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Perfluoroalkyl substances and metabolic syndrome

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ABSTRACT

Background: Perfluoroalkyl substances (PFAS) are a class of contaminants used in many industrial applications and consumer products. Certain PFAS are regulated or voluntarily limited due to concern about environmental persistence and adverse health effects.
Objectives: In this analysis we examine PFAS levels and their association with metabolic syndrome and its components, using a representative sample of the U.S. population.
Methods: Data on PFAS levels and metabolic syndrome components were collected from the 2007–2008, 2009–2010, 2011–2012, and 2013–2014 cycles of the National Health and Nutrition Examination Survey. Twelve different PFAS were measured in serum samples from participants. Logistic regression models were used to identify associations between metabolic syndrome, its individual components, and serum PFAS concentrations.
Results: Over one-third (37%) of participants met the definition for metabolic syndrome, with increased waist circumference and elevated glucose being the most commonly reported components. Seven PFAS were detected in at least 30% of participants and were examined in subsequent analyses (PFDA, PFOA, PFOS, PFHxS, MPAH, PFNA, PFUnDA). The PFAS with the highest concentrations was PFOS (median 8.4 ng/mL), followed by PFOA, PFHxS and PFNA. After adjusting for potential confounders, PFNA was associated with increased risk of metabolic syndrome and well as several individual components, while the highest levels of PFHxS were associated with elevated triglycerides. Other PFAS were associated with decreased risk of at least one outcome.
Conclusions: Associations between PFAS and metabolic syndrome are inconsistent within and across studies. PFNA was consistently associated with increased risk for components of the syndrome, a finding that warrants further investigation.

1. Introduction

Perfluoroalkyl substances (PFAS) are a class of persistent environmental chemicals which are both hydrophobic and lipophobic, as well as heat resistant. These characteristics make PFAS ideal for use in many industrial applications and consumer products, including nonstick coatings, food wrappers, upholstery, firefighting foams, and many others (ATSDR, 2009; Steenland and others 2010). However, these same characteristics make PFAS extremely persistent in environmental media, resulting in widespread exposure in the general population through contact with PFAS containing products and ingestion of contaminated groundwater and seafood (CDC, 2015). Manufacturers in the United States (U.S.) have already phased out use of PFAS with six or more carbons (including perfluorooctane sulfonate, PFOS, in 2002) (reviewed in (Buck and others 2011)), and the U.S. Environmental Protection Agency (EPA) PFOA Stewardship Program was implemented to reduce production and use of perfluorooctanoic acid (PFOA) (EPA, 2009). While there is evidence of decreasing human exposure to common PFASs, their ubiquity and persistence in the environment and long biological half -lives have raised concerns about adverse health effects (Buck and others 2011; Kato and others 2011; Wang and others 2013; Wu and others 2015).

PFAS exposure has been found to be associated with a variety of adverse health outcomes in both human epidemiology and animal toxicology studies, including thyroid disease (Melzer and others 2010), increased uric acid (Gleason and others 2015), elevation of liver enzymes (Gleason and others 2015), and testicular and renal cancers (Benbrahim-Tallaa and others 2014). Given the structural similarity of

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PFAS with fatty acids, they may induce also metabolic derangements. PFAS are able to bind with fatty acid binding protein (Zhang and others 2013), peroxisome proliferator activated receptors (PPARs (Vanden Heuvel and others 2006),), and estrogen receptors (Gao and others 2013). The result may be disruption of lipid metabolism, glucose homeostasis, promotion of inflammation, and the development of metabolic syndrome (Zhang and others 2014).

Metabolic syndrome is a cluster of disorders that include obesity, dyslipidemia, elevated blood pressure, and impaired glucose tolerance, which is highly prevalent in the general population (estimated to be present in 34% of US adults in 2003–2006 (Ervin, 2009)). It is a highly prevalent condition in the US population and is associated with increased risk for cardiovascular disease and premature mortality (Fandriks, 2017; Genser and others 2016). Although the underlying pathophysiology is complex and incompletely understood, the syndrome is generally believed to stem from increased circulating free fatty acids which results in lipid accumulation in adipose tissue, the liver, skeletal muscle, and the heart (Guo, 2014; Meikle and Christopher, 2011). The result is a low-level inflammatory state and peripheral and hepatic insulin resistance (Genser and others 2016; Guo, 2014; Kulkarni and others 2017). PFAS impact several metabolic pathways that may influence the development of metabolic syndrome or its components. Mechanistically, several PFAS have shown *in vitro* and in vivo activation peroxisome proliferator-activated receptors (PPAR) α,β, and γ (Li and others 2017; Lilienthal and others 2017; Vanden Heuvel and others 2006; Zhang and others 2014). Activation of PPARα would be expected to increase fatty acid oxidation and result in decreased serum cholesterol (Yu and others 2015), whereas PPARγ agonism would be expected to exert effects similar to thiazolidinediones and result in decreased insulin resistance and improved glucose metabolism (Kvandova and others 2016). Moreover, both PPARα and PPARγ activation effect triglyceride metabolism and result in lower serum triglyceride levels (Kersten and Stienstra, 2017).

