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Association of perfluoroalkyl substances exposure with cardiometabolic traits in an island population of the eastern Adriatic coast of Croatia

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Abstract

Background: Exposure to perfluoroalkyl substances (PFAS), ubiquitous environmental contaminants, may be related to cardiometabolic diseases in adults. Studies in European populations to examine the association of PFAS exposure and comprehensive cardiometabolic traits and metabolic syndrome (MetS) are limited.

Methods: In this pilot cross-sectional study of a well-characterized adult population of the island of Hvar, situated off the eastern Adriatic coast of Croatia, we measured PFAS concentrations in plasma samples collected during 2007–2008 and examined their cross-sectional associations with

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cardiometabolic traits and MetS after adjustment of covariates (n=122). PFAS investigated in this study included perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA).

Results: The geometric mean (range) was 8.91 (2.36, 33.67) ng/mL for PFOS, 2.87 (1.03, 8.02) ng/mL for PFOA, 0.77 (0.25, 2.40) ng/mL for PFHxS, and 1.29 (0.48, 3.46) ng/mL for PFNA, with frequency of detection at 100%, 100%, 95.9 %, and 100%, respectively. PFOS, PFOA, and PFNA concentrations were positively associated with the risk of MetS as defined by the Adult Treatment Panel III (ATP III) criteria, with estimated odds ratios and 95% confidence intervals at 1.89 (0.93, 3.86), 2.19 (0.88, 5.44), and 2.95 (1.12, 7.80), respectively, with only PFNA reaching statistical significance. PFNA concentrations were associated with increased risk of overweight or obesity.

Conclusions: Background exposure to PFOS, PFOA, and PFNA was marginally associated with increased risk of MetS in this small study, and these results should be confirmed with a larger sample size and longitudinal follow-up.

Keywords

perfluoroalkyl substances; metabolic syndrome; waist circumference; overweight; obesity; total cholesterol

1. Introduction

Genetic predisposition, lifestyle factors like smoking and alcohol abuse, and physical inactivity are known to be implicated in the rise of cardiometabolic disorders. However, only recently have endocrine disrupting chemicals (EDCs) started to be investigated as potential obesogens, daibetogens, and risk factors for cardiometabolic disorders (Alonso-Magdalena et al., 2011; Casals-Casas and Desvergne, 2011; Grun, 2010; Hatch et al., 2010; McAllister et al., 2009; Meeker, 2012; Neel and Sargis, 2011). Among EDCs, perfluoroalkyl substances (PFAS), which were introduced as surfactants and water-and stain-repellants in the 1950s, are of particular concern. Toxicological and epidemiologic evidence is emerging suggesting their potential role in the activation of, peroxisome proliferator activated receptor α and γ (PPARα and PPARγ), disruption of gonadal and thyroid hormones, increasing blood cholesterol and adiposity, and perturbation of insulin and glucose homeostasis (Fletcher et al., 2013; Jensen and Leffers, 2008). PFAS encompass perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA, or C8), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and thousands of other compounds with carbon-fluoride bonds.

Previous studies have suggested associations between PFAS exposure and increased concentrations of total cholesterol, uric acid, glucose, insulin resistance, glycated hemoglobin (HbA1c) (Cardenas et al., 2017; Steenland et al., 2009; Steenland et al., 2010), but the association between PFAS exposure and metabolic syndrome (MetS) and cardiovascular diseases remains to be studied (Lin et al., 2009; Liu et al., 2018b). Limited research has been conducted in European adult populations to examine the association between PFAS exposure and comprehensive cardiometabolic traits (Eriksen et al., 2013;

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Lind et al., 2014; Lind et al., 2018; Lind et al., 2017), and no studies have examined metabolic syndrome. Therefore, we leveraged samples and data from an existing and well-phenotyped cardiometabolic study of a Croatian island population (Deka et al., 2012) to investigate PFAS concentrations and potential associations with cholesterol, glucose, waist circumference, blood pressure, and other cardiometabolic traits.

2. Methods

2.1 Study population

During 2007 and 2008, we collected demographic, socioeconomic, genomic, and cardiometabolic data from 1,430 adults (602 men, 828 women, mean age 55.3±15.8 years) living on the island of Hvar off the eastern Adriatic coast of Croatia (Deka et al., 2012; Karns et al., 2013; Zhang et al., 2010). Adriatic islanders are predominantly of Slavic descent, who emigrated from the interior of the Balkan peninsula during the 6^{th} and 8^{th} century AD, and later between the 15^{th} and 18^{th} centuries (Rudan et al., 1992). Since those times, the island population has remained relatively isolated. In this pilot study, we randomly chose 123 participants between 44–56 years of age, who were already genotyped, phenotyped for cardiometabolic traits, and with plasma available for PFAS measurements. The narrow age range was deliberately selected to reduce the confounding by aging and to consider the introduction of PFAS in the world market in the 1950s or later. The study was approved by Institutional Review Board at University of Cincinnati and Ethics Committee at Institute for Anthropological Research.

