Perfluoroalkyl and polyfluoroalkyl substance levels and total cholesterol in the National Health and Nutrition Examination Survey (2017-2018)

INTRODUCTION

Per- and polyfluoroalkyl substances (PFAS) are a group of anthropogenic chemicals that have been widely used in commercial materials for their ability to repel oil and water. While certain PFAS compounds (e.g., perfluorooctanoic sulfonate/sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA)) have been phased out of usage due to their categorization as possible carcinogens by the World Health Organization, they are still found environmentally alongside other forms of PFAS. PFAS compounds are widely utilized across various consumer and industrial goods such as food packaging, nonstick cookware, cosmetics, carpets, and firefighting foams. Due to the long half-life and extensive usage, we are concerned about the adverse effects of PFAS on human health, specifically on cholesterol levels.

Our objective is to investigate the association between PFOA/PFOS exposure and cholesterol levels in the NHANES 2017- 2018 dataset. We hypothesize that higher levels of blood serum PFOA/PFOS will be associated with higher cholesterol levels.

METHODS

The National Health and Nutrition Examination Survey (NHANES) is a population-based, cross-sectional study with data collected from a physical examination, clinical and laboratory tests, as well as a face-to-face interview and an audio computer-assisted self-interview (ACASI). We evaluated 2133 participants from the 2017-2018 NHANES. We excluded 204 participants

missing PFOA/PFOS measurements. We excluded another 4 participants missing total cholesterol measurements for a total sample size of 1925 participants.

We defined "high" cholesterol using the clinically significant value of ≥200 mg/dL as defined by the CDC, so "low" cholesterol is defined by a total cholesterol level less than this cutoff. Additionally, we summed the concentrations of PFOA and PFOS exposure for the purpose of our analyses.

We used linear regression to evaluate the relationship between total cholesterol serum concentration and PFOA/PFOS serum concentrations.

We considered age and sex to be confounders. We considered serum vitamin C levels to be an effect measure modifier.

RESULTS

A total of 1,925 participants were included in the analysis. These participants were categorized into high- and low-cholesterol groups based on 200 mg/dL, which is the most commonly used cutoff for total cholesterol levels. Notably, 68.2% of participants were classified as having low cholesterol, while 31.8% had high cholesterol (**Table 1**). Specifically, participants with high cholesterol had a higher mean age (51.8 years) compared to those with low cholesterol (42.3 years). Furthermore, there was a slightly higher percentage of females with high cholesterol (54.2%) than with low cholesterol (49.1%).

In the low cholesterol exposure group, Mexican-Americans account for 14.9%, Hispanic and other ethnicities make up 9.76%, non-Hispanic Whites make up 34.7%, non-Hispanic Blacks make up 23.2%, non-Hispanic Asians make up 12.5%, and other/multi-ethnic/racial groups make

up 4.95% of the total in this exposure category. In the high cholesterol exposure group, Mexican-Americans account for 16.3%, Hispanic and other ethnicities make up 7.67%, non-Hispanic Whites make up 34.3%, non-Hispanic Blacks make up 20.6%, non-Hispanic Asians make up 20.2%, and other/multi-ethnic/racial groups make up 6.04% of the total population in this exposure category. Additionally, participants with high cholesterol exhibited a slightly higher geometric mean of PFAS/PFOS exposure (5.3 ng/mL) compared to those with low cholesterol (4.2 ng/mL) (**Table 1**).

Of all of the participants, 976 were males and 949 were females. Gender distribution across the quartiles showed that 35.24% of the female participants were in Quartile 1 and only 18.03% were in Quartile 4, suggesting lower PFAS and PFOS exposure among women overall (**Table 2**).

The arithmetic mean of total cholesterol increased, rising from 173 mg/dL in Quartile 1 to 190 mg/dL in Quartile 4, with the highest PFAS exposure displayed in Quartile 4, indicating a direct correlation between PFAS exposure and cholesterol levels (**Table 2**).

Participants in the highest exposure Quartile 4 had a mean age of 57.91 years, while those in the lowest exposure Quartile 1 had a mean age of 34.74 years, indicating age variation across exposure levels (**Table 2**). Ethnic distribution analysis revealed that Mexican American females had the highest PFAS/PFOS exposure in Quartile 1 at 38.5% and the lowest exposure in Quartile 4 at 9.8%. The highest PFAS/PFOS exposure for female ethnic groups in Quartile 2 is the group of Other Hispanics at 31.4%, and in Quartile 3, it is highest in the group of Non-Hispanic Whites at 29.0%.

