



Relationships Between Serum Levels of Per- and Polyfluoroalkyl Substances and Obesity-Related Conditions in Patients of Okinawa, Japan

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Abstract

Per- and polyfluoroalkyl substances (PFAS) are human-made chemicals used in various manufactured products that accumulate in the environment and human bodies. We examined associations between serum PFAS levels and obesity or obesity-related clinical conditions using data from participants in Okinawa Island, a region in Japan with high PFAS exposure. We conducted a cross-sectional study using blood samples and clinical data from outpatients in a large primary care clinic. Linear regression analysis investigated the relationship between serum PFAS levels and body mass index (BMI) or other obesity-related clinical conditions. We also conducted modified Poisson models with robust standard errors analysis with serum PFAS levels for overweight, obesity, dyslipidemia, and hypertension. Of 399 participants, mean serum levels of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) were 2.80 ng/mL (SD, 1.93) and 7.56 ng/mL (SD, 5.83), respectively. Increased serum levels of PFAS were not associated with higher BMIs. Higher serum levels of perfluorohexane sulfonate (PFHxS) were related to a lower level of high-density lipoprotein cholesterol (HDL) [Beta coefficient: -1.90 ng/mL (95% CI -3.33 to -0.48)]. No adverse associations were found between higher serum PFAS levels and triglycerides, alanine transaminase, or low-density lipoprotein cholesterol. Only high serum PFHxS had a statistically significant odds ratio of 1.91 ng/mL (95% CI, 1.08–3.38; $p=0.04$) on dyslipidemia, but no other adverse relations were found between PFAS levels and overweight, obesity, and hypertension. Greater PFAS levels were not associated with obesity in our participants. However, PFHxS and PFOA were related to lower levels of HDL, and PFHxS was associated with any type of dyslipidemia.

Keywords PFAS · Obesity · Dyslipidemia · Hypertension · HDL-cholesterol · Japan

Introduction

Per- and polyfluoroalkyl substances (PFAS) are human-made chemicals used in various manufactured products since being discovered in 1938 (The New York Times 1994).

Given their chemical stability to heat, light, and other chemical agents, PFAS have been used as water and oil-repellent in food packaging, stain-resistant chemicals for clothes, and firefighting foam in military bases and airports (Organization for Economic Co-operation and Development (OECD)

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2022; National Institutes of Health 2023). Further, the carbon–fluorine bond of PFAS is not appreciably degraded under environmental conditions (Wang et al. 2015). Therefore, PFAS amass in the environment (Brusseau et al. 2020; Koch et al. 2020; Yong et al. 2021; Zhou et al. 2021).

The accumulation of PFAS in humans has been reported since the early 2000s (Giesy et al. 2001; Kotlarz et al. 2020; Pitter et al. 2020; Li et al. 2021). Due to the widespread usage of PFAS, people can be exposed via multiple pathways over their lifetime. For instance, exposure may occur through PFAS-contaminated foods, water, and air (Poothong et al. 2020; Domazet et al. 2020). In humans, the polar hydrophobic nature of fluorine-containing compounds can lead to increased affinity for proteins, resulting in long persistence of PFAS in the body (Pérez et al. 2013). Because PFAS share similar structural features with fatty acids, they can activate signaling pathways necessary for metabolism (Fenton et al. 2021). Consequently, previous hypotheses suggest that PFAS have adverse effects on human health (Canova et al. 2020), such as the development of obesity, dyslipidemia, and nonalcoholic steatohepatitis (NASH) (Canova et al. 2020).

A review highlighted that 22 studies examined the effect of PFAS on obesity, overweight, and abdominal circumference; 32 studies investigated the associations between PFAS and diabetes mellitus; and one study explored the relationship between PFAS and NASH (Qi et al. 2020). Approximately two-thirds of these studies indicated an adverse association between exposure to PFAS and the prevalence of obesity or type 2 diabetes mellitus. For instance, a recent U.S. study (Christensen et al. 2019) suggested a consistent association of perfluorononanoic acid (PFNA) with obesity, overweight, abdominal circumference, and metabolic syndrome. This was within a study population consisting of 49.3% males and 51.7% females; median age of 45.8 years (quartiles: 32.5, 58.8 years); and a majority of non-Hispanic Whites (68.9%, SE = 1.7%), followed by non-Hispanic Blacks (10.2%, SE = 0.8%) and Mexican Americans (8.0%, SE = 0.8%). Among Asian men, an observational study in China compared 81 individuals who had metabolic syndrome to 67 who did not. High serum levels of either PFNA or perfluorooctanoic acid (PFOA) were significantly associated with obesity (Yang et al. 2018).

In 2022, the Ministry of the Environment of Japan conducted a survey to measure water levels of perfluorooctane sulfonate (PFOS) and PFOA in 143 areas located around facilities that could potentially emit PFOA/PFOS. The survey revealed that 21 areas in 12 prefectures, including Okinawa Island, where U.S. military bases use 8% of the land, had higher concentrations of the substances compared to the target levels for the aquatic environment (50 ng/L for PFOS and PFOA combined) (Ministry of the Environment of Japan 2021). A human biomonitoring

survey was also conducted among people living in seven cities or towns near the military bases on Okinawa Island. Survey results showed that several areas had high serum PFAS concentrations, with perfluorohexane sulfonate (PFHxS) levels 14 times higher than the national average (The Mainichi 2022).

In 2022, the United States National Academies of Sciences, Engineering, and Medicine (NASEM) published guidance regarding PFAS. They recommended that individuals with known or suspected exposure to PFAS undergo blood tests for disease screening, including serum cholesterol measurement (The National Academies Press 2022). NASEM suggested that a total serum concentration level of 2 ng/mL or above for seven PFAS [MeFOSAA, PFHxS, PFOA, perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), PFOS, and PFNA] may contribute to adverse health outcomes (The National Academies Press 2022).