2.2 PFAS exposure assessment

We quantified PFAS concentrations (including PFOS, PFOA, PFHxS, and PFNA) in plasma samples collected at the recruitment visit at the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention (CDC). The method involves automated online solid-phase extraction coupled to reversed-phase high-performance liquid chromatography-tandem mass spectrometry (HPLC/MS/MS) (Kato et al., 2011a). The limit of detection (LOD) for all PFAS was 0.1 ng/mL, and concentrations <LOD were replaced by LOD divided by the square root of 2. Quality control samples were analyzed with the study samples and with reagent and serum blanks to ensure the accuracy and reliability of the method. The involvement of the CDC laboratory did not constitute direct engagement in human subjects research for CDC as all biospecimens were deidentified.

2.3 Cardiometabolic traits

We measured anthropometric traits (height, weight, waist circumference [WC] and hip circumference). We obtained systolic and diastolic blood pressure (SBP, DBP) measurements twice (15 min apart) using a mercury sphygmomanometer and took the average. Venous blood samples were collected following a 12-hour fast; plasma was then separated, frozen, and shipped for biochemical testing at an accredited clinical biochemical laboratory, the Labor Center, in Zagreb, Croatia. Eleven biochemical traits were measured – fasting plasma glucose (FPG), fasting plasma insulin (FPI), % hemoglobin A1c (% HbA1c), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), total

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cholesterol (TC), triglycerides (TG), serum creatinine, uric acid, fibrinogen, and serum calcium (Deka et al., 2012). We calculated homeostatic model assessment – insulin resistance (HOMA-IR: [FPI * FPG]/22.5, with FPI in mU/L and FPG in mmol/L), and HOMA β-cell function (HOMA-β: [20 * FPI]/[FPG-3.5], with same unit for FPI and FPG as above) (Matthews et al., 1985; Wallace et al., 2004).

We used both Adult Treatment Panel III (ATP III) (2002) and International Diabetes Federation (IDF) criteria to define traits of metabolic syndrome (MetS) (Alberti et al., 2005). ATP III defines MetS as the co-occurrence of three or more of the following five risk factors: i) WC >102 cm in men and >88 cm in women; ii) TG ≥1.69 mmol/L; iii) HDL <1.03 mmol/L in men and <1.29 mmol/L in women; iv) blood pressure ≥130/85 mm Hg; and v) FPG ≥6.1 mmol/L. The IDF definition includes central obesity as the core criterion with population-specific cut points of WC (≥94 cm for men and ≥80 cm for women in Europeans), and two or more of the following: i) TG ≥1.69 mmol/L or treatment for hypertriglyceridemia; ii) HDL <1.03 mmol/L in men or <1.29 mmol/L in women or treatment for hypercholesterolemia; iii) blood pressure ≥130/85 mm Hg or treatment for hypertension; and iv) FPG ≥5.6 mmol/L or treatment for type 2 diabetes. Anthropometric and biochemical cardiometabolic traits not included in the definition of MetS were also dichotomized using previously published cutoffs (Deka et al., 2012).

2.4 Statistical analyses

We summarized the distribution of plasma PFAS in the study population and examined the association with demographic characteristics, socioeconomic characteristics, smoking, dietary patterns, and physical activity. Three dietary patterns were determined by previously published factor analysis based on the highest loading of the factors for any given individual: (1) Meat, alcohol and fish pattern; (2) Sweets, grains and fats pattern; and (3) Olive oil, vegetables and fruits pattern (Sahay et al., 2013). Because of the low frequency of the last pattern in this pilot (n=1), we combined it with the first pattern. The dietary pattern was associated with MetS in this Croatian population (Sahay et al., 2013), and it may affect PFAS exposure (e.g., through fast food package, cookware, water). Physical activity levels were determined based on work and leisure time activities and categorized as light, moderate, or heavy, using a validated questionnaire in Croatia adapted from the International Physical Activity Questionnaire (Jurakic et al., 2009). We examined the distribution of cardiometabolic traits by each of the ATP III and IDF MetS criteria and then the frequency of MetS, and subsequently we calculated the frequency of metabolic traits not included in the definition of MetS. The final sample size for this analysis was 122 after excluding one subject with missing covariates.

Using general linear models with adjustment for *a priori* putative risk factors for metabolic syndrome: age, sex, education, socioeconomic status, smoking, dietary pattern, and physical activity, we examined the associations between natural log transformed PFAS (lnPFAS, to approximate normal distribution in exposure) and continuous cardiometabolic traits. We then investigated the odds ratios (OR) and 95% confidence intervals (CIs) of binary individual cardiometabolic traits and MetS with the same covariates adjustment in the logistic regression models.

