)	181 (161–205)	+6.08 %	186.15 (34.43)	184 (162–207)	+4.89 %	181.83 (32.24)	179 (160–202)	+6.70 %
	Follow-up	194.06 (34.57)	192 (170–216)		195 (35.6)	193 (170.25–216)		193.22 (33.62)	191 (169–214.5)	
HDL-C	Baseline	57.83 (14.39)	56 (47–67)	+5.36 %	51.81 (12.25)	50 (43–59)	+4.00 %	63.16 (14.04)	62 (53–72)	+4.84 %
	Follow-up	60.57 (15.31)	59 (50–70)		54.03 (12.82)	52 (45–61)		66.36 (15.01)	65 (56–75)	
LDL-C	Baseline	106.29 (31.13)	104 (85–125)	+8.65 %	111.5 (33.01)	110 (89–131)	+8.18 %	101.68 (28.58)	99 (82–119)	+9.09 %
	Follow-up	115.07 (33.04)	113 (93–135)		120.06 (35.54)	119 (98–140)		110.66 (29.98)	108 (90–130)	
PFOA	Baseline	74.39 (87.59)	45.6 (18.7–97.2)	−62.06 %	109.2 (106.76)	79.5 (36.6–144.3)	−57.74 %	43.59 (48.54)	28.4 (12.7–57.5)	−65.85 %
	Follow-up	33.04 (44.81)	17.3 (6.5–42.1)		50.97 (55.81)	33.6 (14.9–67.2)		17.18 (22.19)	9.7 (4.1–21.4)	
PFOS	Baseline	5.52 (4.71)	4.5 (2.9–6.8)	−24.44 %	6.88 (5.46)	5.7 (3.9–8.3)	−15.79 %	4.31 (3.51)	3.6 (2.4–5.3)	−27.78 %
	Follow-up	4.39 (3.86)	3.4 (2.2–5.5)		5.74 (4.38)	4.8 (3.2–7.075)		3.2 (2.85)	2.6 (1.7–3.9)	
PFHxS	Baseline	7.87 (8.66)	4.8 (2.3–10.4)	−35.42 %	11.96 (10.38)	9.4 (4.6–16.1)	−32.98 %	4.1 (3.91)	2.9 (1.6–5.3)	−44.83 %
	Follow-up	5.32 (6.25)	3.1 (1.4–6.9)		8.38 (7.52)	6.3 (3.2–11.2)		2.5 (2.55)	1.6 (0.9–3.2)	