The prevalence of obesity has been increasing globally, and Okinawa is no exception. According to recent reports, the obesity rates in Okinawa have risen over the past few decades, posing significant health challenges for the population (Fukumine and Nakamura 2023). Despite the high prevalence of PFAS exposure and the rising obesity rates, to the best of our knowledge, no studies have explored the health impact of PFAS on obesity and its related conditions on patients in Okinawa, Japan.

Therefore, this study aims to investigate the relationship between PFAS blood concentrations and health effects, focusing on obesity and obesity-related clinical conditions in patients residing in Okinawa. This investigation is crucial to understanding the potential health risks of PFAS and developing appropriate public health interventions.

Methods

Participants and Study Design

This cross-sectional observational study was conducted in a large primary care clinic in Okinawa Island, Japan. The main target of this clinic was lifestyle-related diseases. The tap water used in the city surrounding the clinic was supplied from a water system close to a U.S. military airbase. The recruitment period was from September 2021 to April 2022. We asked 403 outpatients to participate in the research, and 399 voluntarily agreed. All participants provided written informed consent before blood and data collection. The ethics committee approved the study at Muribushi Okinawa Center for Teaching Hospitals (14 June 2021, approval No. 2021-3).

Measurements

Anonymized blood samples were sent to the Departments of Health and Environmental Sciences at Kyoto University, Japan, under refrigerated conditions. Using the blood sample, we measured the plasma/serum levels of 12 PFAS, including PFHxS, perfluoroheptane sulfonate (PFHpS), PFOS, perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), PFOA, PFNA, PFDA, PFUnDA, perfluorododecanoic acid (PFDoDA), perfluorotridecanoic acid (PFTrDA), and perfluorotetradecanoic acid (PFTeDA). Serum/plasma PFAS concentrations were determined by gas chromatography–mass spectrometry as previously reported (Kouji et al. 2020). Detection limits in each sample were adjusted by recoveries of ^{13}C -labelled surrogate compounds and derivatization efficiencies. Linear isomers of them were added as exposure variables.

To assess the health effects of PFAS, we collected demographic and clinical data from the clinic's medical records. Demographic measures included age and sex. Clinical data included the presence of overweight including obesity, dyslipidemia, hypertension, body mass index (BMI), systolic blood pressure (SBP)/diastolic blood pressure (DBP), alanine transaminase (ALT), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG), and the ratio of total cholesterol over HDL. Binary variables were overweight, including obesity status, dyslipidemia, and hypertension. All remaining data were collected as continuous variables. We labeled the participants with dyslipidemia both with documentation of the diagnosis in medical records and those based on the dyslipidemia diagnosis criteria published by the Japan Atherosclerosis Society (Presence of any one of LDL 140 mg/dL or higher, HDL 40 mg/dL or lower, or TG 150 mg/dL or higher) (Japan Atherosclerosis Society 2022). Patients with hypertension included those with documentation of the diagnosis in medical records and blood pressure readings based on the hypertension diagnosis criteria published by the Japanese Society of Hypertension (SBP of 140 mmHg or higher, or DBP of 90 mmHg or higher) (The Japan Society of Hypertension 2019). Overweight and obesity were defined by the World Health Organization (WHO) criteria (BMI 25 kg/m² or higher and BMI 30 kg/m² or higher, respectively) (The World Health Organization 2021).

Statistical Analyses

Linear regression analysis was used to examine the relationship between serum PFAS levels and BMI, metabolic syndrome, fatty liver, or dyslipidemia. We also conducted modified Poisson models with robust standard errors analysis to estimate relative risks and 95% confidence intervals (95% CIs) of binary clinical outcomes. PFAS concentrations

less than detection limits were converted to half the level of the detection limits. Eight PFAS concentrations with higher detection levels over 80% (PFHxS, PFHpS, PFOS, PFOA, PFNA, PFDA, PFUnDA, and PFTrDA) and the sum of serum PFAS concentrations were categorized into quartiles and used as nominal explanatory variables. Six specific PFAS without MeFOSAA (PFHxS, PFOS, PFOA, PFNA, PFDA, and PFUnDA) were summed to classify into three risk groups according to Guidance on PFAS Exposure, Testing, and Clinical Follow-Up published by NASEM (The National Academies Press 2022) and used as a discrete variable. The low-risk group included those who had six total PFAS concentrations lower than 2 ng/mL. The intermediate-risk group included PFAS concentrations equal to and higher than 2 ng/mL and lower than 20 ng/mL. The high-risk group contained those with PFAS concentrations equal to or above 20 ng/mL. Adjusted models included age and sex because they are well-established confounders that influence serum PFAS concentrations and health outcomes such as BMI, dyslipidemia, and liver function. Statistical software STATA 16 and Python 3.8 were used for statistical analyses.

Results

Table 1 shows the participants' characteristics. Of 399 participants, 219 (54.9%) were male, and the mean age was 53.4 years. Of 396 participants available for BMI data, the mean BMI was 25.6 kg/m² (SD, 4.95). A total of 188 (47.5%) were overweight and 78 (19.7%) were obese. Of 399 participants available for lipid data, mean TG, HDL, and LDL were 122.52 mg/dL (SD, 87.93), 53.41 mg/dL (SD, 14.70), and 98.77 mg/dL (SD, 30.58), respectively. 166 (41.6%) participants had dyslipidemia based on medical data or diagnostic criteria. The mean SBP captured from 375 participants was 128.69 mmHg (SD, 17.10). The mean DBP obtained from 374 participants was 76.10 mmHg (SD, 12.49). There were 207 (54.8%) participants with hypertension based on medical data or diagnostic criteria.