Although toxicology studies (Butenhoff and others 2012; Elcombe and others 2012; Seacat and others 2003; Yan and others 2015) have provided evidence in support of these effects, findings from epidemiologic studies have produced inconsistent or conflicting associations between PFAS and metabolic disorders. In this analysis, we use multiple years of NHANES data and updated definitions of metabolic syndrome and its components to identify potential associations with the body burden of common PFAS.

2. Materials and methods

2.1. Study population

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey, designed to provide a representative sample of the US non-institutionalized civilian population (CDC, 2016). For these analyses, the four most recent cycles with PFAS information were used (2007/2008, 2009/2010, 2011/2012, 2013/2014). The analyses presented here include all individuals aged 20 years or older with PFAS measurements, who had information needed for all metabolic syndrome components and information on selected and established confounders (age, sex, race/ethnicity, income, body mass index [BMI]). We did not adjust for serum lipids since PFAS are hydro- and lipo-phobic, and thus do not accumulate in lipid tissue as other persistent environmental contaminants commonly do (Conder and others 2008).

Metabolic syndrome, defined as presence of at least three components in Table 1 (Alberti and others 2009), was determined using examination and questionnaire data. Waist circumference and blood pressure (average of up to 3 measurements) were measured during the medical exam. The triglycerides and glucose levels from the fasting samples were used, while HDL cholesterol (HDL-C) was measured from blood samples taken from all participants. Participants who were currently taking medication for high blood pressure, hypertriglyceridemia, low HDL-C, or diabetes were also classified as having hypertension, elevated triglycerides, reduced HDL-C, or elevated fasting glucose, respectively.

Table 1
Metabolic syndrome component definitions based upon (Alberti and others 2009).

Component	*Definition*
Elevated waist circumference	Males: ≥102 cm Females: ≥88 cm
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L), or Drug treatment for elevated triglycerides
Reduced HDL cholesterol	Males: < 40 mg/dL (1.0 mmol/L) Females: < 50 mg/dL (1.3 mmol/L), or Drug treatment for reduced HDL[a]
Elevated blood pressure	Systolic: ≥130 mm Hg, and/or Diastolic: ≥85 mm Hg, or Antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL, or Drug treatment of elevated glucose

[a] Drug treatment for reduced HDL cholesterol was limited to those reporting use of niacin.

2.2. Laboratory analysis

The laboratory methods for PFAS measurement in serum are described in detail in the NHANES documentation (CDC, 2014). Briefly, serum PFAS levels were measured with solid phase extraction coupled to high performance liquid chromatography-turbo ion spray ionization-tandem mass spectrometry. As stated in the laboratory documentation, values below the limit of detection (LOD) are replaced with the value (LOD/√2). Only those PFAS detected in at least 30% of samples were retained for further analyses: perfluorodecanoic acid (PFDE), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonic acid (PFHxS), 2-(N-methyl-PFOSA) acetate (MPAH), perfluorononanoic acid (PFNA), perfluoroundecanoic acid (PFUnDA).

2.3. Statistical analysis

All data analysis was performed using SAS/STAT software version 9.4.[1] Logistic regression models were used to identify associations between serum PFAS levels and metabolic syndrome, controlling for survey cycle as well as several demographic characteristics: sex, age (years), race/ethnicity (Non-Hispanic white or other), family income as measured by the poverty income ratio (PIR), alcohol intake (non-drinker, 1 to < 5 drinks/month, 5 to < 10 drinks/month, or 10 + drinks/month), and smoking status (current, former, or never smoker). Due to non-normality of the data, PFAS levels were natural logarithm transformed; in addition, associations were examined using quartiles of PFAS serum level as the exposure metric to examine non-linear relationships. All associations described in the Results are statistically significant at the $p < 0.05$ level, unless otherwise stated.

In the main text, we present results which are adjusted for the sampling weights associated with the PFAS measurement sub-group, accounting for multiple survey cycles. However, we recognize that the samples of NHANES participants with PFAS measures, and with fasting lab measures, are partially overlapping and hence the sample weights may not be appropriate (Platt and Harper, 2013). Consequently, we present in the Supplementary Material a second estimate of key results, which are not adjusted for survey design variables. Individuals were excluded from the final analysis if they were missing PFAS

[1] SAS/STAT software, Version 9.4 of the SAS System for Windows. Copyright © 2013 Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

measurements (n = 16,544 removed), any information related to components of metabolic syndrome (n = 3725 of those with PFAS measures removed), or any covariates used in analyses (n = 295 of those with PFAS and metabolic syndrome measures removed). Triglyceride and glucose measures (either physical laboratory data or reported drug information) were the components of metabolic syndrome most frequently missing among individuals.