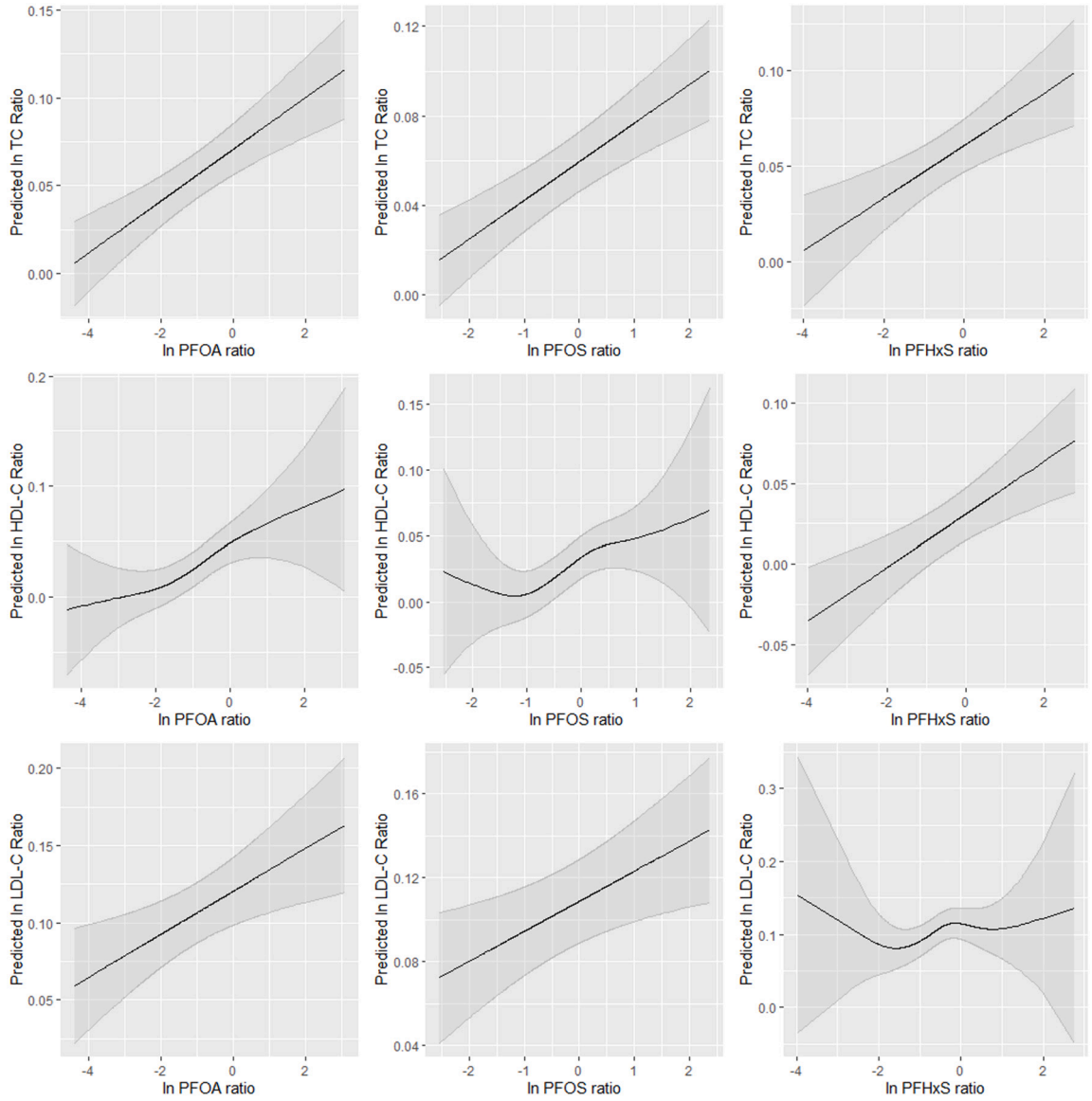

Fig. 1. Exposure–response curves for the ln ratio of PFAS exposure and the ln ratio of serum lipid concentrations from GAM models using thin plate spline, with 95 % confidence intervals. Veneto Region, Italy (2017–2023).

and *p*-values: Table S3). These analyses revealed positive associations between changes TC, HDL—C, LDL-C and changes in all PFAS (p-values <0.05) with approximately linear relationships in almost all cases (EDF close to one). Slight departures from linearity were seen in the relationship of PFOA and PFOS with HDL-C (EDF = 2.49 and EDF = 3.44), and in the relationship between PFHxS and LDL-C (EDF = 3.86).

These trends were confirmed when the changes in exposure were considered as ln-linear predictor in the regression models, expressed as the natural logarithm of the ratio between final and initial values (Table 3). The estimates obtained from the fully adjusted models (Model 2) were similar to the estimates from the partially adjusted models (Model 1), for nearly all outcomes. In Model 2, examining the change in HDL-C versus the change in PFOA, we observed that for a one ln-decrease in PFOA over the study period, HDL-C decreased by an average of 1.99 % (95 % CI: 1.28, 2.70). Additionally, we found that a ln-decrease in PFOA predicted a TC decrease of 1.49 % (95 % CI: 0.88, 2.10), and a decrease in LDL-C of 1.40 % (95 % CI: 0.45, 2.37).

When baseline BMI was included in the set of confounders, similar or slightly higher associations with LDL-C were observed, while those with HDL-C remained unchanged (Table S4). When adjusting for the change

Table 3
Predicted Percentage decreases (95 % CI) in each serum lipid per ln-decrease in PFAS concentrations. Veneto Region, Italy (2017–2023).