Table 2 shows the serum concentrations of PFAS. The mean concentration of the total PFAS was 22.56 ng/mL (SD, 16.41). PFOS had the highest mean PFAS concentration of 7.56 ng/mL (SD, 5.83), and PFHxA showed the lowest at 0.05 ng/mL (SD, 0.02). All comparable PFAS concentrations were higher in our study than in data from a previous biomonitoring study conducted by the Japanese Ministry of the Environment (Ministry of Environment of Japan 2022). The detection rates on PFHxA, PFHpA, PFDoDA, and PFTeDA were 5.0, 11.9, 62.9, and 0%, respectively and these were below the cut-off point of 80% for statistical analyses. Table 3 shows the proportions of participants based on the classification of PFAS health risk by the NASEM. There were 235 (58.9%) participants classified as

Table 1 Characteristics of participants

Characteristic	n	Unit	Mean (SD) or n (%)	Median [IQR]	Minimum, Max
Demographic					
Age	399	(years)	53.4 (15.3)	54.0 [43.0,65.0]	17,97
Sex (male)	399		219 (54.9)		
Clinical variable (continuous data)					
BMI	396	(kg/m ²)	25.65 (4.95)	24.60 [22.20,28.82]	15.40, 48.70
TG	399	(mg/dl)	122.52 (87.93)	99.00 [65.50,147.00]	22.00, 763.00
HDLc	399	(mg/dl)	53.41 (14.70)	52.00 [43.00,62.00]	17.00, 115.00
LDLc	399	(mg/dl)	98.77 (30.58)	96.00 [77.50,118.00]	20.00, 259.00
Total cholesterol/HDLc	399	(/)	3.49 (1.06)	3.24 [2.74,3.97]	1.96, 9.53
ALT	327	(IU/L)	30.00 (27.26)	22.00 [14.00,36.00]	7.00, 260.00
SBP	375	(mmHg)	128.69 (17.10)	128.00 [117.00,140.00]	73.00, 178.00
DBP	374	(mmHg)	76.10 (12.49)	76.00 [67.00,85.00]	42.00, 110.00
Clinical variable (prevalence)					
Overweight + Obesity	396		188 (47.5)		
Obesity	396		78 (19.7)		
Dyslipidemia					
Documented in medical record	399		33 (8.3)		
LDLc 140 mg or higher	399		34 (8.5)		
HDLc 40 mg/dl or lower	399		68 (17.0)		
TG 150 mg/dl or higher	399		97 (24.3)		
Hypertension					
Documented in medical record	399		163 (40.9)		
SBP 140 mmHg or higher	375		96 (24.9)		
DBP 90 mmHg or higher	374		59 (15.3)		

Overweight and obesity were defined by the World Health Organization (WHO) criteria; BMI 25 kg/m² or higher and BMI 30 kg/m² or higher, respectively. Patients with dyslipidemia included both those with documentation of the diagnosis in medical records and those based on the dyslipidemia diagnosis criteria published by the Japan Atherosclerosis Society; LDLc 140 mg/dL or higher, HDLc 40 mg/dL or lower, or TG 150 mg/dL or higher. Patients with hypertension included both those with documentation of the diagnosis in medical records and those based on the hypertension diagnosis criteria published by the Japan Hypertension Society; SBP 140 mmHg or higher, or DBP 90 mmHg or higher

BMI body mass index, *TG* triglyceride, *HDLc* high-density lipoprotein cholesterol, *LDLc* low-density lipoprotein cholesterol, *ALT* alanine aminotransferase, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *SD* standard deviation, *IQR* inter-quartile range

Table 2 Serum concentrations of per- and polyfluoroalkyl substances of participants

		mean (SD)	median [IQR]	mean (SD) of reference data
PFHxS	ng/mL	7.07 (7.35)	4.63 [2.13,9.02]	0.22 (0.17)
PFHpS	ng/mL	0.32 (0.27)	0.27 [0.15,0.44]	n.d.
PFOS	ng/mL	7.56 (5.83)	5.78 [3.76,9.42]	1.4 (0.84)
PFHxA	ng/mL	0.05 (0.02)	0.05 [0.04,0.06]	n.d.
PFHpA	ng/mL	0.10 (0.14)	0.08 [0.07,0.09]	0.0019 (0.017)
PFOA	ng/mL	2.80 (1.93)	2.35 [1.51,3.53]	0.86 (0.45)
PFNA	ng/mL	2.10 (1.37)	1.70 [1.13,2.66]	0.64 (0.39)
PFDA	ng/mL	0.54 (0.36)	0.43 [0.29,0.68]	0.21 (0.18)
PFUnDA	ng/mL	1.33 (1.06)	0.96 [0.60,1.78]	0.65 (0.35)
PFDoDA	ng/mL	0.11 (0.09)	0.08 [0.04,0.16]	n.d.
PFTTrDA	ng/mL	0.37 (0.22)	0.31 [0.22,0.44]	0.062 (0.11)
PFTeDA	ng/mL	0.18 (0.05)	0.19 [0.14,0.22]	n.d.
PFAS(overall)	ng/mL	22.54 (16.41)	17.74 [11.28,28.06]	n.d.

We refer to previous cohort studies conducted by the Japanese Ministry of the Environment as a reference

PFAS per- and polyfluoroalkyl substances, *PFHxS* perfluorohexane sulfonate, *PFHpS* perfluoroheptane sulfonate, *PFOS* perfluorooctane sulfonate, *PFHxA* perfluorohexanoic acid, *PFHpA* perfluoroheptanoic acid, *PFOA* perfluorooctanoic acid, *PFNA* perfluorononanoic acid, *PFDA* perfluorodecanoic acid, *PFUnDA* perfluoroundecanoic acid, *PFDoDA* perfluorododecanoic acid, *PFTTrDA* perfluorotridecanoic acid, *PFTeDA* perfluorotetradecanoic acid, *SD* standard deviation, *IQR* inter-quartile range, *n.d.* no data

Table 3 Proportions of participants classified by per- and polyfluoroalkyl substances health risk

	n (%)
High-risk group (PFAS (≥20))	164 (41.1)
Intermediate-risk group (PFAS(2-20))	235 (58.9)
Low-risk group (PFAS(2<))	0(0)

