Use of a Pooled Index to Examine Associations between Serum Per- and Polyfluoroalkyl Levels and Metabolic Syndrome in NHANES 2005-2018

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Article

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Highlights

Public health relevance—How does this work relate to a public health issue?

- metabolic syndrome
- environmental pollutants

Public health significance—Why is this work of significance to public health?

- multiple exposures
- risk factors

Public health implications—What are the key implications or messages for practitioners, policy makers and/or researchers in public health?

- exposure reduction
- policy and regulation

Abstract

Polyfluoroalkyl substances (PFAS) are synthetic compounds shown to be associated with metabolic disturbances in the experimental literature. Evidence of the relationship between PFAS and MetS from human epidemiological studies remains inconclusive and warrants further study. This study leverages a pooled index to examine associations between a mixture of PFAS and metabolic syndrome in a sample of adults in the United States. Using data from the National Health and Nutrition Examination Survey 2005-2018 (n= 8095), we examined the relationship between serum concentrations of perfluorohexanesulfonic acid, perfluorononanoic acid, perfluorodecanoic acid, perfluoroundecanoic acid and 2-(N-Methyl-perfluorooctane sulfonamido acetic acid, and MetS. We evaluate individual associations with logistic regression and joint associations in a pooled index (PI) model. One standard deviation increase in the PI was associated with 18% decrease in odds of MetS (OR: 0.82, 95% CI: 0.76, 0.89). In logistic regression models, higher PFAS concentrations were also associated with decreased odds of MetS in perfluorodecanoic acid (PFDA) (OR: 0.43, 95% CI: 0.28, 0.64) and perfluoro undecanoic acid (PFUA) (OR: 0.19, 95% CI: 0.11, 0.36). This study found an inverse association between serum PFAS concentration and MetS, in both pooled and individual models; however, given the cross-sectional design, these findings should be interpreted cautiously.

Keywords: polyfluoroalkyl substances; environmental exposures; metabolic syndrome

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1. Introduction

The per-and polyfluoroalkyls or PFAS substances are a unique group of over 4000 synthetic compounds consisting of an alkyl chain with at least one fully fluorinated carbon atom [1–3]. The convenience and versality of PFAS stems from their waterproofing and oil-repelling properties, resulting in myriad industrial applications, from food and beverage containers, non-stick cookware, to waterproof cosmetics and fire-fighting foam [2,4,5].

Due to their stable chemical structure and persistence in the environment, PFAS compounds bioaccumulate in the air, water, soil, plants and animals [4–6].These chemicals have been isolated in samples as far flung as the peak of Mount Everest and the Arctic Ocean [7,8] and identified in the blood of virtually every individual in the developed world [9,10]. The primary exposure route in humans is dietary, and the data indicate that PFAS are not metabolized nor undergo any chemical change in the human body [6,11]. Once absorbed, they can remain in the body by preferentially binding to proteins in the liver or serum [6,12]. Elimination of PFAS occurs via the bile and urinary excretion, with urine being the primary route in humans [6,12]. The most widely manufactured and frequently detected PFAS are the so-called legacy PFAS- perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS)- which are notoriously persistent and bio-accumulative due to their long-chain structure [2,13].

The literature provides support of a positive association between PFAS and various adverse health effects, particularly metabolic disturbances [12,14,15]. Epidemiologic studies suggest that higher levels of PFAS are associated obesity risk and altered lipid profiles, including higher serum total cholesterol and low-density lipoprotein (LDL) cholesterol in adults and children [10,16]. Using data from NHANES (n= 2473), Geiger et al. reported a dose-response relationship between quartiles of PFAS exposure and obesity in children 12-18 years [17]. Consistent with this, a prospective cohort study by Mora et al. (n=1006) reported positive associations between pre-natal exposures to PFAS and increases in adiposity measurements in mid-childhood [18]. Increasing concentrations of prenatal serum PFOA were associated with higher body mass index, skinfold thickness, and total fat mass index. Positive associations were also observed for PFHxS, PFOS and PFNA [18]. A similar trend has been reported in studies of PFAS and obesity in adults. In the Diabetes Prevention Program Outcomes study (n=957), Cardenas et al reported positive associations between serum PFAS, increased weight gain and body size in adults [19]. Likewise, in the Pounds Lost randomized clinical trial (n=621), higher baseline levels of PFAS were associated with greater regained weight, especially in women [20].