3. Results

Across the 2007–2014 NHANES cycles, there were 2975 individuals included in these analyses. Participants were evenly distributed by sex (49.3% male, 50.7% female, SE = 1.0% for both). The median age at screening was 45.8 years (quartiles: 32.5, 58.8 years). The majority of participants were non-Hispanic white (68.9%, SE = 1.7%), followed by non-Hispanic Black (10.2%, SE = 0.8%) and Mexican-American (8.0%, SE = 0.8%). Other or multiracial race/ethnicity was reported by 7.6% (SE = 0.7%) of participants, and other Hispanic by 5.4% (SE = 0.7%). Due to the small number of participants in non-white race/ethnicity categories, race/ethnicity was re-categorized as non-Hispanic white vs. other. The median PIR was 2.9, indicating household income 2.9 times the federal poverty level (interquartile range: 1.4, 4.9). Most participants had between 1 and 4 alcoholic drinks per month (70.2%, SE = 1.5%) while 18.3% (SE = 1.2%) had none; very few reported having 5 to 9 (9.4%, SE = 0.9%) or more (2.1%, SE = 0.4%) alcoholic drinks per month. About one fifth (20.3%, SE = 1.3%) of participants were current smokers. Over half (56.6%, SE = 1.3%) were never smokers, and 23.1% (SE = 0.9%) were former smokers. With respect to biological measures (Table 2), the median BMI was 27.7, indicating that most participants were overweight or obese; indeed, about one-third of participants fell in the overweight (34.1%, SE = 1.2%) and in the obese (35.1%, SE = 1.2%) categories of BMI, while 28.9% (SE = 1.1%) were in the normal weight range and only 1.9% (SE = 0.3%) were underweight. Similarly, the median waist circumference was 100.4 cm in males and 93.8 cm in females, not far from the cutoffs of 102 and 88 cm, respectively, defining elevated circumference (Alberti and others 2009). The 75th percentile of triglycerides was over the cutoff for elevated triglycerides at 154.3 mg/dL (cutoff is 150 mg/dL); similarly, the 25th percentile of HDL cholesterol was below the cutoff for reduced HDL cholesterol in both men (38.2 compared with a cutoff of 30 mg/dL) and women (46.4 compared with a cutoff of 50 mg/dL). Median blood pressure was 118/69.4 mm Hg, and the median fasting glucose was 98.3 mg/dL, close to the cutoff of 100 mg/dL for elevated glucose.

Overall, 37.0% (SE 1.3%) of the survey participants had at least 3 of the metabolic syndrome components present (Table 3). Just over 7% met the criteria for all 5 components. The most commonly reported components were increased waist circumference (55.4% [SE = 1.3%]) and elevated glucose (48.4% [SE = 1.3%]), followed by elevated blood pressure (40.1% [SE = 1.3%]), reduced HDL cholesterol (31.1% [SE = 0.9%]), and elevated triglycerides (28.9% [SE = 1.3%]).

Seven PFAS were detected in at least 30% of samples and were retained in subsequent analyses. The distributions of these PFAS are shown in Table 4. All PFAS significantly correlated with each other, with (unweighted) Spearman correlation coefficients ranging from 0.13 (MPAH with PFUnDA) to 0.78 (PFDE with PFNA), as shown in Supplementary Table 1. The correlation between PFOS and PFOA (the two PFAS showing highest average concentrations) was 0.70.

Table 5 displays results for models including each PFAS individually, as well as including all PFAAS simultaneously. In single-PFAS models, PFDE, MPAH, PFUnDA, and PFHxS (linear model only for the latter) were associated with a decreased risk of metabolic syndrome. When including all PFAS simultaneously, PFHxS, as well as PFDE, MPAH and PFUnDA, was associated with decreased risk of the metabolic syndrome in the continuous exposure model. In contrast, continuous PFNA as well as each increasing quartile of PFNA were associated with increased risk in the categorical model (MPAH and PFUnDA remained associated with decreased risk). Further, the odds ratios for PFNA showed a dose-response pattern in the model simultaneously adjusting for all PFAS, but not in the model with PFNA alone.