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3. Results

The geometric mean (range) plasma concentrations were 8.91 (2.36, 33.67) ng/mL for PFOS, 2.87 (1.03, 8.02) ng/mL for PFOA, 0.77 (0.25, 2.40) ng/mL for PFHxS, and 1.29 (0.48, 3.46) ng/mL for PFNA, and detection frequencies were 100%, 100%, 95.9 %, and 100%, respectively. The Spearman correlation coefficients of PFOA with PFOS, PFNA and PFHxS were 0.71, 0.82, and 0.65, respectively. Correlation coefficients of PFOS with PFNA and PFHxS were 0.72 and 0.79, respectively; and the correlation coefficients of PFNA with PFHxS was 0.55. The mean age of the participants in this pilot study was 50.65 years with a standard deviation (SD) of 3.26 years, 55.7% were female, 26.2% had lower than high school education, and 37.7% were current smokers. In comparison to 310 subjects in the same age range but not included in this analysis, the included 122 subjects did not differ in mean age, sex, smoking, dietary pattern, and physical activity, but had lower education and socioeconomic status. PFAS plasma concentrations did not vary by age, sex, education, socioeconomic status, smoking, dietary pattern, or physical activity among the study participants (Table 1).

About 22.1% of the participants met the ATP III criteria for MetS and 42.6% of participants met the IDF criteria for MetS (Table 2). The prevalence of obesity (body mass index [BMI] ≥30 kg/m^2) was 25.4%, and the prevalence of BMI in the overweight and obesity range (≥25 kg/m^2) was 75.4% (Table 3). The mean HbA1c was 5.62% and the mean HOMA-IR was 2.87.

Plasma PFNA concentrations were non-significantly related to total cholesterol (0.36 mmol/L [95% CI: −0.01, 0.73] per lnPFNA, p=0.06). Plasma PFOS concentrations were non-significantly associated with waist circumference after adjustment for covariates (2.45 cm [95% CI: −0.45, 5.35] per lnPFOS, p=0.10, Table 4). In addition, higher PFOS concentrations were also non-significantly associated with increased HOMA-β (17.94, [95% CI: −1.55, 37.44] per lnPFOS, p=0.07), as well as statistically significant higher fibrinogen and lower calcium concentrations. No statistically significant associations were observed between any of the investigated four PFAS concentrations and triglycerides, HDL, blood pressure, fasting plasma glucose, hip circumference, BMI, LDL, fasting insulin, creatinine, uric acid, HbA1c, and HOMA-IR when these cardiometabolic traits were continuous outcomes in the regression models.

For binary outcome variables, PFOS concentrations were positively and non-significantly associated with increased risk of high waist circumference (OR=1.76 [95% CI: 0.97, 3.18], p=0.06, Table 5) and MetS as defined by the ATP III criteria (OR=1.89 [95% CI: 0.93, 3.86], p=0.08, Figure 1) after adjusting for covariates. PFOA and PFNA concentrations were also associated with a risk of MetS defined by the ATP III criteria, with OR=2.19 (95% CI: 0.88, 5.44, p=0.09, non-significant) and OR=2.95 (95% CI: 1.12, 7.80, p=0.03, Figure 1), respectively. Both PFOA and PFNA concentrations were related to increased risk of BMI in the overweight or obesity range (≥25 kg/m^2), with OR=2.09 (95% CI: 0.88, 5.00, p=0.10, non-significant) and OR=2.60 (95% CI: 1.05, 6.44, p=0.04), respectively. PFNA concentrations were also non-significantly associated with higher risk of high waist circumference as defined by the IDF criterion (OR=2.30 [95% CI: 0.88, 6.06], p=0.09) and

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high total cholesterol (OR=2.47 [95% CI: 0.95, 6.37], p=0.06). No additional statistically significant associations were observed for the relations between PFAS concentrations and binary cardiometabolic traits.

4. Discussion

In this Croatian island population, we identified suggestive associations between PFAS exposures and cardiometabolic traits with a modest pilot sample. Our main findings were increased risk of MetS as defined by the ATP III criteria in relation to PFOS, PFOA, and PFNA plasma concentrations, with borderline to statistical significance. Additionally, PFNA concentrations were related to BMI ≥25 kg/m^2. The PFAS plasma concentrations in this study, similar to the U.S. general adult population serum concentrations in 2007–2008 (Kato et al., 2011b), suggested widespread exposure to PFAS in the study population.