Seven Specific PFAS (PFHxS, PFOS, PFOA, PFNA, PFDA, PFUnDA, and PFTTrDA) were summed to classify into three risk groups according to Guidance on PFAS Exposure, Testing, and Clinical Follow-Up. The low-risk group included those who had lower seven total PFAS concentration than 2 ng/mL, the intermediate-risk group included those who had equal to and higher concentration than 2 ng/mL and lower than 20 ng/mL, and the high-risk group included those who had equal to and higher than 20 ng/mL

PFAS per- and polyfluoroalkyl substances, *PFHxS* perfluorohexane sulfonate, *PFOS* perfluorooctane sulfonate, *PFOA* perfluorooctanoic acid, *PFNA* perfluorononanoic acid, *PFDA* perfluorodecanoic acid, *PFUnDA* perfluoroundecanoic acid, *PFTTrDA* perfluorotridecanoic acid

Table 4 Linear regression analysis of serum per- and polyfluoroalkyl substances quartile and clinical data adjusted by age and sex

	BMI(N = 396)		TG(N = 399)		HDL(N = 399)		LDL(N = 399)		Total cholesterol/HDL(N = 399)		ALT(N = 327)		SBP(N = 375)		DBP(N = 374)										
	Coefficient	95% CI	P values	Coefficient	95% CI	P values	Coefficient	95% CI	P values	Coefficient	95% CI	P values	Coefficient	95% CI	P values	Coefficient	95% CI	P values							
PFHxS	0-25%(reference)	-0.19	-1.51-1.14	0.78	8.18	-15.98-32.35	0.51	-2.82	-6.77-1.14	0.16	-1.61	-10.27-7.06	0.72	0.09	-0.2-0.37	0.54	-5.49	-13.71-2.73	0.19	0.18	-4.33-4.89	0.94	1.01	-2.4-4.42	0.56
	25-50%	-0.94	-2.32-0.44	0.18	0.80	-24.41-26.02	0.95	-4.44	-8.57-0.32	0.03	-5.10	-14.14-3.94	0.27	0.08	-0.21-0.38	0.58	1.56	-7.06-10.17	0.72	-0.87	-5.64-3.89	0.72	-0.94	-4.54-2.66	0.61
	75-100%	-0.93	-2.41-0.55	0.22	-15.86	-42.96-11.24	0.25	-5.71	-8.87	0.01	1.17	-8.55-10.88	0.81	0.21	-0.11-0.54	0.19	-0.72	-6.79-8.38	0.88	-2.69	-7.78-2.37	0.30	-1.32	-5.16-2.53	0.50
PFHpS	0-25%(reference)	-0.49	-1.86-0.87	0.48	11.53	-13.21-36.26	0.36	-0.87	-4.95-3.22	0.68	1.01	-7.92-9.94	0.82	0.18	-0.12-0.47	0.24	-0.40	-8.81-8.01	0.93	1.87	-2.75-6.5	0.43	1.43	-2.08-4.94	0.42
	25-50%	-0.72	-2.1-0.67	0.31	-7.18	-32.25-17.89	0.57	-2.72	-6.86-1.42	0.20	-2.01	-11.06-7.04	0.66	-0.01	-0.3-0.3	0.99	2.95	-5.64-11.54	0.50	-0.52	-5.26-4.22	0.83	-0.02	-3.62-3.57	0.99
	75-100%	-0.72	-2.26-0.82	0.36	-22.76	-50.77-5.25	0.11	-3.99	-8.62-0.63	0.09	-2.25	-12.36-7.86	0.66	0.06	-0.27-0.4	0.71	1.14	-8.22-10.5	0.81	-2.81	-8.08-2.47	0.30	-0.54	-4.57-3.48	0.79
PFOS	0-25%(reference)	-2.02	-3.34-0.7	<0.01	-17.99	-42.27-6.3	0.15	2.12	-1.86-6.11	0.30	0.94	-7.78-9.67	0.83	-0.16	-0.45-0.13	0.28	-1.99	-10.19-6.22	0.63	-3.11	-7.61-1.4	0.18	-2.04	-5.46-1.38	0.24
	25-50%	-1.92	-3.26-0.58	0.01	-23.77	-48.49-0.96	0.06	2.85	-1.21-6.9	0.17	1.82	-7.06-10.71	0.69	-0.21	-0.5-0.09	0.17	2.28	-6.18-10.74	0.60	-4.62	-9.21-0.04	0.05	-2.06	-5.54-1.42	0.25
	75-100%	-1.89	-3.09-0.28	0.02	-25.48	-51.41-0.44	0.05	-1.78	-6.03-2.47	0.41	-3.56	-12.88-5.76	0.45	-0.13	-0.43-0.18	0.42	0.46	-8.39-9.32	0.92	-3.60	-8.52-1.33	0.15	-1.00	-4.75-2.75	0.60
PFOA	0-25%(reference)	-1.37	-2.68-0.06	0.04	8.88	-15.28-33.05	0.47	-1.86	-5.77-2.06	0.35	-1.47	-10.59-7.15	0.74	0.13	-0.16-0.41	0.38	-1.71	-9.92-6.5	0.68	-0.32	-4.78-4.14	0.89	-1.37	-4.74-2.0	0.43
	25-50%	-1.97	-3.28-0.65	0.01	4.68	-29.04-19.72	0.71	1.64	-2.31-5.59	0.41	2.42	-6.28-11.12	0.59	-0.03	-0.32-0.26	0.85	2.42	-5.84-10.69	0.56	-2.75	-7.22-1.72	0.23	-0.36	-3.74-3.01	0.83