Table 6 displays associations between quartile of PFAS serum levels and individual components of the metabolic syndrome. As before, these results indicated potential non-linearity, thus results treating PFAS as a continuous variable are included in Supplementary Table 2. As noted in the models for metabolic syndrome overall, PFNA was generally associated with increased risk of the components (significant associations for waist circumference, triglycerides, and HDL cholesterol). In addition, PFHxS was associated with increased risk of elevated triglycerides. In contrast, PFDE, PFOA, PFHxS, MPAH and PFUnDA were associated with decreased risk of certain components, with the most consistent pattern seen for PFUnDA.

As noted in the Methods section, we reproduced key results (Tables 5 and 6) but without adjusting for survey design variables. The results were very similar to those shown in the main text, and are presented in Supplementary Tables 4-6.

Table 3
Prevalence of metabolic syndrome component definitions based upon (Alberti and others 2009).

Component	Percent (SE)
Elevated waist circumference	55.4 (1.3)
Elevated triglycerides	28.9 (1.3)
Reduced HDL-C	31.1 (0.9)
Elevated blood pressure	40.1 (1.3)
Elevated fasting glucose	48.4 (1.3)
At least 3 components	37.0 (1.3)
Medication for elevated triglycerides or reduced HDL-C	2.9 (0.4)
Medication for hypertension	25.8 (1.1)
Medication for diabetes	9.3 (0.7)

*Participants on lipid regulating prescription medications were considered to meet the definition for both reduced HDL cholesterol, and for elevated triglycerides.

Table 2
Distribution of biological measures (n = 2975).

Measure	Median (SE)	25th (SE), 75th (SE) percentiles	95th percentile (SE)
Body Mass Index (kg/m^2)	27.7 (0.2)	24.1 (0.1), 32.1 (0.3)	41.1 (0.8)
Waist circumference (cm)	97.5 (0.4)	87.3 (0.5), 108.0 (0.6)	127.2 (0.9)
Males	100.4 (0.4)	92.0 (0.6), 110.2 (0.9)	129.7 (2.2)
Females	93.8 (0.7)	83.4 (0.7), 105.7 (0.7)	126.5 (0.8)
Triglycerides (mg/dL)	104.5 (1.8)	72.1 (1.2), 154.3 (3.4)	275.3 (9.4)
HDL cholesterol (mg/dL)	50.6 (0.5)	41.7 (0.4), 61.8 (0.7)	83.6 (1.6)
Males	45.5 (0.6)	38.2 (0.4), 54.5 (0.6)	74.0 (2.4)
Females	56.1 (0.9)	46.4 (0.6), 68.8 (1.0)	89.1 (1.9)
Systolic blood pressure (mm Hg)	118.0 (0.5)	108.5 (0.5), 129.0 (0.7)	151.1 (1.4)
Diastolic blood pressure (mm Hg)	69.4 (0.4)	62.3 (0.5), 76.2 (0.4)	88.1 (0.7)
Fasting glucose (mg/dL)	98.3 (0.3)	91.1 (0.4), 106.9 (0.5)	148.9 (4.5)

Table 4
Distribution of PFAS measured in serum, given in μg/L (n = 2975 for NHANES combined 2007–2012 data).[a]