Studies examining MetS as a binary outcome in relation to PFAS are scarce. One cross-sectional analysis of NHANES 1999–2000 and 2003–2004 data did not reveal statistical significant associations for PFOS, PFOA, PFHxS, and PFNA in adults (Lin et al., 2009). Subsequent analysis of NHANES 2013–2014 data confirmed the null association for PFOS and PFOA (Liu et al., 2018b). A cross-sectional study of 81 MetS cases and 67 non-MetS controls, all Chinese males, found increased risk related to PFNA (OR=6) and PFOA (OR=29) concentrations despite only adjusted for age (Yang et al., 2018). No association was found for PFOS concentrations. The geometric mean serum PFOS concentration was 24 ng/mL in the analyses of earlier NHANES data, and 5 ng/mL in the analysis of 2013–2014 NHANES, and the mean PFOS concentration was 4 ng/mL in the Yang et al. study. The geometric mean PFOS concentration in our Croatian participants was 9 ng/mL, suggesting concentrations do not explain the discrepancy in results between different studies. We identified a 2–3 times risk of MetS as defined by the ATP III criteria for a natural log unit increase of PFOS, PFOA, and PFNA, which cannot be directly compared with the odds ratios from the Yang et al. study when the exposures were dichotomized as above the median vs. below the median (Yang et al., 2018). Inadequate covariate adjustment and small sample size in the Yang et al. study may have led to large but unstable estimate of effect size.

For individual cardiometabolic traits, the literature is not entirely consistent because of differences in traits associated with each PFAS, PFAS concentrations (occupational vs. environmental exposures), and study design (cross-sectional vs. longitudinal studies). Workers occupationally exposed to PFOA showed increased total cholesterol and uric acid levels (Costa et al., 2009), although null findings have also been reported (Olsen et al., 2012; Olsen and Zobel, 2007). Research of the C8 Health Project among Ohio and West Virginia community residents in USA (with median serum PFOA concentration 27 ng/mL, median PFOS concentration 20 ng/mL) found higher total cholesterol levels associated with increased PFOA and PFOS concentrations in adults (Steenland et al., 2009). A follow-up of a subset of C8 Health Project subjects in 2010 revealed that a 4–5% decline of low-density lipoprotein (LDL) cholesterol was related to halving of the serum concentrations of either PFOA or PFOS (Fitz-Simon et al., 2013). The C8 Health Project also identified higher uric acid levels in persons with increased PFOA and PFOS serum concentrations (Steenland et al., 2010), although it did not find associations with Type 2 Diabetes (T2D) and fasting

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glucose levels (Karnes et al., 2014; MacNeil et al., 2009). Recently, studies combining community and worker cohorts in the C8 Health Project revealed an elevated risk of hypercholesterolemia and stroke with cumulative PFOA exposure (Simpson et al., 2013; Winquist and Steenland, 2014).

The U.S. National Health and Nutrition Examination Survey (NHANES) data analyses suggested associations of general population's PFAS background exposures and total cholesterol levels. Additionally, the these analyses reported associations with cardiovascular diseases and peripheral arterial diseases (Lin et al., 2009; Lin et al., 2010; Nelson et al., 2010; Shankar et al., 2012). Other cross-sectional studies in Canada, China, and Denmark reported positive associations between cholesterol and PFAS concentrations in plasma or serum (Eriksen et al., 2013; Fisher et al., 2013; Fu et al., 2014; Skuladottir et al., 2015). Two studies identified a trend of high total cholesterol levels with increased quartiles of PFNA concentrations (Fu et al., 2014; Nelson et al., 2010). Our results showed positive associations between PFNA and total cholesterol in both continuous and binary outcome analyses, however, the PFOS results were generally null and the PFOA results suggested positive associations but were not significant.

We identified borderline but non-significant associations between PFOS and PFNA and high waist circumference (ATP III and IDF criterion, respectively), between PFNA and BMI ≥ 25 kg/m^2 although no remarkable association with obesity (BMI ≥ 30 kg/m^2) was observed. Previous two analyses of NHANES data did not show the associations between PFOS or PFNA and high waist circumference as defined by the ATP III criterion (Lin et al., 2009; Liu et al., 2018b). The limited age range and homogenous population in the present pilot may have partially contributed to detection of the associations, however, because the sample size was too small the associations did not approach statistical significance.