	75-100%	-1.03	-2.38-0.31	0.13	2.33	-22.31-26.98	0.85	-5.05	-9.05-1.06	0.01	-5.91	-14.7-2.89	0.11	0.16	-0.13-0.46	0.27	4.15	-4.21-12.51	0.33	-0.36	-5.03-4.31	0.88	1.71	-1.83-5.25	0.34
PFNA	0-25%(reference)	-1.66	-2.97-0.35	0.01	-2.14	-26.36-22.08	0.86	-0.87	-4.86-3.12	0.67	-3.63	-12.29-5.02	0.41	-0.04	-0.32-0.25	0.81	-5.42	-13.56-2.71	0.19	-1.13	-5.6-3.33	0.82	-1.51	-4.89-1.87	0.38
	25-50%	-2.03	-3.37-0.69	<0.01	0.66	-24.1-25.42	0.96	-0.63	-4.7-3.45	0.76	-1.93	-10.78-6.92	0.67	0.01	-0.28-0.31	0.93	0.09	-8.35-5.54	0.98	-1.18	-5.75-3.39	0.61	0.10	-3.36-3.56	0.95
	75-100%	-1.68	-3.05-0.32	0.02	-12.99	-38.26-12.28	0.31	-1.17	-5.33-2.99	0.58	-7.35	-16.38-1.68	0.11	-0.20	-0.5-0.09	0.18	-2.06	-10.63-6.51	0.64	-3.08	-7.89-1.73	0.21	-1.18	-3.83-3.47	0.92
PFDA	0-25%(reference)	-0.74	-2.04-0.56	0.26	-18.06	-41.86-5.74	0.14	0.93	-3.0-4.86	0.64	-1.49	-10.05-7.08	0.73	-0.20	-0.48-0.08	0.17	0.31	-7.74-8.37	0.94	1.88	-2.49-6.24	0.40	1.30	-1.99-4.6	0.44
	25-50%	-1.50	-2.81-0.19	0.02	0.54	-29.33-24.4	0.96	0.20	-3.74-4.14	0.92	-6.53	-15.72-2.06	0.14	-0.14	-0.42-0.14	0.34	0.16	-7.86-8.19	0.97	-0.42	-4.88-4.03	0.85	0.05	-3.33-3.42	0.98
	75-100%	-1.67	-3.01-0.35	0.01	-25.85	-50.09-1.61	0.04	3.29	-0.71-7.29	0.11	-1.25	-9.98-7.47	0.78	-0.34	-0.62-0.05	0.02	0.14	-8.51-8.23	0.97	0.65	-4.0-5.3	0.78	1.60	-1.91-5.12	0.37
PFUnDA	0-25%(reference)	-1.60	-2.89-0.31	0.01	-21.32	-45.06-2.41	0.08	3.37	-0.54-7.27	0.09	0.02	-8.53-5.89	1.00	-0.30	-0.58-0.02	0.04	-4.10	-12.15-3.96	0.32	-0.44	-4.79-3.92	0.84	-0.25	-3.54-3.04	0.88
	25-50%	-2.18	-3.47-0.89	<0.01	-14.40	-38.2-9.4	0.24	4.28	0.37-8.2	0.03	-4.89	-13.47-3.69	0.26	-0.37	-0.65-0.09	0.01	0.61	-7.29-8.52	0.88	-0.12	-4.54-4.3	0.96	1.24	-2.11-4.58	0.47
	75-100%	-2.35	-3.65-1.04	<0.01	-31.56	-55.62-7.5	0.01	4.79	0.83-8.74	0.02	-3.81	-12.48-4.86	0.39	-0.47	-0.75-0.19	<0.01	-3.13	-11.45-5.19	0.46	0.07	-4.58-4.72	0.98	1.58	-1.93-5.09	0.38
PFTrDA	0-25%(reference)	-2.04	-3.33-0.76	0.01	-8.19	-32.0-15.62	0.50	2.97	-0.9-6.83	0.13	3.92	4.6-12.45	0.37	-0.16	-0.44-0.12	0.27	-4.94	-12.87-3.0	0.22	-3.85	-8.19-0.48	0.08	-1.63	-4.92-1.65	0.33
	25-50%	-0.86	-2.16-0.43	0.16	-1.92	-25.98-22.14	0.88	3.39	-0.52-7.29	0.09	-2.11	-10.72-6.51	0.63	-0.24	-0.53-0.04	0.09	2.41	-5.62-10.44	0.56	-2.90	-7.34-1.54	0.20	-1.19	-4.57-2.18	0.46
	75-100%	-2.33	-3.62-1.05	<0.01	-16.03	-40.01-7.94	0.19	6.90	3.01-10.79	<0.01	-0.80	-8.18-7.98	0.89	-0.39	-0.69-0.11	0.01	-2.14	-10.23-5.94	0.80	-0.54	-5.03-3.95	0.81	0.88	-2.73-0.98	0.70
PFAS (overall)	0-25%(reference)	-1.40	-2.72-0.07	0.04	-6.87	-32.14-16.85	0.54	-0.87	-4.89-3.35	0.74	-2.25	-11.03-6.52	0.61	-0.02	-0.31-0.27	0.87	-4.42	-12.68-3.85	0.29	2.06	-2.42-6.55	0.37	0.81	-2.6-4.23	0.64
	25-50%	-2.18	-3.55-0.82	<0.01	-10.28	-35.49-14.94	0.42	-2.10	-6.23-2.04	0.32	-0.74	-9.77-8.3	0.87	0.05	-0.25-0.35	0.74	-1.07	-9.56-7.41	0.80	-4.64	-9.31-0.02	0.05	-2.02	-5.58-1.54	0.27
	75-100%	-1.05	-2.47-0.38	0.15	-16.24	-42.64-10.16	0.23	-3.48	-7.81-0.85	0.11	-3.23	-12.69-6.23	0.50	0.04	-0.27-0.36	0.79	2.03	-6.91-10.98	0.65	-1.65	-6.61-3.31	0.51	-0.22	-4.01-3.57	0.91
PFAS health risk classification	Intermediate risk (reference)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	High-risk	-0.64	-1.65-0.36	0.21	-18.49	-36.87-0.1	0.05	-2.62	-5.64-0.41	0.09	0.40	-6.22-7.01	0.91	0.05	-0.16-0.27	0.62	2.91	-3.22-9.03	0.35	-1.35	-4.84-2.15	0.45	-0.44	-3.09-2.21	0.74