PFAS	Percent (SE) above the LOD	Median (SE)	25th (SE), 75th (SE) percentiles	95th percentile
Perfluorodecanoic acid (PFDE)	82.0 (1.3)	0.2 (0.01)	0.1 (0.01), 0.4 (0.02)	0.8 (0.03)
2007–2008 (n = 751)	70.1	0.2 (0.02)	0.1 (0.01), 0.4 (0.02)	0.8 (0.10)
2009–2010 (n = 799)	93.7	0.2 (0.02)	0.1 (0.004), 0.4 (0.02)	0.9 (0.07)
2011–2012 (n = 667)	85.2	0.19 (0.01)	0.12 (0.01), 0.3 (0.02)	0.7 (0.16)
2013–2014 (n = 758)	79.4	0.1 (0.01)	0.08 (0.002), 0.3 (0.02)	0.7 (0.05)
Perfluorooctanoic acid (PFOA)	99.9 (0.1)	2.8 (0.08)	1.8 (0.05), 4.3 (0.13)	7.8 (0.27)
2007–2008 (n = 751)	99.9	1.3 (0.14)	2.9 (0.12), 6.3 (0.23)	9.7 (0.36)
2009–2010 (n = 799)	99.8	3.2 (0.17)	2.1 (0.12). 4.6 (0.28)	7.6 (0.99)
2011–2012 (n = 667)	99.9	2.1 (0 09)	1.4 (0.07), 3.1 (0.13)	5.2 (1.0)
2013–2014 (n = 758)	99.9	2.0 (0.08)	1.3 (0.05), 3.1 (0.2)	5.7 (0.48)
Perfluorooctane sulfonate (PFOS)	99.9 (0.03)	8.4 (0.28)	4.8 (0.14), 14.0 (0.53)	32.2 (1.90)
2007–2008 (n = 751)	99.9	13.8 (0.59)	8.9 (0.29), 21.1 (0.73)	39.3 (3.72)
2009–2010 (n = 799)	99.9	9.5 (0.63)	5.8 (0.35), 15.2 (1.4)	33.7 (12.4)
2011–2012 (n = 667)	99.9	6.8 (0.32)	4.3 (0.20), 10.4 (0.47)	19.2 (4.0)
2013–2014 (n = 758)	99.9	5.3 (0.27)	3.2 (0.21), 9.0 (0.59)	18.8 (2.20)
Perfluorohexane sulfonic acid (PFHxS)	99.2 (0.2)	1.6 (0.05)	0.9 (0.03), 2.8 (0.10)	6.3 (0.40)
2007–2008 (n = 751)	99.7	2.0 (0.10)	1.1 (0.04), 3.5 (0.22)	7.5 (1.25)
2009–2010 (n = 799)	99.4	1.7 (0.15)	0.92 (0.08), 2.9 (0.20)	5.9 (0.52)
2011–2012 (n = 667)	99.1	1.3 (0.07)	0.76 (0.06), 2.3 (0.16)	5.5 (0.73)
2013–2014 (n = 758)	99.0	1.4 (0.07)	0.8 (0.07), 2.6 (0.11)	5.6 (0.56)
2-(N-methyl-PFOSA) acetate (MPAH)	62.3 (1.7)	0.2 (0.02)	0.07 (0.001), 0.3 (0.02)	1.0 (0.05)
2007–2008 (n = 751)	69.7	0.2 (0.02)	0.1 (0.01), 0.5 (0.04)	1.1 (0.03)
2009–2010 (n = 799)	79.7	0.2 (0.01)	0.07 (0.003), 0.3 (0.01)	0.92 (0.10)
2011–2012 (n = 667)	54.2	0.09 (0.02)	0.06 (0.01), 0.3 (0.02)	0.70 (0.04)
2013–2014 (n = 758)	46.3	0.07 (0.003)	0.07 (0.003), 0.2 (0.01)	0.9 (0.12)
Perfluorononanoic acid (PFNA)	99.5 (0.1)	1.0 (0.02)	0.7 (0.02), 1.5 (0.04)	2.9 (0.27)
2007–2008 (n = 751)	99.3	1.2 (0.04)	0.8 (0.03), 1.7 (0.07)	3.3 (0.21)3.3 (0.21)
2009–2010 (n = 799)	99.9	1.2 (0.07)	0.79 (0.03), 1.8 (0.21)	3.9 (−)
2011–2012 (n = 667)	99.7	0.8 (0.05)	0.6 (0.03), 1.2 (0.06)	2.4 (0.2)
2013–2014 (n = 758)	98.9	0.63 (0.03)	0.4 (0.02), 1.0 (0.07)	2.0 (0.1)
Perfluoroundecanoic acid (PFUnDA)	52.4 (1.7)	0.1 (0.01)	0.1 (0.003), 0.2 (0.01)	0.7 (0.05)
2007–2008 (n = 751)	32.1	0.1 (0.01)	0.1 (0.01), 0.2 (0.01)	0.6 (0.06)
2009–2010 (n = 799)	73.4	0.1 (0.01)	0.07 (0.002), 0.27 (0.03)	0.8 (0.10)
2011–2012 (n = 667)	61.6	0.1 (0.01)	0.07 (0.005), 0.2 (0.02)	0.6 (0.13)
2013–2014 (n = 758)	56.6	0.07 (0.004)	0.07 (0.004), 0.1 (0.02)	0.5 (0.07)

The LOD for each PFAS is as follows: PFOA – 0.10 for all cycles; PFOS – 0.20 for 2007–2012, 0.10 for 2013–2014; PFHxS – 0.10 for all cycles; EPAH – 0.20 for 2007–2008, 0.20 for 2009–2012, not measured in 2013–2014; MPAH – 0.20 for 2007–2008, 0.10 for 2009–2010 and 2013–2014, 0.09 for 2011–2012; PFDE – 0.20 for 2007–2008, 0.10 for 2009–2014; PFBS – 0.10 for all cycles; PFHP – 0.40 for 2007–2008, 0.10 for 2009–2014; PFNA – 0.08 for 2007–2012, not measured in 2013–2014; PFUnDA – 0.20 in 2007–2008, 0.10 in 2009–2014; PFDO – 0.20 for 2007–2008, 0.10 for 2009–2014. In 2013–2914, PFOA and PFOS were calculated as the sum of linear and branched isomers (each had the same LOD of 0.10).