PFAS	Outcome	β (95 % CI)	
		Model 1[a]	Model 2[b]
PFOA	*TC*	1.56 (0.95; 2.17)	1.49 (0.88; 2.10)
	HDL-C	1.99 (1.29; 2.70)	1.99 (1.28; 2.70)
	LDL-C	1.55 (0.59; 2.51)	1.40 (0.45; 2.37)
PFOS	*TC*	1.78 (1.08; 2.47)	1.74 (1.05; 2.44)
	HDL-C	2.42 (1.62; 3.23)	2.47 (1.66; 3.28)
	LDL-C	1.52 (0.44; 2.61)	1.45 (0.37; 2.54)
PFHxS	*TC*	1.40 (0.64; 2.15)	1.39 (0.64; 2.15)
	HDL-C	1.66 (0.79; 2.53)	1.68 (0.81; 2.56)
	LDL-C	1.88 (0.70; 3.07)	1.83 (0.65; 3.02)

[a] Model 1 is adjusted for age in spline, sex, and interval between measurements in spline.

[b] Model 2 is adjusted for age in spline, sex, interval between measurements in spline, smoking habit, alcohol consumption, country of birth and educational level.

in BMI between the two examinations (with a median increase of 1 %), the association with LDL-C slightly increased, while those with HDL-C got slightly lower (Table S4).

As expected, stronger associations with all three lipid parameters were observed among older women (Table S5). However, including menopausal status in the set of confounders did not result in significant variations, except for moderately stronger effects on HDL-C and moderately weaker effects on LDL-C (Table S5).

We observed a significant interaction between the changes in PFAS and age-group in some of the examined association, while no significant interactions were observed with other characteristics.

When stratifying fully adjusted models according to participants' sex, a greater effect of PFOS on HDL in females (of 2.88 % against 2.02 % in males), and on LDL in males (of 1.90 % against 1.28 % in females) were observed (Fig. 2, Table S6). Also, a ln-decrease in PFHxS exhibited a stronger association with all lipid parameters in males, in particular with LDL-C (of 2.54 % against 0.91 % in females). Results stratified by age-groups, highlighted stronger associations for all PFAS with both TC and LDL-C in older subjects, and stronger associations between all PFAS and HDL-C in younger subjects (Fig. 2, Table S7).

Models for the cross-sectional association between serum lipids and PFAS at baseline and follow-up are reported in Table S8. Results derived from these separate analyses at subsequent timepoints indicated a tendency for the association between PFAS and lipids to either weaken or remain consistent from the baseline to the follow-up examinations in both sexes. Notably, there were exceptions, such as a more pronounced effect of a ln-unit increase in PFOS on the predicted percentage increase of LDL-C in males and a greater impact of PFHxS on HDL-C in females.

4. Discussion

In this longitudinal study, we explored the association between changes in serum concentrations of specific PFASs and changes in lipid biomarkers, using repeated measures from a large sample of highly-exposed adults participating in the Regional Health Surveillance Plan.

During the study period, overall serum PFAS concentrations decreased substantially, while small increases in all cholesterol biomarkers were observed, which can be mainly due to the ageing of our population. We identified positive association between changes in plasma levels of three different PFAS (PFOA, PFOS, and PFHxS) and changes in plasma levels of TC, HDL—C, and LDL-C over an average follow-up period of four years. A decrease in the natural logarithm of PFOA and PFOS concentrations showed the highest association with a percentage reduction of HDL—C, followed by TC and LDL-C; while for a decrease in ln-PFHxS the biggest predicted percentage decrease was observed for LDL-C, followed by HDL-C and TC.

Most epidemiological studies reporting associations between PFAS exposure and cholesterol levels are based on cross-sectional designs, often involving general population samples or specific groups with occupational exposure (Batzella, 2022 p. 20; Olsen et al., 2012; Sakr et al., 2007). Other studies, including our previous works, have focused on populations with significantly higher exposure to PFAS exposure due to contaminated community drinking water (Batzella et al., 2022; Canova et al., 2020; Frisbee et al., 2010; Li et al., 2020). These studies generally show positive associations between blood levels of PFAS and TC and LDL-C, while the results for HDL-C are inconsistent. Despite these reported associations, establishing causality remains uncertain due to the inherent limitations of cross-sectional designs. Confounding factors affecting serum concentrations of both PFAS and blood lipids could influence these associations. Addressing the potential reversibility of these associations within a longitudinal framework is less susceptible to confounding, considering factors like specific genotypes or pre-existing chronic conditions.