Linear regression analysis was used to examine the relationship between serum PFAS levels and each metabolic factor. Eight PFAS concentrations (PFHxS, PFHpS, PFOS, PFOA, PFNA, PFDA, PFUnDA, and PFTrDA) and stratified serum PFAS concentrations were categorized into quartiles and used as nominal explanatory variables. PFAS health risk groups were also used as explanatory variables. Each regression was adjusted by demographic factors of age and gender

BMI body mass index, *TG* triglyceride, *HDL* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol, *ALT* alanine aminotransferase, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PFAS* per- and polyfluoroalkyl substances, *PFHxS* perfluorohexane sulfonate, *PFHpS* perfluoroheptane sulfonate, *PFOS* perfluoro-octane sulfonate, *PFOA* perfluoro-octanoic acid, *PFNA* perfluorononanoic acid, *PFDA* perfluoro-decanoic acid, *PFUnDA* perfluoro-undecanoic acid, *PFTrDA* perfluoro-tridecanoic acid, *95% CI* 95% confidence interval

intermediate-risk, 164 (41.1%) high-risk, and no participant was identified as low-risk.

Table 4 shows the results of the linear regression analysis of PFAS effects on BMI, TG, HDL, LDL, total cholesterol/HDL, ALT, SBP, and DBP. Higher serum levels of PFHxS were significantly related to lower levels of HDL. Compared with the first PFHxS quartile group, the third [beta coefficient: -4.44 (95% CI -8.57 to -0.32)] and fourth quartile groups [beta coefficient: -5.71 (95% CI -10.15 to -1.28)] had negative relations on serum HDL levels, respectively. The PFOA fourth quartile group also had negative relations on serum HDL levels [beta coefficient: -5.05 (95% CI -9.05 to -1.06)]. Besides these associations, there were no other statistically significant adverse associations between higher serum levels of PFAS and clinical data, and rather, there were protective relations of several types of PFAS and BMI, TG, HDL, LDL, and DBP. Supplementary Tables 1 and 2 shows the classified linear regression results for males and females.

Table 5 summarizes the results of modified Poisson models with robust standard errors analysis with PFAS effects on overweight, obesity, dyslipidemia, and hypertension. The PFHxS second quartile group had a statistically significant

odds ratio of 1.46 (95% CI, 1.02-2.08, p=0.04) on dyslipidemia. No statistically significant adverse relationship was found between other PFAS levels or PFAS risk classification and the presence of overweight, obesity, dyslipidemia, or hypertension. Protective relations were found between several PFAS and overweight, obesity, and hypertension. Supplementary Tables 3 and 5 show the classified results of modified Poisson models with robust standard errors analysis for males and females. Of the all relatives and groups, the PFHpS quartile male group had both statistically significant higher risks of overweight, obesity and hypertension with Odds ratio of 2.86 (95% CI 1.05-7.78, p value=0.04), 4.32 (95% CI 1.18-15.76, p value=0.03) and 2.93 (95% CI 1.01-8.49, p value=0.05).

Discussion

Exposure to PFAS has been postulated as a risk factor for obesity and obesity-related diseases. We examined the relationship between serum PFAS concentrations and obesity-related health conditions in the people of Okinawa Island, one of the highest PFAS-exposed areas in Japan. We found

Table 5 Modified Poisson models with robust standard errors analysis of serum per- and polyfluoroalkyl substances quartile and clinical conditions (adjusted by age and sex)