PFAS can affect sex steroids and thyroid hormones, induce peroxisome proliferator activated receptors α and γ (PPARα and PPARγ), and alter gene expression levels of fatty acid metabolism, lipid transport, and cholesterol synthesis (Lau et al., 2007). Prenatal exposure to PFAS has been associated with alterations of glucocorticoid hormones (cortisol and cortisone) (Goudarzi et al., 2017), sex hormones (estrogen, testosterone, progesterone, inhibin B) (Goudarzi et al., 2017; Itoh et al., 2016; Maisonet et al., 2015), thyroid hormones (thyroxine and triiodothyronine) (Preston et al., 2018), and pituitary hormones (luteinizing hormone, follicle stimulating hormone, prolactin) in offspring (Itoh et al., 2016; Vested et al., 2013), indicating developmental origin of hormonal disruption by PFAS. In adulthood, associations between PFAS and sex and thyroid hormones were also found (Kim et al., 2018; Tsai et al., 2015; Webster et al., 2016). PPARα is involved in lipid homeostasis, fatty acid catabolism, peroxisome proliferation, and inflammation (Escher and Wahli, 2000; Gonzalez et al., 1998). PPARγ is involved in target gene expression of lipoprotein lipase used in triglyceride and aquaporin 7 in glycerol transportation (Janesick and Blumberg, 2011; Kishida et al., 2001). Experimental studies also revealed changes in *CYP7A1* gene expression (involved in cholesterol metabolism), production of reactive oxygen species, dissipation of mitochondria membrane potential, and differential expression of apoptotic genes in cell or animal models exposed to PFAS (Arukwe and Mortensen, 2011; Hu and Hu, 2009; Ren et al., 2009; Rosen et al., 2010). PFNA has a longer half-life in experimental mice

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than PFOA (De Silva et al., 2009); it induces oxidative stress and apoptosis, and upregulates PPARα and PPARγ and interlukin-1 activities (Fang et al., 2010; Fang et al., 2008). In diabetic rats, PFNA increases lipid and fatty acid synthesis and reduces lipolytic enzyme activities, leading lipid accumulation in the liver (Fang et al., 2015). These mechanisms are consistent with our findings of PFNA in relation to metabolic syndrome and obesity outcomes. A recent weight loss study has found baseline PFNA exposure was related to higher weight regain and lower resting metabolic rate during weight loss and regain periods, suggesting a role on metabolic regulation (Liu et al., 2018a).

This study has several strengths. It is the first study in Croatia reporting PFAS exposure in an adult population. The study population from the Adriatic island is ethnically homogeneous, which may reduce the concern of certain confounding factors. The detailed phenotype of cardiometabolic traits provides an opportunity to investigate anthropometrics, lipids, and glucose metabolic changes. We further restricted age range to reduce the concern of additional variations associated with older age, including medications use, and advanced diseases. The study also has several limitations. First, the sample size is small and the precision of estimation is reduced. The covariates adjustment can be insufficient for residual confounding, including medication use, fast food packing, and eating out frequency. The residual confounding may be differential in people with and without MetS. Selection bias was not completely removed as the included study participants had lower education and socioeconomic status than those in the same age range but not included, although these factors did not affect PFAS concentrations in the study participants. We did not adjust for multiple testing with false discovery rate, as this study is limited by sample size and of exploratory nature in design. PFAS concentrations were moderately correlated and the cardiometabolic traits were not independent. In our binary outcome analyses, out of 76 comparisons from 19 outcomes and 4 chemicals, we observed 2 significant associations only and cannot rule out chance finding. Second, this analysis measured PFAS and cardiometabolic outcomes at the same time, and is not a prospective study. We cannot rule out the possibility of reverse causation in this cross-sectional study. The relatively long half-lives of the four PFAS examined may partially mitigate this concern, although it is better to conduct prospective studies in the future. Third, the study did not have mechanistic intermediate biomarkers (e.g., inflammation, lipid metabolism) to provide insights on the pathways from exposure to outcome. Fourth, the study findings may not be directly applicable to continental Europe due to the confined population on the Hvar Island.

In summary, we identified suggestive positive associations between PFAS plasma concentrations and metabolic syndrome, total cholesterol, and high waist circumference in an islandic population in Croatia with background PFAS exposures, however the study is limited by samples size, cross-sectional nature, and not reaching statistical significance for some associations. Prospective studies are needed to examine environmental PFAS exposure and potential perturbation of lipid and glucose metabolism, inflammation and oxidative stress, and subsequent cardiometabolic outcomes.

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Highlights

- PFAS (PFOS, PFOA, PFHxS, PFNA) were detected in >95% of participants from Croatia.
- Plasma PFAS concentrations were similar to generation populations in the U.S.
- Plasma PFAS concentrations may be related to higher risk of metabolic syndrome.