The available evidence from longitudinal studies in general populations is limited, with most studies having only baseline measurement of PFAS and assessing lipid levels at follow-up only. A study within the C8 cohort, a community exposed to PFOA emissions from a fluoropolymer manufacturing facility, employing a longitudinal design, found a relationship between modelled serum PFOA and increased serum cholesterol levels but did not observe any association with the incidence of cardiovascular disease (Winquist and Steenland, 2014). Overall, evidence linking PFAS exposure to adverse outcomes associated with dyslipidaemia remains relatively sparse. A longitudinal occupational study in the same fluoropolymer manufacturing facility, used mixed models to explore the association between repeated measurements of serum PFOA and lipids (TC, triglycerides, LDL-C, and HDL—C) in 454 workers (Sakr et al., 2007). The only positive association they identified was between serum PFOA and total cholesterol. However, the lack of information on lipid-lowering medication use could contribute to the discrepancies with other findings. A longitudinal study within the C8 cohort, focusing on 560 adults living in a previously contaminated area, used a similar analysis method as in the present study for investigating

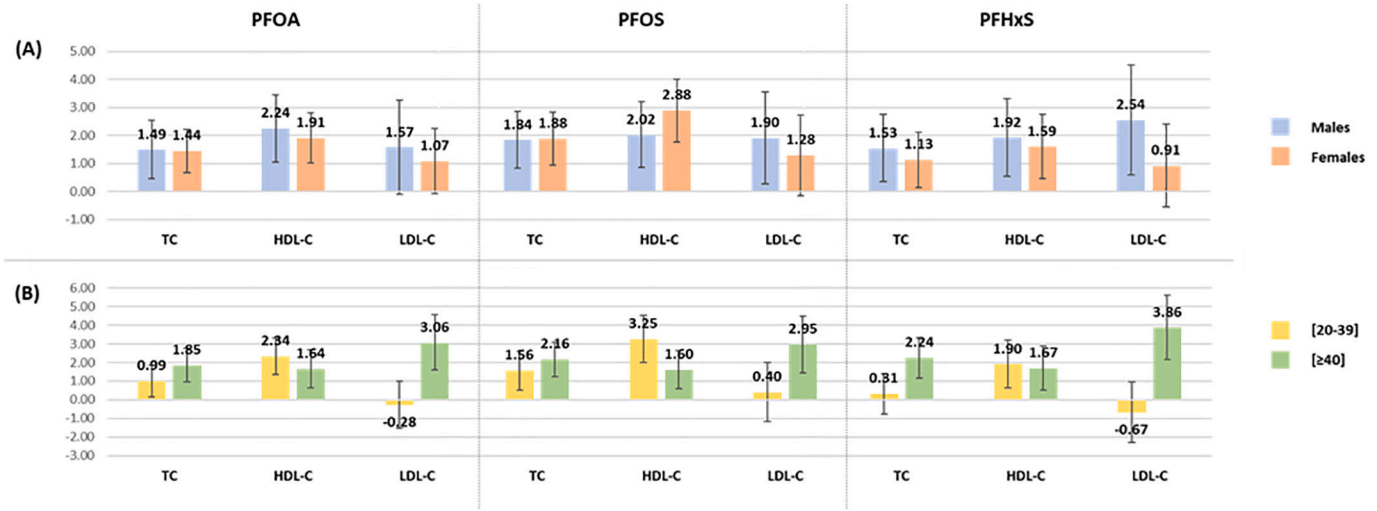

Fig. 2. Predicted Percentage decreases (95 % CI) in each serum lipid per ln-decrease in PFAS concentrations, stratified by sex (A) and age-group (B). Veneto Region, Italy (2017–2023).