Table 1: Participant characteristics overall and stratified by cholesterol status

	All participants	**Low cholesterol (<200 mg/dL)**	**High cholesterol (≥200 mg/dL)**
N, %	1925	1312 (68.2%)	613 (31.8%)
Age (mean, SD)	45.3 (20.8)	42.3 (21.9)	51.8 (16.5)
Female (n, %)	976 (50.7%)	644 (49.1%)	332 (54.2%)
Race/ethnic group (n, %)			
Mexican-American	296 (15.4%)	196 (14.9%)	100 (16.3%)
Other, Hispanic	175 (9.1%)	128 (9.76%)	47 (7.67%)
NH White	665 (34.5%)	455 (34.7 %)	210 (34.3%)
NH Black	430 (22.3%)	304 (23.2 %)	126 (20.6 %)
NH Asian	257 (13.4%)	164 (12.5%)	93 (15.2%)
Other/Multi	102 (5.3%)	65 (4.95%)	37 (6.04%)
Total PFOA/PFOS (Geometric mean and SD)	4.5 (7.1)	4.2 (6.2)	5.3 (8.7)

Table 2: Participant characteristics overall and stratified by summed PFOA/PFOS exposure quartile

	All participants	**Q1 (sum ≤ 2.6)**	**Q2 (2.6 < sum ≤ 4.4)**	**Q3 (4.4 < sum ≤ 7.3)**	**Q4 (7.3 < sum)**
N, %	1925	482 (25%)	481 (25%)	481 (25%)	481 (25%)
Age, years (mean, SD)	45.3 (20.8)	34.7 (18.5)	38.6 (19.5)	50.0 (19.1)	57.9 (17.6)
Female (n, %)	976 (50.7%)	344 (35.24%)	250 (25.61%)	206 (21.11%)	176 (18.03%)
Race/ethnicity (n, %)					
Mexican American	296 (15.4%)	114 (38.5%)	92 (31.1%)	61(20.6%)	29 (9.8%)
Other Hispanic	175 (9.1%)	41 (23.4%)	55 (31.4%)	49 (28.0%)	30 (17.1%)
Non-Hispanic White	665 (34.5%)	117 (17.6%)	174 (26.2%)	193 (29.0%)	181 (27.2%)
Non-Hispanic Black	430 (22.3%)	114 (26.5%)	81 (18.8%)	100 (23.3%)	135 (31.4%)
Non-Hispanic Asian	257 (13.4%)	66 (25.7%)	51 (19.8%)	50 (19.5%)	90 (35.0%)