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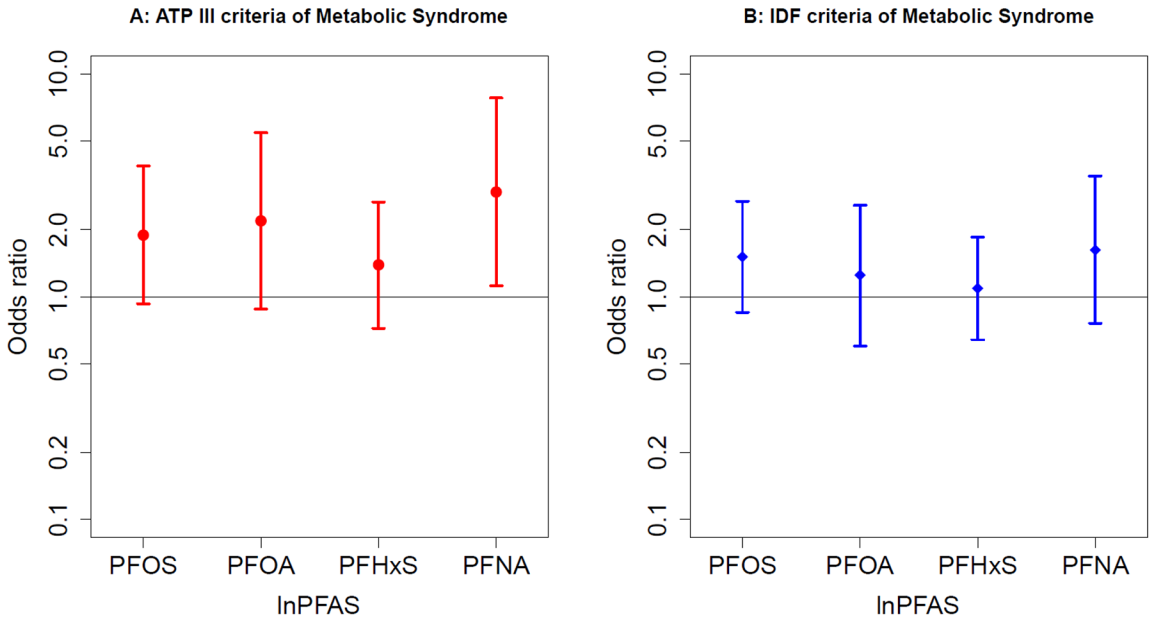

Figure 1.

Adjusted odds ratios and 95% CIs of metabolic syndrome defined by ATP III (A) and IDF (B) criteria

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Table 1.

Distribution of plasma PFAS concentrations by demographic and lifestyle characteristics

Characteristics	n (%)	Correlation coefficient (with age) or geometric mean (ng/mL) by groups				Subjects in the same age range but not included
		PFOS	PFOA	PFHxS	PFNA	
Age (mean±SD: 50.65±3.26 years)	122 (100)	0.06	0.10	0.06	0.06	n=310 (100) 50.49±3.36 years
Sex						
Male	54 (44.3)	8.77	2.94	0.67	1.28	128 (41.3)
Female	68 (55.7)	9.03	2.82	0.72	1.30	182 (58.7)
Education *						
<High school	32 (26.2)	10.27	3.10	0.81	1.34	58 (18.7)
High school	81 (66.4)	8.59	2.81	0.69	1.29	190 (61.3)
College or above	9 (7.4)	7.54	2.65	0.43	1.15	62 (20.0)
Socioeconomic status *						
Low	42 (34.4)	8.89	2.82	0.74	1.25	74 (23.9)
Medium	48 (39.3)	8.67	2.87	0.62	1.29	110 (35.5)
High	32 (26.2)	9.33	2.94	0.77	1.35	126 (40.6)
Smoking						
Current	46 (37.7)	8.85	2.92	0.70	1.30	100 (32.2)
Former	18 (14.8)	7.66	2.37	0.54	1.12	68 (21.9)
Never	58 (47.5)	9.40	3.01	0.76	1.34	142 (45.8)
Dietary pattern						
Meat, alcohol and fish	36 (29.5)	8.55	2.69	0.62	1.31	72 (23.2)
Sweets, grains and fats	86 (70.5)	9.07	2.95	0.74	1.28	238 (76.8)
Physical activity						
Light	40 (32.8)	8.80	2.82	0.73	1.25	138 (44.5)
Moderate	67 (54.9)	8.70	2.98	0.68	1.32	133 (42.9)
Heavy	15 (12.3)	10.28	2.53	0.71	1.30	39 (12.6)

*: $p<0.05$ for comparison between subjects included and not included but in the same age range

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Table 2.