Similar findings on serum lipids have been reported in pregnant women. In the World Trade Center birth cohort study by Spratlen et al., significant associations were observed between multiple PFAS, elevated triglycerides, and total lipids in cord blood [23]. These human studies are corroborated by experimental findings, including a physiologically based pharmacokinetic (PBPK) model to assess toxicity of PFOS, which predicted a 20% increase in serum cholesterol with higher PFOS concentrations [24]. A study of short-chained PFAS - PFBS, PFHxS and PFHxA, by Liu et al reported evidence of induced adipogenesis, and intracellular lipid accumulation, at higher concentrations [25]. In addition, a review of toxicology and population data revealed identified dyslipidemia as the strongest metabolic outcome of PFAS exposure [2,10].

The association between PFAS, diabetes and markers of insulin resistance has been examined in numerous epidemiological studies. However, while the literature provides evidence of a positive association between PFAS levels and glycemic changes, inconsistencies have been noted. A scoping review of 39 studies examined the link between PFAS exposure and risk for prediabetes, diabetes, gestational diabetes and insulin resistance [26]. While 24 of the studies reported a positive association between PFAS and at least one glycemic disorder, the other 15 reported either negative or null associations between PFAS and all diabetes related terms [26].

Metabolic syndrome (MetS) is defined as three or more of the following conditions: abdominal obesity, high triglycerides levels, low high-density lipoprotein (HDL) cholesterol, increased blood pressure, and elevated fasting glucose level [27,28]. MetS has been associated with a two-fold and

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five-fold risk for Type II diabetes (T2D) and cardiovascular disease respectively, in addition to increased risk of cancer, neurodegenerative, reproductive diseases and all-cause mortality [29–36]. These statistics are of particular concern considering the steady increase in MetS over the past several decades [31–33]. A study of adults with MetS from NHANES identified significant positive associations between measures of metabolic disease including the triglyceride-glucose index, insulin resistance (IR) and obesity, with cardiovascular mortality [37]. IR and obesity were also associated with all-cause mortality, with the strongest hazard ratio observed for the waist circumference index [37]. Similar findings were reported in adults from The Kailuan Study (n= 97,777) diagnosed with cardiovascular-kidney-metabolic (CKM) disease. Advanced stages of CKM were significantly associated with increased risk of all-cause mortality [38].

While there is substantial evidence of a positive relationship between PFAS and various metabolic conditions, the relationship with MetS has been inconsistent in the literature. A recent study using data from NHANES (n=13,921) indicated an overall inverse association between joint PFAS exposure and metabolic syndrome severity score. However, associations between PFAS and the individual metabolic components varied, with some positive associations observed[39]. Similar variations were reported by Lin et al in a cross-sectional study examining age-specific associations of PFAS and MetS (n=5850). A positive association was observed for PFNA in adolescents, an inverse association was seen for PFHxS and MePFOSA in young and middle-aged adults, while the overall mixture effect was null for all age groups [15].

Considering the extensive evidence linking elevated serum PFAS levels with metabolic disturbances, and the significant public health impact of this disease, we aim to assess whether higher serum concentrations of PFAS are associated with prevalence of metabolic syndrome in a large nationally representative sample.

2. Materials and Methods

Data from the Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) 2005-2006 through 2017-2018 were downloaded and merged. NHANES is a series of nationally representative, cross-sectional surveys designed to assess the health and nutrition status of the non-institutionalized population in the United States [40]. This survey employs a stratified, muti-stage sampling design, characterized by probability sampling units (PSUs), census blocks, homes and lastly individuals. NHANES sampling methods are described in depth on the CDC website [40].