Note: Models were adjusted for age, interval between measurements, smoking habit, alcohol consumption, country of birth and educational level. When stratifying by age-group, models were also adjusted for sex.

the association between within-individual changes in serum PFOA and PFOS and changes in serum lipid levels (TC, triglycerides, LDL-C and HDL—C) over a 4.4-year period (Fitz-Simon et al., 2013). Their findings indicated an association between the degree of decline in PFOA and PFOS levels and decrease in TC and LDL-C levels. In a longitudinal Swedish study by Dunder et al., a similar analysis method as in the Sakr et al. study was employed (Dunder et al., 2022; Sakr et al., 2007). This study examined the relationship between repeated measurement of eight different PFAS with lipids (TC, triglycerides, LDL-C and HDL—C) in an elderly population of 864 subjects exposed to background levels, using three measurements over 10 years of both plasma PFAS and lipids, and overcoming some of the limitations of the C8 longitudinal study. Changes in plasma levels of six out of the eight investigated PFAS were positively associated with changes in plasma lipids.

The biological mechanisms of PFAS effect on lipid metabolism are not fully elucidated in experimental studies, but different possible mechanisms have been proposed. It is well known that there is interference by PFAS on nuclear receptors, such as peroxisome proliferator-activated receptors and farnesoid X receptors, which may affect in turn lipid synthesis and transport (Evans et al., 2022; Roth et al., 2020; Szilagyi et al., 2020). Additionally, PFAS have also been involved in the alteration of enzyme and transporter expression and activity in lipid metabolism, such as lipoprotein lipase, fatty acid synthase, and ATP-binding cassette transporters (Lin et al., 2024). Furthermore, more recently the involvement of gut microbiota composition and function has emerged as a significant mechanism involved in bile acids and short-chain fatty acids production and absorption, along with the regulation of inflammation and immunity (Lamichhane et al., 2023). Indeed the involvement of PFAS on inflammation is well recognised, as PFOA induces pro- inflammatory cytokine production, including IL-1β, as recently confirmed in a population study on prenatal and postnatal PFAS exposure from six European cohorts (Papadopoulou et al., 2021).

We assessed a number of features for their interaction in the examined association, with the most marked contrasts observed for age. Older subjects showed the tendency to have a larger decrease in LDL-C per PFAS ln-decrease compared to younger subjects, for whom there was no evidence of association between changes of LDL-C and changes of all three PFAS. No great differences were observed when stratifying the results by participants' sex, except for a stronger effect of a PFAS reduction on reducing LDL-C in males.

None of the few comparable studies to ours explored the effect of sex or age in modifying the longitudinal association between cholesterol levels and PFAS concentrations, which we believe might be primarily due to their limited sample sizes and to the characteristics of their selected populations. In our study, the modest sex-specific differences might be partially attributed to the presence of additional excretion pathways of women, emphasizing the role that they might play in reducing serum PFAS levels while mitigating the resulting adverse health effect on lipids (Criswell et al., 2023; Wong et al., 2014). However, sex differences may only be partially explained by the presence of additional excretion routes, as other sex-specific mechanisms of PFAS elimination could be related to hormonal regulation of renal reabsorption of PFAS and uptakes of PFAS from the enterohepatic circulation (Chiu et al., 2022; Lin et al., 2021). When models were further adjusted by menopausal status no significant variations were observed in the PFAS/lipids associations, except for a stronger effect on HDL-C and a weaker effect on LDL-C.

The age-related effect might instead be attributable to differences in dilution and excretion patterns among younger subjects resulting from ongoing growth, influencing both lipids and PFAS biological mechanisms. Given the longitudinal design, with confounding factors being largely constant within subjects during the study period, we can speculate that our findings reflect a dose effect, as older people usually have higher PFAS levels, which leads a steeper decrease with higher magnitude and so the effect on lipids too.

The observed differences in the PFAS/lipids associations across various subgroups can, to some extent, be attributed to the mechanism of action of individual characteristics that influence PFAS elimination. As highlighted in the literature, several factors, contribute to the variation in PFAS half-lives among individuals. While the full extent of these factors and their complex interactions, which also depend on the specific type of PFAS being considered, cannot be precisely measured, the shorter half-life of PFAS in women—especially those of childbearing age—and in younger individuals may partly explain the observed differences in associations (Batzella et al., 2024). These differences were most pronounced in males and older subjects, as evidenced by the stratified analyses. However, these sex- and age-related differences may only be partially explained by these factors, prompting further studies to explore other potential causes.