Cardiometabolic traits for metabolic syndrome in the study population

Metabolic traits	Mean±SD	ATP III	n (%)	IDF	n (%)
Waist circumference (cm)	Men: 101±8 Women: 89±12	>102 cm in men or >88 cm in women	Men: 21 (38.9) Women: 31 (45.6)	≥94 cm in men or ≥80 cm in women	Men: 48 (88.9) Women: 49 (72.1)
Triglycerides (mmol/L)	1.60±1.08	≥1.69 mmol/L	38 (31.1)	≥1.69 mmol/L or treatment of hyperlipidemia	38 (31.1)
HDL (mmol/L)	Men: 1.24± 0.29 Women: 1.49± 0.30	<1.03 mmol/L in men or <1.29 mmol/L in women	Men: 10 (18.5) Women: 19 (27.9)	<1.03 mmol/L in men or <1.29 mmol/L in women or treatment of hypercholesterolemia	Men: 10 (18.5) Women: 19 (27.9)
Blood pressure (mmHg)	SBP: 127±18 DBP: 81±9	≥130/85 mmHg	37 (30.3)	≥130/85 mmHg or treatment of hypertension	37 (30.3)
Fasting plasma glucose (mmol/L)	5.62±0.84	≥6.1 mmol/L	25 (20.5)	≥5.6 mmol/L or treatment of T2D	52 (42.6)
Metabolic syndrome		≥3 of the 5 criterion	27 (22.1)	Waist circumference criterion plus ≥2 of other 4 criteria	52 (42.6)

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Table 3.

Descriptive statistics of other cardiometabolic traits not included in the definition of metabolic syndrome or prevalence of binary metabolic traits

Metabolic traits	Mean±SD	Binary metabolic traits	n (%)
Hip circumference (cm)	Men: 105±8 Women: 105±10	Waist hip ratio >0.9 in men or >0.85 in women	Men: 47 (87) Women: 31 (45.6)
Body mass index (kg/m^2)	27.67±3.90	≥25 (Overweight or obesity)	92 (75.4)
		≥30 (Obesity)	31 (25.4)
LDL (mmol/L)	3.63±0.97	>3	90 (73.8)
Total cholesterol (mmol/L)	5.76±1.09	>5	94 (77.0)
Fasting insulin (μIU/mL)	11.24±7.42	>24.9	3 (2.5)
Creatinine (μmol/L)	Men: 94.57±20.31 Women: 76.29±14.06	>125 in men or >107 in women	Men: 3 (5.6) Women: 2 (2.9)
Uric acid (μmol/L)	Men: 355.33±90.30 Women: 236.97±61.02	>404 in men or >337 in women	Men: 13 (24.1) Women: 6 (8.8)
Fibrinogen (g/L)	3.81±1.26	>3.5	65 (53.7)
Calcium (mmol/L)	2.32±0.15	>2.53	2 (1.6)
HbA1c (%)	5.62±0.80	>6	18 (14.8)
HOMA-IR	2.87±2.16	>3.8	24 (19.7)
HOMA-β	113.96±74.34		

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Table 4.

Adjusted regression coefficients and 95% CI of continuous cardiometabolic traits by lnPFAS

Cardiometabolic traits	lnPFOS	lnPFOA	lnPFHxS	lnPFNA
Waist circumference (cm)	2.45 (−0.45, 5.35)	0.59 (−3.23, 4.42)	−0.01 (−2.81, 2.78)	2.20 (−1.72, 6.12)
Triglycerides (mmol/L)	0.09 (−0.20, 0.37)	0.17 (−0.21, 0.54)	0.07 (−0.21, 0.34)	0.27 (−0.11, 0.66)
HDL (mmol/L)	0.00 (−0.08, 0.07)	−0.04 (−0.13, 0.06)	0.03 (−0.04, 0.11)	−0.03 (−0.13, 0.08)
Systolic blood pressure (mmHg)	1.40 (−3.46, 6.25)	−2.15 (−8.49, 4.18)	−0.69 (−5.33, 3.95)	−3.10 (−9.62, 3.41)
Diastolic blood pressure (mmHg)	1.42 (−0.95, 3.79)	−1.00 (−4.11, 2.11)	0.37 (−1.90, 2.65)	−1.00 (−4.21, 2.20)
Fasting plasma glucose (mmol/L)	−0.17 (−0.38, 0.05)	−0.16 (−0.44, 0.12)	−0.16 (−0.37, 0.04)	−0.11 (−0.40, 0.18)
Hip circumference (cm)	0.69 (−1.77, 3.15)	−0.99 (−4.20, 2.23)	−0.66 (−3.01, 1.69)	0.81 (−2.50, 4.12)
Body mass index (kg/m^2)	0.47 (−0.59, 1.53)	0.15 (−1.24, 1.54)	−0.13 (−1.15, 0.89)	0.48 (−0.95, 1.91)
LDL (mmol/L)	−0.02 (−0.27, 0.23)	0.18 (−0.15, 0.50)	0.12 (−0.12, 0.35)	0.27 (−0.06, 0.59)
Total cholesterol (mmol/L)	0.01 (−0.27, 0.29)	0.22 (−0.15, 0.58)	0.17 (−0.10, 0.43)	0.36 (−0.01, 0.73)
Fasting insulin (μIU/mL)	0.93 (−1.07, 2.94)	−0.48 (−3.10, 2.15)	0.64 (−1.27, 2.56)	−0.14 (−2.84, 2.56)
Creatinine (μmol/L)	−3.36 (−7.96, 1.24)	0.46 (−5.60, 6.52)	0.56 (−3.87, 4.98)	1.32 (−4.92, 7.55)
Uric acid (μmol/L)	−4.87 (−25.63, 15.89)	5.02 (−22.09, 32.14)	−4.42 (−24.23, 15.38)	4.76 (−23.16, 32.67)
Fibrinogen (g/L)	0.34 (0.02, 0.67)*	0.16 (−0.27, 0.59)	0.12 (−0.19, 0.44)	0.29 (−0.15, 0.73)
Calcium (mmol/L)	−0.05 (−0.09, −0.01)*	−0.02 (−0.07, 0.03)	−0.02 (−0.06, 0.01)	0.00 (−0.05, 0.05)
HbA1c (%)	0.05 (−0.17, 0.27)	0.09 (−0.20, 0.37)	−0.03 (−0.23, 0.18)	0.14 (−0.15, 0.43)
HOMA-IR	0.18 (−0.40, 0.77)	−0.20 (−0.96, 0.57)	0.09 (−0.47, 0.65)	−0.08 (−0.87, 0.71)
HOMA-β	17.94 (−1.55, 37.44)	6.74 (−19.05, 32.53)	14.13 (−4.56, 32.81)	6.77 (−19.78, 33.33)