Exposure Assessment

Serum PFAS were collected on a one-third subsample of NHANES participants 12 years of age and older [41]. The following five PFAS were included based on prior association in the literature with metabolic disturbances- perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUA) and 2-(N-Methyl-perfluorooctane sulfonamido) acetic acid (MePFOSA).

Laboratory Methods

Quantitative detection of PFAS was performed in NHANES using online soli phase extraction coupled to high performance liquid chromatography-turboionspray ionization-tandem mass spectrometry (online SPE-HPLC-TIS-MS/MS). The complete laboratory procedure manual is available on the website [42]. NHANES reports no changes to the lab method, lab equipment, or lab site for this component in the NHANES 2005-2006 through 2017-2018 cycle.[42] Detection limits were constant for all analytes in the data set. Individual observations with values below the limit of detection (LOD) were imputed with LOD/√2 [41].

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Outcome Assessment

The main outcome of interest is MetS, defined as three or more of the following conditions: abdominal obesity, high triglycerides levels, low high-density lipoprotein (HDL) cholesterol, hypertension (HTN), and elevated fasting glucose level [27,28]. Per established criteria, abdominal obesity was defined as waist circumference > 35 inches for women and > 40 inches for men, high triglycerides as triglycerides levels > 150 mg/dL, low HDL cholesterol as HDL < 40 mg/dL for men and < 50 mg/dL for women, increased blood pressure as SBP >130 or DBP > 85 mm Hg, and elevated fasting blood sugar as fasting glucose > 100 mg/dL or higher [43]. Participants who completed the household interview component (HIC) of the survey are invited to a mobile examination center (MEC) for the physical evaluation component and collection of laboratory data.

Covariates

Covariates were selected a priori based on prior literature. Demographic information was collected via questionnaire during the household interview component of NHANES [44]. Covariates included age- 20-29, 30-44, 45-64 and 65 and older, gender, race/ethnicity -non-Hispanic Whites (NHW), non-Hispanic Blacks (NHB), Hispanic, and Non-Hispanic of other races, and poverty income ratio (PIR). PIR was obtained from NHANES demographic datafile and is calculated by dividing family income by federal poverty level (FPL) based on the guidelines provided by the Department of Health and Human Services [45]. PIR was categorized as PIR 1- less than 200% of the FPL, PIR 2 - between 200% and 400% of the FPL, PIR 3 - between 400% and 500% of the FPL.

Diet quality was measured by the Healthy Eating Index-2020 (HEI-2020) - a scoring metric that can be used to determine overall diet quality and the quality of several dietary components [46]. Serum cotinine, a widely used biomarker for smoking status, was also included with recent exposure to tobacco smoke characterized as serum cotinine ≥ 10 ng/mL [47,48].

Exclusions

Due to a lack of clear consensus regarding diagnostic criteria for metabolic syndrome in children and adolescents, participants under 20 were excluded from this study. In addition, due to the numerous metabolic changes during pregnancy, women of childbearing age were only included if they had a negative pregnancy test. A CONSORT chart is shown in Figure 1.