	Overweight + Obesity (N = 396)			Obesity (N = 396)			Dyslipidemia (N = 399)			Hypertension (N = 378)			
	Odds ratio	95% CI	P values	Odds ratio	95% CI	P values	Odds ratio	95% CI	P values	Odds ratio	95% CI	P values	
PFHxS	0-25%(reference)												
	25-50%	1.04	0.51 - 2.11	0.91	1.09	0.61 - 1.96	0.78	1.91	1.08 - 3.38	0.03	0.70	0.36 - 1.36	0.29
	50-75%	0.61	0.29 - 1.29	0.20	0.97	0.53 - 1.78	0.93	1.22	0.67 - 2.22	0.52	0.58	0.28 - 1.17	0.13
	75-100%	0.53	0.24 - 1.17	0.12	0.99	0.51 - 1.9	0.97	1.45	0.76 - 2.76	0.26	0.35	0.16 - 0.75	0.01
PFHpS	0-25%(reference)												
	25-50%	1.09	0.54 - 2.21	0.81	1.08	0.6 - 1.95	0.80	1.50	0.84 - 2.69	0.17	1.14	0.59 - 2.22	0.69
	50-75%	0.60	0.27 - 1.32	0.21	1.19	0.65 - 2.18	0.58	1.55	0.85 - 2.81	0.15	0.71	0.36 - 1.41	0.32
	75-100%	0.56	0.25 - 1.28	0.17	1.26	0.64 - 2.48	0.50	1.38	0.71 - 2.7	0.34	0.52	0.24 - 1.14	0.10
PFOS	0-25%(reference)												
	25-50%	0.60	0.3 - 1.2	0.15	0.69	0.39 - 1.24	0.21	0.91	0.52 - 1.6	0.74	0.50	0.26 - 0.97	0.04
	50-75%	0.57	0.28 - 1.18	0.13	0.62	0.34 - 1.13	0.12	1.05	0.59 - 1.88	0.87	0.35	0.18 - 0.7	<0.01
	75-100%	0.43	0.19 - 0.94	0.03	0.78	0.41 - 1.47	0.44	1.04	0.56 - 1.93	0.89	0.49	0.23 - 1.05	0.07
PFOA	0-25%(reference)												
	25-50%	0.50	0.25 - 1.01	0.05	0.90	0.51 - 1.57	0.70	1.35	0.78 - 2.35	0.28	0.62	0.32 - 1.18	0.15
	50-75%	0.68	0.35 - 1.34	0.27	0.61	0.34 - 1.1	0.10	1.06	0.59 - 1.88	0.86	0.34	0.17 - 0.68	<0.01
	75-100%	0.52	0.25 - 1.09	0.08	0.83	0.45 - 1.5	0.53	1.73	0.96 - 3.11	0.07	0.60	0.3 - 1.21	0.16
PFNA	0-25%(reference)												
	25-50%	0.40	0.19 - 0.81	0.01	0.83	0.47 - 1.48	0.53	1.18	0.68 - 2.07	0.55	0.50	0.26 - 0.96	0.04
	50-75%	0.53	0.26 - 1.09	0.09	0.45	0.24 - 0.83	0.01	1.15	0.64 - 2.07	0.64	0.56	0.28 - 1.11	0.09
	75-100%	0.42	0.2 - 0.89	0.02	0.64	0.34 - 1.19	0.16	1.00	0.55 - 1.83	1.00	0.71	0.35 - 1.46	0.36
PFDA	0-25%(reference)												
	25-50%	0.68	0.34 - 1.35	0.27	0.97	0.55 - 1.73	0.93	0.89	0.5 - 1.56	0.67	0.68	0.36 - 1.28	0.23
	50-75%	0.67	0.34 - 1.32	0.25	0.63	0.35 - 1.13	0.12	1.12	0.64 - 1.96	0.70	0.61	0.32 - 1.17	0.14
	75-100%	0.44	0.21 - 0.94	0.03	0.67	0.37 - 1.21	0.19	0.83	0.47 - 1.49	0.54	0.76	0.38 - 1.5	0.43
PFUnDA	0-25%(reference)												
	25-50%	0.70	0.36 - 1.36	0.29	0.64	0.36 - 1.14	0.13	0.83	0.48 - 1.45	0.52	0.72	0.38 - 1.33	0.29
	50-75%	0.64	0.32 - 1.25	0.19	0.44	0.24 - 0.78	0.01	0.78	0.45 - 1.37	0.39	0.67	0.35 - 1.27	0.22
	75-100%	0.36	0.17 - 0.78	0.01	0.50	0.27 - 0.91	0.02	0.69	0.39 - 1.24	0.22	0.68	0.34 - 1.36	0.28
PFDoDA	0-25%(reference)												
	25-50%	0.68	0.33 - 1.4	0.30	0.75	0.42 - 1.33	0.32	1.19	0.68 - 2.08	0.55	0.62	0.33 - 1.19	0.15
	50-75%	0.64	0.31 - 1.31	0.22	0.77	0.43 - 1.36	0.37	0.91	0.52 - 1.6	0.74	0.53	0.27 - 1.03	0.06
	75-100%	0.94	0.48 - 1.83	0.85	0.91	0.52 - 1.62	0.76	0.91	0.52 - 1.6	0.74	0.44	0.23 - 0.84	0.01
PFTrDA	0-25%(reference)												
	25-50%	0.51	0.25 - 1.05	0.07	0.61	0.35 - 1.08	0.09	0.81	0.47 - 1.4	0.45	0.52	0.28 - 0.97	0.04
	50-75%	1.08	0.56 - 2.07	0.82	0.77	0.43 - 1.37	0.37	1.02	0.59 - 1.78	0.94	0.58	0.3 - 1.11	0.10
	75-100%	0.49	0.24 - 1.04	0.06	0.50	0.28 - 0.89	0.02	0.62	0.35 - 1.1	0.10	0.53	0.27 - 1.04	0.06
PFAS (overall)	0-25%(reference)												
	25-50%	0.71	0.35 - 1.41	0.32	0.80	0.44 - 1.43	0.45	1.02	0.57 - 1.8	0.96	0.78	0.4 - 1.5	0.45
	50-75%	0.43	0.2 - 0.92	0.03	0.61	0.33 - 1.13	0.12	1.39	0.77 - 2.5	0.27	0.32	0.16 - 0.65	<0.01
	75-100%	0.44	0.2 - 0.97	0.04	0.94	0.49 - 1.78	0.84	1.18	0.63 - 2.22	0.60	0.60	0.28 - 1.28	0.18
PFAS health risk classification	Intermediate risk (reference)												
	High-risk	0.98	0.65 - 1.48	0.93	0.78	0.47 - 1.29	0.33	1.08	0.72 - 1.62	0.71	0.51	0.32 - 0.83	0.01

Modified Poisson models with robust standard errors was used to examine the relationship between serum PFAS levels and each metabolic disease. Eight PFAS concentrations (PFHxS, PFHpS, PFOS, PFOA, PFNA, PFDA, PFUnDA, and PFTrDA) and stratified serum PFAS concentrations were categorized into quartiles and used as nominal explanatory variables. PFAS health risk groups were also used as explanatory variables. Each regression was adjusted by demographic factors of age and gender

OW overweight, *OB* obesity, *DLP* dyslipidemia, *HT* hypertension, *PFAS* per- and polyfluoroalkyl substances, *PFHxS* perfluorohexane sulfonate, *PFHpS* perfluoroheptane sulfonate, *PFOS* perfluorooctane sulfonate, *PFOA* perfluorooctanoic acid, *PFNA* perfluorononanoic acid, *PFDA* perfluorodecanoic acid, *PFUnDA* perfluoroundecanoic acid, *PFTrDA* perfluorotridecanoic acid, *95%CI* 95% confidence interval

no significant association between PFAS exposure and higher BMIs. However, two PFAS (PFHxS and PFOA) were associated with lower levels of HDLC and dyslipidemia.