Adjusted for age, sex, education, socioeconomic status, smoking, dietary pattern, physical activity

*: P<0.05

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Table 5.

Adjusted odds ratios and 95% CIs of binary cardiometabolic traits by lnPFAS

	lnPFOS	lnPFOA	lnPFHxS	lnPFNA
ATP III criteria				
High waist circumference	1.76 (0.97, 3.18)	0.85 (0.41, 1.77)	0.97 (0.56, 1.66)	1.16 (0.55, 2.46)
High triglycerides†	1.23 (0.66, 2.28)	1.49 (0.66, 3.36)	1.13 (0.64, 2.02)	1.95 (0.82, 4.60)
Low HDL †	1.38 (0.69, 2.79)	1.53 (0.61, 3.80)	0.95 (0.50, 1.81)	2.05 (0.78, 5.38)
High blood pressure †	1.24 (0.67, 2.31)	0.72 (0.32, 1.63)	1.14 (0.63, 2.05)	0.89 (0.39, 2.04)
High FPG	0.81 (0.41, 1.62)	1.32 (0.50, 3.49)	0.79 (0.40, 1.54)	1.22 (0.45, 3.29)
IDF criteria				
High waist circumference	1.67 (0.84, 3.35)	1.16 (0.47, 2.85)	1.28 (0.67, 2.44)	2.30 (0.88, 6.06)
High FPG	0.56 (0.29, 1.07)	0.65 (0.28, 1.51)	0.55 (0.29, 1.05)	0.77 (0.33, 1.82)
Other metabolic traits				
High hip circumference	1.23 (0.65, 2.31)	1.04 (0.45, 2.38)	0.85 (0.46, 1.59)	1.13 (0.49, 2.62)
Overweight or obesity	1.46 (0.76, 2.80)	2.09 (0.88, 5.00)	1.15 (0.63, 2.11)	2.60 (1.05, 6.44) *
Obesity	1.28 (0.65, 2.52)	0.98 (0.41, 2.34)	0.89 (0.47, 1.71)	0.94 (0.38, 2.31)
High LDL	0.75 (0.38, 1.49)	1.23 (0.50, 3.05)	0.98 (0.51, 1.88)	1.59 (0.64, 3.93)
High total cholesterol	1.24 (0.61, 2.51)	1.60 (0.64, 4.00)	1.60 (0.82, 3.12)	2.47 (0.95, 6.37)
High creatinine	0.46 (0.10, 2.12)	1.00 (0.14, 7.15)	1.13 (0.34, 3.81)	0.54 (0.05, 5.61)
High uric acid	1.19 (0.53, 2.68)	1.53 (0.52, 4.48)	0.90 (0.44, 1.87)	1.27 (0.44, 3.73)
High fibrinogen	1.33 (0.75, 2.36)	1.39 (0.66, 2.93)	1.06 (0.62, 1.83)	1.64 (0.75, 3.57)
High HbA1c	0.91 (0.41, 2.03)	1.04 (0.35, 3.09)	0.76 (0.36, 1.63)	1.38 (0.46, 4.15)
High HOMA-IR	1.29 (0.61, 2.75)	0.91 (0.35, 2.39)	0.97 (0.47, 2.01)	1.11 (0.40, 3.12)

Adjusted for age, sex, education, socioeconomic status, smoking, dietary pattern, physical activity

†: Results also apply to IDF criteria

*: P<0.05