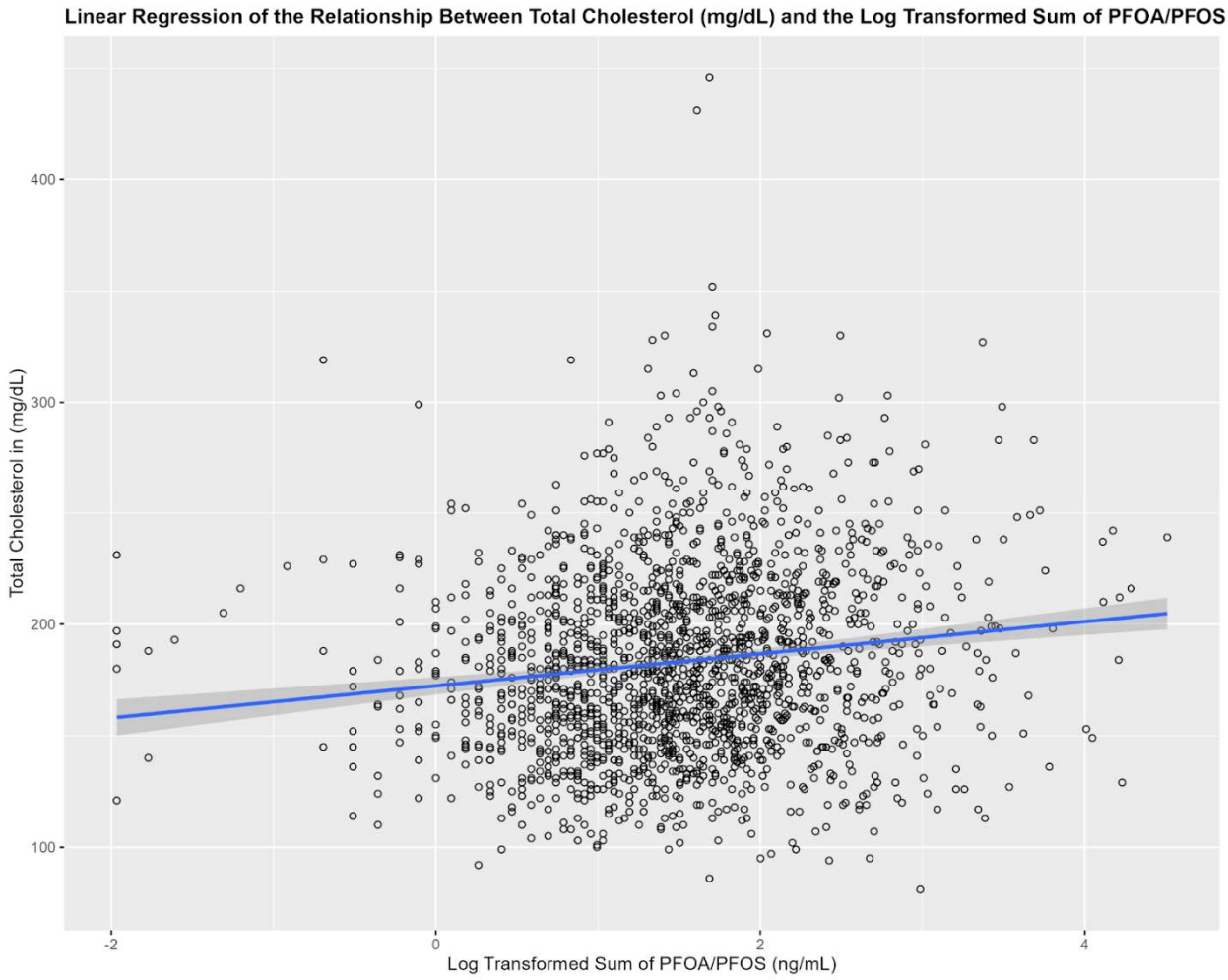
Other/Multi	102 (5.3%)	30 (29.4%)	28 (27.5%)	28 (27.5%)	16 (15.7%)
Total Cholesterol mg/dL (mean and SD)	183.2 (42)	173 (35.7)	181 (40.7)	188 (45.9)	190 (43.1)
High Cholesterol (n, %)	613 (31.8%)	107 (17.5%)	149 (24.3%)	165 (26.9%)	192 (31.3%)

Table 3 shows the odds ratio of a high cholesterol classification for every 1-unit increase in sum PFOA/PFOS exposure level. There were 613 cases of high cholesterol and 1312 non-cases of high cholesterol in the dataset. Before adjusting for potential confounders, a 1-unit increase in sum-PFOA/PFOS is expected to increase the odds of high cholesterol by 7.5% (OR = 1.075, 95% CI: 1.049, 1.103). After adjusting for age and sex, the odds of high cholesterol are expected to increase by 4.1% instead (OR = 1.041, 95% CI: 1.012, 1.07). Both confidence intervals, unadjusted and adjusted, exclude the null value of 1.0 meaning this relationship is statistically significant.

Table 3: Odds ratio (95%) of high cholesterol per 1 log-unit higher PFOA/PFOS exposure level (n = 1925). Estimates presented unadjusted and adjusted for age and sex.

	Cases / non-cases	Odds ratio (95% CI)	
		Unadjusted model	Adjusted model
Overall	613 / 1312	1.075 (1.049, 1.103)	1.041 (1.012, 1.070)

Figure 4: Scatterplot Between Sum PFOA/PFOS and Total Cholesterol



In the unadjusted model, a 7.19-unit increase in cholesterol is estimated for every unit increase in log-sum PFOA/PFOS (**Table 5**). The respective p-value for this association is less than 0.05, indicating that this association is significant.