Throughout the study period, median serum concentrations of all cholesterol levels increased by 5 % to 9 %, with similar trends in both men and women, and a more pronounced increase observed for LDL-C. Notably, this increase may largely be attributed to the ageing of our study population over the elapsed time between the baseline and follow-up examinations. In addition, the BMI increase between rounds could contribute to the observed increases in cholesterol levels. Indeed, BMI is known to increase with age in both sexes from adolescence to middle age, peaking between age 50 to 69 years, before beginning to decline after age 70 (Yang et al., 2021). Thus, the combination of these two factors, ageing and BMI increase, may explain the overall increased cholesterol in our study group, as confirmed when further adjusting the models by BMI change.

This study has several notable strengths, including its large sample size and a longitudinal design, which involved two measurements of both plasma PFAS and lipid levels. This design allowed for an in-depth exploration of the associations between temporal changes in PFAS and corresponding changes in lipids. By employing this approach, the impact of reverse causation is minimized, increasing confidence that the observed associations genuinely represent causal relationships, though this can never be fully ascertained in observational studies. Also, no previous studies considered how these association may differ between sexes.

However, there are also some certain limitations. We had only two time points to estimate the association between changes in serum cholesterol and changes in PFAS, limiting our ability to detect more complex than linear association.

Several potential biases could have influenced our study findings, which should be considered when interpreting the results. Our study population was derived from participants enrolled in the Surveillance Plan, which may not fully represent the entire exposed population. Individuals who chose to participate might systematically differ from those who did not, potentially leading to selection bias. However, it is reassuring that our cross-sectional analysis on this subset did not reveal significant discrepancies in the magnitude of the estimated associations compared to those reported in previous studies conducted on larger samples (Batzella et al., 2022; Canova et al., 2020). The accuracy of PFAS exposure assessment and outcome measurements is crucial. Both PFAS concentrations and cholesterol levels were measured using standardized and validated laboratory methods, which minimizes the likelihood of significant measurement error and enhances the reliability of our findings. Participants who were more health-conscious may have been more likely to engage in the second wave of the surveillance programs, potentially influencing both exposure and outcome variables. While this type of bias is challenging to eliminate or control entirely, we believe it did not significantly affect our results. Although we assessed potential confounding by numerous socio-demographic factors, we cannot completely rule out the possibility of residual confounding from uncontrolled variables such as diet and physical activity. While diet-related confounding is considered unlikely (EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020), other unmeasured factors could still have influenced the associations observed in this study.

Also, although we couldn't adjust for fasting status due to a lack of data on time since the last meal, research indicates that food consumption modestly influences serum lipid levels. Studies have shown no significant changes in TC, LDL-C, and HDL-C between fasting and non-fasting states (Dipankar and Pawar, 2019; Langsted and Nordestgaard, 2019), making it unlikely that fasting variability significantly affected our results.

Furthermore, the relatively young and narrow age range of the participants included in these analyses limits the generalizing of our findings to other populations. Future work will extend this research to other age groups as the surveillance program, which initially started with younger cohorts, will recruit older individuals for the second-round examination.

5. Conclusions

Our findings contribute valuable understanding into how PFASs could interfere with the lipid metabolism, confirming the presence of significant associations between changing PFAS levels and alterations in different cholesterol parameters. Given it longitudinal nature, this study offers great potential for addressing whether the association highlighted in cross-sectional studies are reversible, while shedding light on potential modifiers.

There is a need for continued monitoring and understanding of PFAS-related health effects and effectiveness of water treatment measures in reducing PFAS exposure, emphasizing the importance of ongoing research to inform public health strategies and interventions.

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CRediT authorship contribution statement

Erich Batzella: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Tony Fletcher:** Writing – original draft, Methodology, Conceptualization. **Gisella Pitter:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Filippo da Re:** Writing – review & editing, Investigation, Conceptualization. **Francesca Russo:** Writing – review & editing, Resources, Investigation, Funding acquisition. **Andrea di Nisio:** Writing – review & editing, Supervision, Methodology. **Cristina Canova:** Writing – original draft, Methodology, Investigation, Funding acquisition, Conceptualization.

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.

Data availability

The authors do not have permission to share data.

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Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Regional (Veneto Region) Ethics Committee (24 maggio 2017 prot. n. 203,638).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.176227.

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