[a] Only includes analytes detected in ≥30% of samples. The following PFAS were detected in < 30% of samples: 2-(N-ethyl-PFOSA) acetate (EPAH; detected in 4.1 [SE = 0.6]%); Perfluorobutane sulfonic acid (PFBS; detected in 0.8%, SE = 0.2]%); Perfluoroheptanoic acid (PFHP; detected in 13.5 [SE = 1.0]%); Perfluorooctane sulfonamide (PFSA; detected in 0.4 [SE = 0.2]%); Perfluorododecanoic acid (PFeDA; detected in 7.4 [SE = 1.1]%).

Table 5
Odds ratios (ORs) and 95% confidence intervals (CIs) for association between serum PFAS levels and metabolic syndrome.[a]

	Ln(PFAS)	Quartile 4 vs. Quartile 1	Quartile 3 vs. Quartile 1	Quartile 2 vs. Quartile 1
Models including one PFAS at a time				
PFDE	**0.84 (0.71, 0.99)**	**0.72 (0.53, 0.99)**	0.84 (0.59, 1.21)	1.01 (0.73, 1.42)
PFOA	0.93 (0.77, 1.12)	0.89 (0.59, 1.33)	0.76 (0.52, 1.10)	0.83 (0.58, 1.19)
PFOS	0.91 (0.78, 1.06)	0.83 (0.54, 1.29)	0.84 (0.58, 1.22)	0.79 (0.57, 1.07)
PFHxS	**0.87 (0.76, 0.99)**	0.77 (0.56, 1.07)	0.80 (0.57, 1.12)	0.88 (0.65, 1.18)
MPAH	**0.81 (0.70, 0.94)**	**0.57 (0.39, 0.83)**	0.72 (0.50, 1.04)	**0.69 (0.50, 0.96)**
PFNA	1.10 (0.92, 1.33)	1.08 (0.74, 1.58)	1.25 (0.87, 1.82)	1.10 (0.80, 1.53)
PFUnDA	**0.79 (0.66, 0.93)**	**0.63 (0.42, 0.95)**	0.69 (0.47, 1.01)	0.98 (0.66, 1.45)
Models including all PFAS simultaneously				
PFDE	**0.72 (0.54, 0.97)**	0.56 (0.31, 1.01)	0.71 (0.43, 1.18)	0.93 (0.64, 1.35)
PFOA	0.87 (0.63, 1.20)	0.93 (0.50, 1.73)	0.75 (0.46, 1.21)	0.88 (0.59, 1.32)
PFOS	1.00 (0.78, 1.29)	1.10 (0.63, 1.94)	1.01 (0.62, 1.65)	0.86 (0.59, 1.25)
PFHxS	**0.84 (0.72, 0.99)**	0.81 (0.55, 1.18)	0.87 (0.58, 1.31)	0.92 (0.65, 1.31)
MPAH	**0.81 (0.71, 0.94)**	**0.58 (0.40, 0.84)**	0.75 (0.51, 1.11)	**0.72 (0.52, 0.99)**
PFNA	**2.25 (1.58, 3.20)**	**2.83 (1.54, 5.20)**	**2.45 (1.50, 4.00)**	**1.60 (1.07, 2.42)**
PFUnDA	**0.69 (0.54, 0.88)**	**0.55 (0.31, 0.98)**	0.63 (0.39, 1.01)	0.89 (0.58, 1.38)

[a] Metabolic syndrome defined as the presence of at least 3 components described in Table 1. All models are adjusted for survey cycle, age, sex, race/ethnicity, family income, alcohol intake, and smoking status. Bolded values indicate statistically significant result.

Table 6
Odds ratios (ORs) and 95% confidence intervals (CIs) for association between quartile of serum PFAS levels (in relation to quartile 1) and metabolic syndrome components,[a] adjusting for all PFAS.