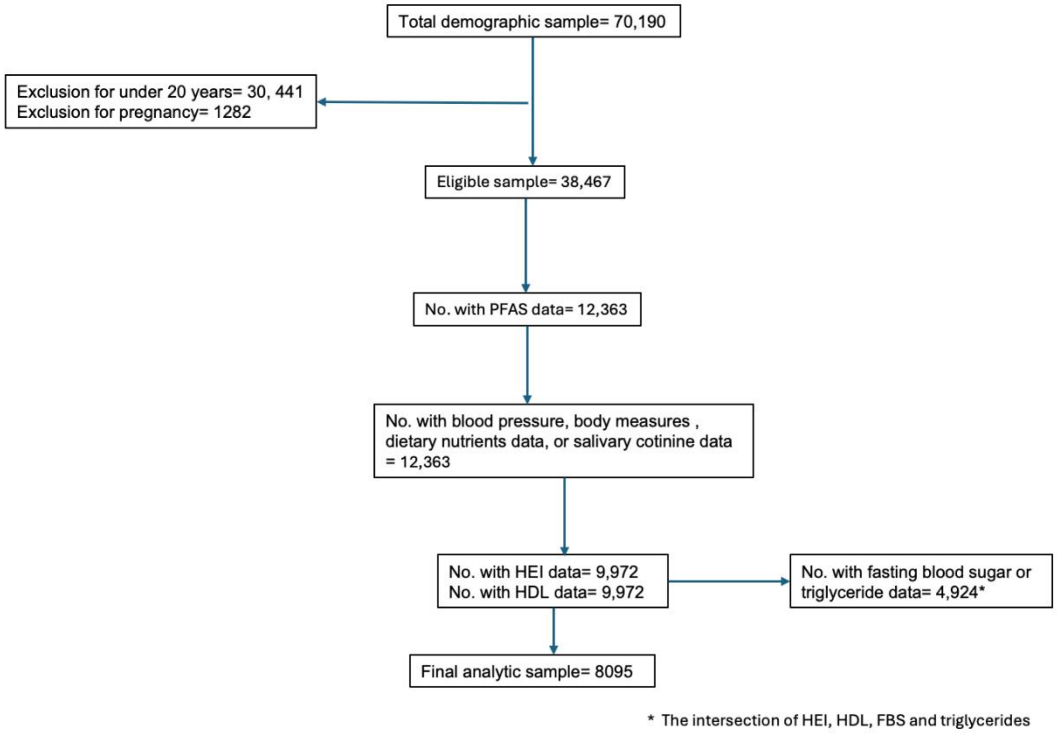

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Figure 1. CONSORT chart showing sample size after exclusions and subsample selection.

Statistical Analysis

Statistical analysis was conducted using R Software (version R 4.1.0) in RStudio (Version 1.2.1335). The NHANES R package was used for data extraction and the R survey package for analysis of survey data.[49,50]. Descriptive statistics of the eligible study sample were calculated, including mean with standard error and frequency with percentage. Serum PFAS has a right skewed distribution, therefore a log transformation was performed. As per NHANES guidelines, appropriate subsample weights were included to obtain unbiased estimates, standard errors and confidence intervals [51].

For the primary analysis, a pooled index (PI) was used to estimate the joint effect of the five PFAS under study. Since humans are exposed to multiple chemicals in the environment simultaneously, a pooled index provides a more realistic exposure scenario, by estimating the overall mixture effect. Conversely, regression models with individual exposures provide an estimated effect of a single chemical while holding all others constant. To create the PI, individual PFAS concentrations are first standardized to a Z-score, then the mean of these Z-scores is calculated [52,53]. A logistic regression model was fit, and coefficients interpreted as the odds of MetS per standard deviation increase in the PI. Logistic regression models were also fit with PFAS and each metabolic condition, and individual PFAS with MetS.

We also examined model sensitivity to other dietary quality scores, specifically the self-reported healthy diet variable from NHANES Diet Behavior and Nutrition data file.

3. Results

3.1. Sample Characteristics

The demographic characteristics of the analytic and non-analytic sample are summarized in Table 1. Overall, participants in the two groups were similar in terms of gender, age distribution and diet quality, however differences were observed in race/ethnicity and income level. In the analytic sample there was a higher proportion of non-Hispanic White participants (70.4%) compared to 58.7% in the non-analytic sample. In addition, a higher proportion of participants were at the lowest poverty income level (43.1%) in the non-analytic sample, compared to the analytic sample (33.1%) (Table 1). Approximately 28% of study participants in the eligible study sample fit the diagnostic criteria for MetS. The prevalence of metabolic syndrome within covariate groups is summarized in Table 2. In general, the highest prevalence of MetS was observed in non-Hispanic Whites (29.5%), males (31%) , participants 65 and older (36.6%) and those whose PIR is <200% of the FPL (34%).

On average, PFAS concentrations were detectable in 80% of analyzed samples, with highest concentrations observed for PFHxS (median: 1.46, ng/mL range: 0.07 - 23.80 ng/mL). Limits of detection and ranges of PFAS concentrations may be found in Table A1 in Appendix A.