Table 5: Unadjusted Linear Regression

Linear regression summary of the association between sum PFOA/PFOS and total cholesterol

	Estimate	Standard Error	Test Statistic	P-value	Confidence Interval
intercept	172.358	1.984	86.855	< 2e-16	(168.467, 176.250)
log_sum	7.193	1.158	6.212	6.41e-10	(4.922, 9.464)

Adjusting for age and sex, for every one-unit increase in log-sum PFOA/PFOS a 4.86-unit increase in cholesterol is estimated (**Table 6**). The p-value for this model is 0 indicating that this association is significant.

Table 6: Linear Regression Adjusted for Confounders

Linear regression summary of the association between sum PFOA/PFOS and total cholesterol adjusting for age and sex

	Estimate	Standard Error	Test Statistic	P-value	Confidence Interval
intercept	155.272	2.734	56.799	0	(149.910, 160.633)
log_sum	4.863	1.276	3.812	0	(2.361, 7.365)
sex: Female	8.851	1.918	4.615	0	(5.090, 12.612)
age	0.355	0.049	7.284	0	(0.260, 0.451)

Adjusting for age and sex including and incorporating vitamin C serum levels as an interaction term, an 8.18-unit increase in cholesterol is estimated for every unit increase in log-sum PFOA/PFOS (**Table 7**). The p-value of the interaction term for log-transformed PFOA/PFOS and Vitamin C (log_sum:vitc) is 0.022, which is less than 0.05 indicating that this association is statistically significant.

Table 7: Linear Regression Adjusted for Vitamin C Levels

Linear regression summary of the association between sum PFOA/PFOS and total cholesterol adjusting for age and sex and incorporating vitamin C serum levels as an interaction term.

	Estimate	Standard Error	Test Statistic	P-value	Confidence Interval
intercept	152	3.42	44.4	0	(145, 159)
log_sum	8.18	1.93	4.25	0	(4.40, 12.0)
vitc	2.65	2.32	1.14	0.254	(-1.90, 7.21)
sex: Female	9.62	1.95	4.94	0	(5.80, 13.4)
age	0.358	0.049	7.3	0	(0.262, 0.454)
log_sum:vitc	-3.54	1.54	-2.29	0.022	(-6.56, -0.511)

DISCUSSION

Summary of findings:

Without adjusting for any potential confounders or effect measure modifiers, total serum cholesterol is expected to increase by 7.193 mg/dL (95% CI 4.922, 9.464) for every log-unit increase in combined PFOA/PFOS level (Table 5). Adjusting for age and sex as confounders, the average change of total cholesterol per log-unit increase in PFOA/PFOS is 4.863 mg/dL (Table 6). However, when considering serum vitamin C as an effect measure modifier and incorporating it as an interaction term, the regression coefficient increased to an expected change in total cholesterol of 8.18 mg/dL per log-unit increase in PFOA/PFOS (Table 7).

The magnitude of the difference in crude and adjusted regression coefficients after adjusting for age and sex, considering a difference in 10% as significant, confirms that they act as confounders in the association between cholesterol and PFOA/PFOS. Additionally, the p-value of the interaction term and magnitude of the difference when adjusting for vitamin C confirms our hypothesis that it acts as an effect measure modifier. Overall, the positive association between cholesterol and PFOA/PFOS is in agreement with our initial hypothesis that higher levels of blood serum PFOA/PFOS will be associated with higher cholesterol levels.

Limitations:

One of the limitations of this study concerns the missing serum PFOA/PFOS data from participants. Some participants did not provide any biospecimen samples or, if they did, the volume provided was not enough to run all laboratory tests conducted in this NHANES cycle. This non-response may have been differential by high-cholesterol status, potentially driven by other predictor variables that haven't been taken into account. This same concern applies to serum cholesterol detection.

Public Health Implications:

Our findings have several public health implications in the field of exposure science. First, our findings suggest that there is an association between PFOA/PFOS exposure and higher cholesterol levels, with a (potential, which has to be confirmed with analytical figures) dose-response relationship being observed as shown in Table 2. With the established knowledge of how different marginalized communities (e.g., Black and Hispanic/Latino Americans) are exposed to PFAS through consumer products or residential water supply, it is important to consider disparities in heart health that could be due to this differential exposure. Additionally, our results show the importance of considering an individual's social determinants of health when conducting clinical exams to better the attributable factors that potentially contribute to adverse health outcomes.