Quartile	Increased waist circumference	Elevated triglycerides	Reduced HDL cholesterol	Elevated blood pressure	Elevated glucose
PFDE, quartile 4	0.79 (0.48, 1.31)	**0.45 (0.25, 0.80)**	**0.48 (0.30, 0.77)**	1.08 (0.60, 1.93)	0.89 (0.55, 1.45)
PFDE, quartile 3	0.88 (0.50, 1.53)	**0.61 (0.39, 0.96)**	0.75 (0.51, 1.10)	1.27 (0.72, 2.22)	1.10 (0.70, 1.73)
PFDE, quartile 2	0.85 (0.59, 1.22)	0.82 (0.56, 1.18)	0.80 (0.60, 1.08)	1.07 (0.70, 1.63)	0.94 (0.67, 1.31)
PFOA, quartile 4	0.83 (0.47, 1.46)	1.27 (0.73, 2.22)	1.26 (0.73, 2.16)	1.06 (0.58, 1.94)	0.81 (0.49, 1.33)
PFOA, quartile 3	**0.62 (0.39, 0.98)**	0.96 (0.60, 1.54)	1.13 (0.72, 1.76)	1.19 (0.73, 1.95)	1.00 (0.60, 1.67)
PFOA, quartile 2	**0.66 (0.46, 0.92)**	1.05 (0.65, 1.68)	1.08 (0.71, 1.63)	1.22 (0.77, 1.96)	0.88 (0.59, 1.32)
PFOS, quartile 4	1.66 (0.98, 2.81)	0.64 (0.37, 1.08)	1.33 (0.80, 2.21)	0.71 (0.36, 1.42)	0.87 (0.50, 1.50)
PFOS, quartile 3	1.45 (0.94, 2.22)	0.74 (0.46, 1.18)	1.03 (0.70, 1.52)	0.99 (0.57, 1.70)	1.08 (0.64, 1.81)
PFOS, quartile 2	1.28 (0.93, 1.77)	0.74 (0.51, 1.09)	1.00 (0.75, 1.34)	0.82 (0.51, 1.30)	1.00 (0.69, 1.45)
PFHS, quartile 4	0.86 (0.58, 1.28)	1.07 (0.68, 1.70)	**0.55 (0.35, 0.86)**	0.79 (0.49, 1.27)	0.85 (0.55, 1.31)
PFHS, quartile 3	0.88 (0.59, 1.30)	1.13 (0.75, 1.71)	**0.61 (0.38, 0.98)**	0.80 (0.54, 1.19)	0.87 (0.59, 1.29)
PFHS, quartile 2	1.10 (0.76, 1.58)	**1.54 (1.02, 2.33)**	0.84 (0.54, 1.30)	0.69 (0.44, 1.08)	0.88 (0.61, 1.27)
MPAH, quartile 4	**0.68 (0.48, 0.96)**	0.80 (0.54, 1.18)	0.76 (0.50, 1.15)	0.92 (0.62, 1.35)	**0.69 (0.48, 0.99)**
MPAH, quartile 3	0.75 (0.56, 1.01)	0.89 (0.63, 1.26)	0.77 (0.54, 1.10)	0.82 (0.56, 1.18)	**0.71 (0.54, 0.93)**
MPAH, quartile 2	0.89 (0.61, 1.28)	1.21 (0.87, 1.70)	0.83 (0.60, 1.16)	**0.68 (0.47, 0.97)**	**0.67 (0.48, 0.93)**
PFNA, quartile 4	**2.20 (1.08, 4.51)**	**2.37 (1.27, 4.44)**	**1.75 (1.02, 3.02)**	1.58 (0.82, 3.04)	1.62 (0.90, 2.92)
PFNA, quartile 3	**2.12 (1.14, 3.93)**	**1.75 (1.05, 2.92)**	1.34 (0.93, 1.94)	1.27 (0.77, 2.09)	1.37 (0.83, 2.25)
PFNA, quartile 2	**1.67 (1.05, 2.65)**	**1.45 (1.00, 2.12)**	0.99 (0.72, 1.36)	0.98 (0.63, 1.51)	1.36 (0.89, 2.07)
PFUnDA, quartile 4	**0.34 (0.24, 0.50)**	0.57 (0.31, 1.05)	0.63 (0.38, 1.05)	0.65 (0.38, 1.11)	0.73 (0.44, 1.21)
PFUnDA, quartile 3	**0.47 (0.33, 0.69)**	0.99 (0.64, 1.52)	0.69 (0.46, 1.03)	**0.46 (0.28, 0.76)**	**0.64 (0.42, 0.98)**
PFUnDA, quartile 2	**0.68 (0.51, 0.91)**	1.06 (0.62, 1.81)	1.19 (0.82, 1.74)	0.73 (0.48, 1.09)	0.64 (0.41, 1.01)

[a] All models are adjusted for survey cycle, age, sex, race/ethnicity, family income, alcohol intake, and smoking status. Bolded values indicate statistically significant result.

4. Discussion

In the current study, we examined multiple PFAS that are prevalent in US adults and explored relationships with the metabolic syndrome and its components. Most PFAS failed to show consistent associations across statistical models and were either protective or deleterious, depending upon the specific compound and outcome under investigation. However, multiple models consistently demonstrated that PFNA was associated with an increased risk of metabolic syndrome, increased waist circumference, elevated triglycerides, and decreased HDL cholesterol when controlling for multiple PFAS. In contrast, PFUnDA was consistently associated with decreased risk for metabolic syndrome and for all but one of its components.