Table 1. Characteristics (mean±SD) or N (%) of NHANES Sample. National Health and Examination Survey 2005-2018.

Characteristics		Analytic sample	Non-Analytic
		(n = 8095)	(n = 30,372)
Healthy Eating Index	(13.84891	53.7 ± 13.4 0.25)	54.3 ± 13.3 0.44
Age 20-29		1273 (17.0)	4783 (21.6)

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30-44	2033 (27.3)	7456 (26.6)
45-54	1425 (20.1)	5125 (17.3)
55-64	1434 (17.0)	5236 (14.3)
65 and older	1930 (18.6)	7772 (20.2)
Gender		
Male	3926 (48.5)	15324 (49.8)
Female	4169 (51.5)	15048 (50.2)
Poverty income ratio		
PIR 1[a]	3740 (33.1)	13031 (43.1)
PIR 2[b]	2168 (28.5)	7032 (26.5)
PIR 3[c]	2187 (38.4)	6644 (30.3)
Race/ethnicity		
Non-Hispanic White	3694 (70.4)	12406 (58.7)
Non-Hispanic Black	1682 (10.1)	6667 (14.3)
Hispanic	1924 (12.9)	7708 (16.5)
Other race[1]	795 (6.7)	3591 (10.5)
Serum cotinine		
≥ 10 ng/mL	1972 (23.8)	6765 (27.5)
< 10 ng/mL	6123 (76.2)	20230 (72.5)

Legend: a. *PIR 1*: family income to poverty ratio less than 2, b. *PIR2:* family income to poverty ratio less than 4, c. *PIR3:* family income to poverty ratio less than or equal to 5.

Table 2. Prevalence of Metabolic Syndrome within Eligible Sample (n=38,467). National Health and Examination Survey 2005-2018.

	MetS[a] Present N(%)	MetS Absent N (%)	Missing N(%)
Age Group			
20-29	430 (7.6)	4773 (81.4)	853 (11.0)
30-44	1458 (15.0)	6782 (75.4)	1249 (9.6)
45-54	1313 (20.5)	4400 (71.6)	837 (7.9)
55-64	1607 (25.1)	4188 (66.5)	875 (8.4)
65 and older	2289 (23.6)	5538 (64.6)	1875 (11.8)
Sex			
Female	3722 (17.8)	12725 (72.1)	2770 (10.1)
Male	3375 (18.2)	12956 (72.5)	2919 (9.3)
Poverty Income Ratio			
PIR1[b]	3391 (19.5)	10821 (68.9)	2528 (11.6)
PIR2[c]	1733 (19.9)	6243 (70.0)	1224 (10.1)
PIR3[d]	1322 (15.1)	6407 (77.9)	1102 (7.0)
Race			
Non-Hispanic White	3134 (18.5)	10821 (72.9)	2145 (8.6)
Non-Hispanic Black	1295 (15.7)	5492 (68.8)	1562 (15.5)
Hispanic	2076 (19.4)	6279 (71.6)	1277 (9.0)
Other race	592 (14.2)	3089 (73.4)	705 (12.4)

Legend: a. *MetS:* Metabolic Syndrome b. *PIR 1*: family income to poverty ratio less than 2 c. *PIR2:* family income to poverty ratio less than 4 d. *PIR3:* family income to poverty ratio less than or equal to 5.

3.2. PFAS and Individual Metabolic Conditions

Overall PFAS tended to be inversely associated with individual metabolic conditions.

A significant inverse association was seen for high triglycerides with PFDA (OR: 0.57, 95% CI: 0.37, 0.88) and PFUA (OR: 0.31, 95% CI: 0.16, 0.61). A similar association was observed for obesity with all five PFAS-PFHxS (OR: 0.82, 95% CI: 0.72, 0.93), PFNA (OR: 0.78, 95%CI: 0.64, 0.96), PFDA (OR: 0.49, 95%CI: 0.33, 0.73), PFUA (OR: 0.29, 95%CI: 0.18, 0.46), (OR: 0.65, 95%CI: 0.48, 0.89). For low

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HDL cholesterol, inverse associations were found with PFHxS (OR: 0.87, 95% CI: 0.76, 0.99), PFDA (OR: 0.58, 95% CI: 0.41, 0.83), PFUA (OR: 0.31, 95% CI: 0.19, 0.52), and MePFOSA (OR: 0.66, 95% CI: 0.49, 0.90). For elevated blood glucose only one PFAS- PFHxS (OR: 0.77, 95% CI: 0.64, 0.93), showed a significant association. No significant associations were observed between PFAS and high blood pressure.