Among our participants, the mean BMI was 25.65 kg/m², which was higher than the cut-off of “overweight”. A previous study demonstrated that the prevalence of metabolic syndrome among men in Okinawa was higher than that of men in the U.S. and the national average for men in Japan (Tanaka et al. 2005; Okinawa Prefectural Government 2023). According to the 2021 Prefectural Health and Nutrition Survey conducted by Okinawa prefecture, the proportion of obesity among the 20-year-old population was 41.6% in males and 24.8% in females, which was higher than the national average (33% in males and 22.3% in females) (Okinawa Prefectural Government 2023). In this survey, over 70% of people aged 20 years or older consumed less than

the target daily vegetable intake (350 g). The average intake for males was 262.5 g and 280 g for females. Moreover, the percentage of those who consumed alcohol with the amount that increased non-communicable disease risk (i.e., alcohol intake per day is above 40 g in males and 20 g in females) was 17.2% in males and 13.1% in females: both higher than the national average (14.9% in males and 9.1% in females) (Okinawa Prefectural Government 2023). One of the reasons for the high prevalence of obesity in Okinawa may be Okinawan food habits. Before World War II, Okinawa had its original food culture, with abundant vegetables, fruits, and seafood. However, during the postwar period when the U.S. army occupied Okinawa, its food culture was Westernized (Todoroki 2007). This resulted in increased intake of high-carbohydrate, high-fat meals, and processed or ultra-processed foods—such as canned pork products. After the

reversion of Okinawa from the U.S. to Japan, Japan's high salt meal culture influenced Okinawa's culture. This was associated with less exercise and a greater intake of foods high in carbohydrates, fat, and sodium (Todoroki 2007). These lifestyle factors are likely associated with increased obesity and obesity-related clinical conditions in people of Okinawa Island.

In Okinawa, we did not find any significant association between PFAS and adverse health events—except possible lower HDLC, the risk of dyslipidemia and overweight, obesity and hypertension in males. However, we found that this area's mean cumulative blood concentration of all PFAS was higher than the recent serum data collected by the Ministry of Environment of Japan. Furthermore, when comparing the criteria of the risk concentration of PFAS according to the NASEM, all the participants in our study were classified into intermediate-risk or high-risk groups (The National Academies Press 2022). These results suggested that the citizens in Okinawa potentially have a higher risk of exposure to PFAS. Thus, it may be recommended that these patients undergo disease screening, at least for patients in the high-risk group.

We found a possible link between PFHxS and PFOA to lower levels of HDLC. PFHxS was also significantly related to an increase in the risks of dyslipidemia with an odds ratio of 1.91, overweight in males with an odds ratio of 2.86, obesity in males with an odds ratio of 4.32, and hypertension in males with an odds ratio of 2.93. Future studies comparing higher and lower-exposed participants to PFAS are required to determine the effect on lower HDLC and dyslipidemia more precisely. In addition, we discovered that several PFAS showed potentially positive effects on clinical data or conditions (e.g., BMI, TG, HDLC, presence of hypertension). One study also showed a J-shaped relation between PFAS and hypertension (Liao et al. 2020). The study suggested there might be negative effects of PFAS on blood pressure that require a certain pathogenic dose (Liao et al. 2020).

We observed that PFHxS and PFOS blood concentrations were higher than other PFAS. These results were compatible with previous studies in Tokyo (Japan) and Australia (Rotander et al. 2015; The Asahi Shimbun 2023). The main usage of PFOS and PFHxS is aqueous film-forming foam (AFFF), which is used in some fire extinguishers. A study in Australia (Rotander et al. 2015) examined the blood concentration levels of PFOS and PFHxS in firefighters. It showed that the concentrations of PFOS and PFHxS were positively associated with the number of years worked as a firefighter and AFFF contact. AFFF is also used in military bases. According to an examination by the U.S. Department of Defense in 2018, PFOS and PFOA were found in 401 locations among 524 military bases in the U.S. Twenty-four of those locations had drinking water contamination levels greater than the Environmental Protection Agency's lifetime health advisory of 70 parts per trillion (Maureen et al. 2018).

It is important to note that we collected participants' data from a primary care clinic located 3.8 km from a large US military base of the Marine Corps. As such, we expected participants to have higher concentrations of PFAS levels than the general population in Japan.

To our knowledge, this is the first study that examined the PFAS serum levels and obesity-related conditions among Okinawan people. However, the study has potential limitations. First, our participants were outpatients of a clinic and did not represent the general population of Okinawa Prefecture. Participants might have had health problems before the exposure to PFAS. This might have complicated the analysis of the PFAS effect. For example, a high proportion of participants were previously diagnosed with hypertension. Second, we conducted a cross-sectional study, limiting identification of causality. We found out that the PFAS (PFHxS and PFOA) were associated with lower levels of HDLC in the patients of Okinawa Island. However, we had no data on HDLC levels before the exposure to PFAS. Thus, we could not eliminate the possibility that the participants with higher PFHxS and PFOA originally had lower levels of HDLC before exposure to PFAS. Third, we could not obtain information on the presence of treatment or prescription for hypertension and dyslipidemia among participants, and thus we could not eliminate the treatment effect on the biochemical data. Moreover, because of the data collection barrier, we could not obtain socioeconomic data such as occupation and meal habits, which might be confounding factors. Fourth, other factors, including poor diet, low exercise habits, or socioeconomic status, might contribute to obesity. As such, the small effects of PFAS on increased obesity could not be ruled out because of our relatively small sample size. Finally, we could not collect residential and occupational information of the participants, which may affect the amount and duration of their exposure to PFAS.

Conclusion

Greater PFAS exposure was not associated with an increased risk of obesity. However, two types of PFAS (PFHxS and PFOA) were associated with lower levels of HDLC in the patients of Okinawa Island, one of the highest PFAS-exposed areas in Japan. This study has several limitations. The sample, drawn from a single clinic, may not represent the wider Okinawan population and included many with pre-existing conditions like hypertension. Its cross-sectional design prevents causal inference, especially without baseline HDLC data. Missing information on treatments, socioeconomic status, lifestyle, and exposure history further limits interpretation. Further studies are needed to investigate PFAS's effects on human health, including obesity-related conditions and other diseases.

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Data Availability The data that support the findings of this study are available from the authors upon appropriate request.

Declarations

Competing Interests The authors have no interest to declare.

Ethical Approval The study was approved by the ethics committee at Muribushi Okinawa Center for Teaching Hospitals (14 June 2021, approval No. 2021-3).

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent to Publish The authors affirm that human research participants provided informed consent for publication.

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