Few studies have specifically examined the potential effect of PFAS on metabolic syndrome using nationally representative surveys. Fisher et al. examined PFOA, PFOS, and PFHxS using the Canadian Health Measures Survey and also found no associations with metabolic syndrome, glucose-related outcomes, or triglycerides (Fisher and others 2013). Additionally, PFHxS was not associated with HDL as in the current study. Lin et al. examined earlier cycles of NHANES data and found that PFHxS, PFOA, and PFOS were not associated with the prevalence of metabolic syndrome in adults, but PFOS was associated with lower HDL cholesterol (Lin and others 2009). In contrast, Nelson et al. showed no significant associations between PFOA, PFOS, PFHxS, or PFNA and HDL cholesterol or body size (Nelson and others 2010). Some of our findings were different from earlier studies. This may be due to including more recent data resulting in larger sample size, or differences in selected statistical approaches.

A recent study by Liu et al. investigated PFOA and PFOS overall as well as by isomer (linear vs. branched) with respect to metabolic syndrome and components (Liu and others 2018). They did find evidence that the form of the PFAS could affect observed associations; for example, while linear PFOA was associated with cholesterol, albumin, and globulin in serum, only branched PFOA was associated with glucose. However, there were no associations noted for metabolic syndrome as a whole with PFOA or PFOS, regardless of how they were included in statistical models. We did not investigate differences by isomeric form in our analyses since these data were not available for all NHANES cycles, but this does provide some evidence that form as well as specific PFAS congener, may make a difference in how they affect health outcomes – possibly by affecting binding affinity. It is important to recognize that distribution of isomeric form varies by PFAS; < 5% of PFOS is branched, while over a quarter of PFOA is branched, in the NHANES population.

Although PFOA and PFOS have been extensively examined in toxicologic and epidemiology studies, less is known about longer chain PFAS and the potential effects on health. Biological activity may vary depending on chain length, as has been shown in studies of PPARα activation (Wolf and others 2012). PFNA in particular has been associated with prevalent diabetes in one large cross sectional study (Lind and others 2014) and with multiple components of metabolic syndrome in a smaller cross-sectional study (Yang and others 2017), although this has not been the case in other analyses (Conway and others 2016; Su and others 2016). PFUnDA is even less understood, although current evidence is consistent with our findings. A study of in Norwegian pregnant women showed a strong, monotonic dose-response relationship with HDL cholesterol (Starling and others 2014), while PFUnDA exposure was associated with decreased risk of diabetes in Taiwanese adults (Su and others 2016). Although longer chain lengths are believed to be associated with increased toxicity, this was not seen in the current analysis. The associations observed for PFNA may be linked to differences in bioaccumulation, elimination, and biological activity. Animal models suggest that PFNA has greater body distribution and accumulation than PFUnDA (Guruge and others 2016), and an *in vitro* study demonstrated that PFNA results in higher PPARα activation compared to longer chain lengths (Wolf and others 2012). Further studies are needed to better understand the effect of chain length on toxic endpoints.

Human biomonitoring studies have shown that while levels of PFOS and PFOA may be stable or decreasing in recent years, levels of other PFAS are increasing (e.g., a Swedish study finding increased PFBS, PFHxS, PFNA and PFDA from 1996 to 2010 (Glynn and others 2012); NHANES study finding increasing PFNA and PFHxS levels from 1999 to 2008 (Kato and others 2011). This could be due in part to the phase-out of PFOS and PFOA. In general, it indicates the need to examine multiple PFAS in relation to health outcomes. In recent cycles of the NHANES data, we previously reported a decrease in PFAS concentrations when comparing more recent waves of NHANES to the 2007/2008 wave, with the greatest decreases seen for PFOS and PFOA (Christensen and others 2017).

Limitations of this analysis included the use of self-reported data, which increase measurement error. With respect to the ability to identify associations between PFAS body burden and metabolic syndrome outcomes, we note that due to the skewed nature of the distribution of the PFAS, the narrower range in the lower three quartiles makes it more difficult to discern contrasts, compared with the higher and more variable levels in the highest quartile. Another limitation is how to evaluate individuals currently taking medication for conditions included in the metabolic syndrome – it is possible that medication usage may affect PFAS metabolism or that those with well-controlled disease are different from those with untreated disease. Therefore, we performed a sensitivity analysis excluding individuals taking medication for hypertension or diabetes (Supplementary Table 3). However, this analysis showed very similar results to the full results, although due to the smaller sample size most effect estimates were attenuated, such that only the decreased risk associated with higher PFUNDA exposure remained statistically significant. Strengths include the use of a multiple years of data from a large and nationally representative sample, consideration of multiple potential confounders, and examination of multiple PFAS in combination.

5. Conclusions

Associations between PFAS and metabolic syndrome are inconsistent within and across studies. PFNA was consistently associated with increased risk for components of the syndrome, a finding that warrants further investigation.

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Conflicts of interest

None to declare.

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Appendix A. Supplementary data

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