3.3. PFAS and MetS

All five PFAS were included in the pooled index model. Overall results were similar in adjusted pooled and individual logistic regression models (Figure 1; Table A2 in Appendix A). In the pooled model, one standard deviation increase in the index was associated with 18% decreased odds of MetS (OR: 0.82, 95% CI: 0.76, 0.89). Similarly, in individual logistic regression models, higher PFAS concentrations were associated with decreased odds of MetS for all five PFAS.

3.4. Interaction Models

Results from interaction models show that the effect of PFAS on MetS differed across age groups. While PFNA was associated with lower odds of the outcome in the 20-29 (referent) age group (OR = 0.39, 95% CI: 0.18–0.85). This inverse association was attenuated among individuals aged 45–54 (p=0.03) (Table A3 in Appendix A).

3.5. Sensitivity Analyses

In the sensitivity analysis, the pooled index model with quantitatively measured HEI score, was compared to a second model using a self-reported diet quality indicator. Results were virtually unchanged in the second model (OR: 0.84, 95% CI: 0.78, 0.90).

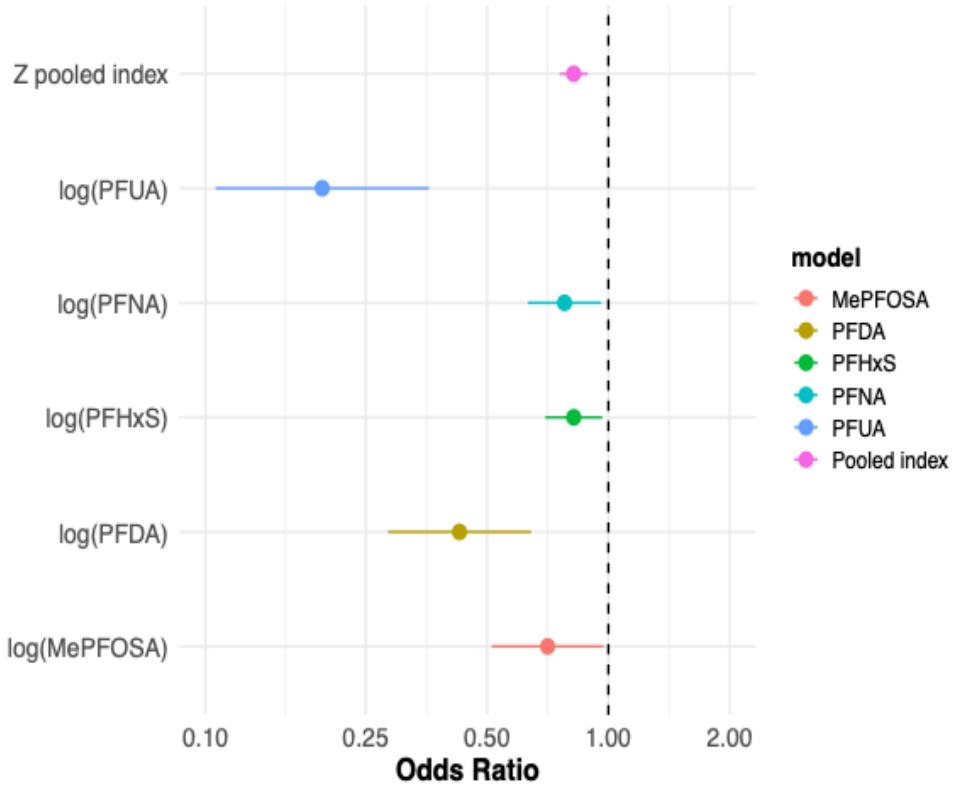

Figure 2. Pooled index and logistic regression models examining associations between log-transformed PFAS and MetS adjusted for covariates, (n=8095).

4. Discussion

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In this nationally representative sample of US adults, an inverse association was observed between a mixture of 5 PFAS- PFHxS, PFNA, PFDA, PFUA and MePFOSA, and MetS, with similar findings in the individual PFAS models. These results should be interpreted cautiously, however, given the cross-sectional design and the possibility of reverse causation.

The literature shows considerable variation in the association between PFAS and individual metabolic disturbances. While there is substantial evidence of a positive association between PFAS concentration and lipid dysregulation [21,54–56], the relationship between PFAS and glycemic changes such as diabetes is shown to be inconsistent [26,57,58]. For example, a scoping review of 39 studies which examined the link between PFAS exposure and risk of various glycemic outcomes, 24 studies reported positive associations while the others reported inverse, non-linear or null associations [26]. Additionally, a Canadian study on the effects of PFAS on multiple pregnancy outcomes, found an inverse association with both infant birth weight and maternal fasting glucose concentrations during pregnancy [13,59,60].

Understanding the relationship between PFAS and MetS is complex for several reasons. First, MetS is a composite outcome, defined as the presence of 3 or more metabolic conditions. Therefore, the overall association is determined by the prevalence and distribution of these metabolic conditions in study sample, and their individual relationships with PFAS. Our results and the prior literature, show variation in the relationships between PFAS and each metabolic condition. Furthermore, the range in PFAS concentrations varied substantially across the five chemicals, with lowest maximum concentration observed for MePFOSA. Therefore, while PFAS may indeed be positively associated with some metabolic outcomes, this mechanism is possibly dose-dependent and only observed above certain thresholds [61].

Since NHANES data is cross-sectional, the observed inverse association between PFAS and MetS might be explained by reverse causation. There is evidence in the experimental literature that obesity is associated with increased glomerular filtration rate (GFR) and albuminuria (the presence of excess albumin protein in the urine) [62,63]. Both increased GFR and albuminuria are linked to greater elimination of PFAS from the body [63–65]. This could partially account for lower serum PFAS concentrations in obese individuals. Reverse causation may also be explained by protein binding of PFAS in the body. Various studies have reported an association between obesity and decreased serum albumin levels, possibly related to nutritional deficiencies or malnutrition (e.g., lack of antioxidants) [66,67]. Since PFAS preferentially bind to blood proteins such as albumin, a decrease in serum albumin levels would effectively lower serum PFAS concentrations [65].

There are several key differences between the present study and others which reported positive associations between PFAS and metabolic disease. Many studies include PFOA and PFOS, legacy compounds which are known to be highly persistent, toxic and bioaccumulative in humans [2,13]. The inclusion in this study of other PFAS, which have been introduced more recently into consumer products and studied less extensively, may partly be responsible for the differences in results. In addition, some studies reporting large positive effects for PFAS and metabolic outcomes, were conducted on populations with high PFAS contamination. Key examples include studies of cardiometabolic outcomes in pregnant women living near the World Trade Center, Swedish adults exposed to water contaminated with fire-fighting foam, and Wilmington North Carolina residents exposed to contaminated drinking water from a fluorochemical manufacturing facility [23,68,69]. Finally, multiple studies indicate that the association between PFAS and several metabolic conditions varies markedly across the lifespan. Therefore, differences in the age range of sample participants will impact the observed results [15,17,59,70].

While an inverse association may appear to suggest a "protective effect" of PFAS on MetS, this interpretation is likely inaccurate. As previously discussed, the experimental literature provides evidence of PFAS' ability to interfere with the body's endogenous hormones and disrupt cellular processes including lipid synthesis, accumulation and adipogenesis [24,25]. The proposed mechanism of toxicity involves possible binding of PFASs to peroxisome proliferator-activated receptors (PPARs) and other nuclear receptors which may in impact lipid regulation [71]. Regardless

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of whether there is up or down regulation of a given metabolic endpoint, PFAS demonstrates the ability to adversely affect normal hormonal function.

The environmental persistence of PFAS in developed countries and increasing incidence of metabolic syndrome worldwide, constitute a global public health threat. Public health intervention should therefore focus on exposure reduction including PFAS regulation and public education, and disease prevention including health screenings and lifestyle modifications to mitigate risk.

Strengths and Limitations

There are important limitations that should be acknowledged. The final analytic sample differed somewhat from those excluded on race/ethnicity and income, and this may affect generalizability of results. Since serum PFAS and MetS were measured at the same time, we cannot establish temporality or rule out reverse causation. In addition, despite best attempts at controlling for confounders in regression models, the potential for confounding due to unobserved factors still exists. In addition, the use of a PI assumes that each PFAS is of equal importance (i.e. by taking the average of their Z-scores they are all weighted equally). Finally, the study design limits our ability to track PFAS exposure trends.

Despite these limitations, this study has several strengths. First, the inclusion of a PI in addition to individual logistic regression models, allows for assessment of the joint effect of multiple PFAS on MetS. Since humans are exposed to multiple environmental chemicals simultaneously, examining a mixture of PFAS may provide a more realistic picture of potential adverse effects. To our knowledge, this is the only study apply this pooled index method to examine associations between a PFAS mixture and MetS using NHANES data. In addition, estimating the association between PFAS and MetS across 14 survey years provides a more stable estimate of the association at the population level. Finally, models were adjusted for diet quality to provide greater confidence that observed differences in odds of MetS are due to the exposure of interest. The literature provides ample evidence of increased risk of MetS with diets high in added sugars, saturated fat and processed foods (87,88).

5. Conclusions

Our study found an inverse association between serum PFAS concentration and MetS using a pooled index and logistic regression models. While these results must be interpreted with caution, the findings provide preliminary evidence PFAS could disrupt the body's metabolic processes. A longitudinal analysis with repeated exposure measurements would allow more accurate assessment of potential causal relationships between PFAS and incidence of MetS.

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Data Availability Statement: The datasets supporting the conclusions of this article is publicly available at: https://wwwn.cdc.gov/nchs/nhanes/default.aspx.

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Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Appendix A.1

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Table A1. Distributions of PFAS concentrations (ng/mL) in study participants (n=38, 467)

PFAS	Percent > LOD	Min	Q1 (25%)	Median	Q3 (75%)	Max	Mean (SE)
PFHxS	99	0.07	0.80	1.50	2.60	81.60	2.17 (0.06)
PFNA	98	0.06	0.50	0.88	1.39	80.77	1.12 (0.04)
PFDA	82	0.07	0.14	0.20	0.40	51.30	0.34 (0.01)
PFUA	52	0.07	0.07	0.14	0.20	77.40	0.22 (0.008)
MePFOSA	61	0.06	0.07	0.13	0.30	12.20	0.39 (0.02)

Appendix A.2

Table A2. Associations between log-transformed PFAS and metabolic syndrome, adjusted for covariates (n= 8095)

	OR	95% CI	*p*
Pooled Index	0.82	0.76, 0.89	<0.001
Individual PFAS			
PFHxS	0.82	0.70, 0.97	0.02
MePFOSA	0.71	0.51, 0.97	0.03
PFNA	0.78	0.63, 0.96	0.02
PFDA	0.43	0.28, 0.64	<0.001
PFUA	0.19	0.11, 0.36	<0.001

Appendix A.3

Table A3. Associations between log-transformed PFAS and MetS including interaction term for PFAS and age, adjusted for covariates, (n=8095)

	OR	95% CI	*p*
PFNA	0.39	0.18, 0.85	0.02
Interaction terms			

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PFNA: 30-44	1.59	0.63, 4.05	0.32
PFNA: 45-54	2.57	1.09, 6.06	0.03
PFNA: 55-64	2.28	0.93, 5.55	0.07
PFNA: 65 and older	2.10	0.92, 4.75	0.08

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