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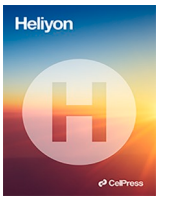

Research article

Perfluoroalkyl substances and metabolic syndrome: A cross-sectional study using data from the US national health and nutrition examination survey

Jing Wu [a], Xiaoqian Zhang [b], Qiong Wang [b], Ning Ma [b], Fangjieyi Zheng [a], Kening Chen [c,d], Wenquan Niu [a,*]

[a] Center for Evidence-Based Medicine, Capital Institute of Pediatrics, Beijing, China
[b] Graduate School, Beijing University of Chinese Medicine, Beijing, China
[c] Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[d] Institute of Clinical Medical Sciences, China-Japan Friendship Hospital, Beijing, China

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ABSTRACT

Background: Epidemiological studies linking metabolic syndrome (MetS) and exposure to perfluoroalkyl substances (PFASs) are limited, and the observations gleaned thus far are inconclusive. The study was performed to explore the association of serum PFASs both singly and in a mixed manner with MetS, and meanwhile to examine whether this association was mediated by serum albumin in a US national population.

Methods: Total 8108 participants from the National Health and Nutrition Examination Survey, 2007–2018 were included. Four PFASs - including perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluoromethylheptane sulfonic acid (PFOS), and perfluorooctanoic acid (PFOA), were selected. Weighted quantile sum regression was used to evaluate mixed PFAS exposure and MetS. Multivariable logistic regression models were used to calculate odd ratio (OR) and 95 % confidence interval (95 % CI). Mediating analyses were used to evaluate the mediating effects of albumin.

Results: Comparing the highest with lowest quartile yielded a multivariable-adjusted OR (95 % CI) of 1.40 (1.14–1.72) for PFHxS, 1.36 (1.09–1.70) for PFNA, 1.26 (1.00–1.58) for PFOA, and 1.50 (1.19–1.88) for PFOS when associating MetS. Per unit increment in ln-transformed PFHxS, PFNA, PFOA, and PFOS concentrations was significantly associated with 16 %, 17 %, 13 %, and 15 % increased risk of MetS, respectively. When stratified by sex, the significant association between four PFASs and MetS was only noted in females. Mixed PFAS exposure was inversely associated with MetS, and 8.1 % of this association was mediated by serum albumin ($P < 0.001$).

Conclusions: Our findings indicate a significant and independent association of serum PFASs with MetS, and importantly this association was dose-dependent, sex-specific, and possibly mediated by serum albumin.

* Corresponding author. No.2 Yabao Rd., Chaoyang District, Beijing, 100020, China.
E-mail address: niuwenquan_shcn@163.com (W. Niu).

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1. Introduction

Metabolic syndrome (MetS) covers a cluster of cardiometabolic risk factors, including abdominal obesity, hypertension, hyperglycemia, hypertriglyceridaemia, and low high-density lipoprotein cholesterol (HDLC). The prevalence of MetS is rising over the past decades [1,2], mainly because of its prevalent components [3,4]. Latest statistics from the World Health Organization and Global Burden of Disease Study 2021 showed that an estimated 1.28 billion and 529 million adults worldwide are affected by hypertension and diabetes, respectively [5]. Reports from the National Health and Nutrition Examination Survey (NHANES) revealed that the prevalence of MetS increased from 36.2 % in 1999–2000 to 47.3 % in 2017–2018 among US adults [6], which reflects an approximately 30 % increase. In the long run, MetS can not only trigger the onset and progression of cardiovascular disease, cerebrovascular disease, and type 2 diabetes [2,7], but also act as a powerful predictor for all-cause mortality [8]. The prevention of MetS is therefore a major public health priority that should be made more urgent by identifying potential risk factors to prevent or delay the development of MetS.

Perfluoroalkyl substances (PFASs) are a group of synthetic organic chemicals that have been widely applied in industrial and consumer fields, including fabrics, cleaners, food packaging, and electronics due to hydrophobic, oil-resistant, and heat-resistant properties [9,10]. Currently, the detrimental effects of PFASs on human health have aroused global attention [11,12]. Several epidemiological studies have investigated the association between PFAS and MetS, but there was no reachable consensus [13,14]. Noteworthily, most studies have focused on individual PFASs, disregarding mixed PFAS exposure. Considering that PFASs usually exist as a complex mixture, the effect of any single PFAS on MetS may be small when assessed individually, and PFAS mixtures may provide additional insights into the complex pathogenesis behind MetS [15]. Additionally, there is evidence implicating a mediating role of albumin in transporting PFASs in the development of metabolic components [16,17], yet national data on this role are lacking.

To yield more information, we aimed to explore the association of serum PFASs, both singly and in a mixed manner, with the risk for MetS by analyzing data from the NHANES, 2007–2018. Meanwhile, we tested whether this association was mediated by serum albumin.

Table 1
Characteristics of study participants by metabolic syndrome (MetS), NHANES 2007–2018.

Variables	Total	Without MetS	With MetS	*P*
Number	8108	5807	2301	
Age, mean ± SD, years	49.04 ± 18.06	44.49 ± 17.56	60.51 ± 13.68	<0.001
BMI, mean ± SD, kg/m^2	29.18 ± 6.93	27.79 ± 6.53	32.72 ± 6.63	<0.001
Sex				0.005
Female	4125 (50.88)	2898 (49.91)	1227 (53.32)	
Male	3983 (49.12)	2909 (50.09)	1074 (46.68)	
Marital status				<0.001
Married	4686 (57.79)	3308 (56.97)	1378 (59.89)	
Separated	1734 (21.39)	1033 (17.79)	701 (30.47)	
Never married	1491 (18.39)	1272 (21.90)	219 (9.52)	
Race				<0.02
Non-Hispanic white	3282 (40.48)	2316 (39.88)	966 (41.98)	
Non-Hispanic black	1700 (20.97)	1208 (20.80)	492 (21.38)	
Mexican American	1292 (15.93)	916 (15.77)	376 (16.34)	
Others	1834 (22.62)	1367 (23.54)	467 (20.30)	
Educational attainment				<0.001
Less than high school	1991 (24.56)	1271 (21.89)	720 (31.29)	
High school or equivalent	1732 (21.36)	1205 (20.75)	527 (22.90)	
College or above	4180 (51.55)	3131 (53.92)	1049 (45.59)	
Smoking status				<0.001
Non-smoker	4492 (55.40)	3331 (57.36)	1161 (50.46)	
Smoker	3489 (43.03)	2351 (40.49)	1138 (49.46)	
Drinking status				<0.001
Non-drinker	1715 (21.15)	1115 (19.20)	600 (26.08)	
Drinker	4356 (53.72)	3230 (55.62)	1126 (48.94)	
Sleep problems				<0.001
No	6057 (74.70)	4596 (79.15)	1461 (63.49)	
Yes	2048 (25.26)	1208 (20.80)	840 (36.51)	
Physical activity				<0.001
No physical activity	2140 (26.39)	1277 (21.99)	863 (37.51)	
Low intensity	3366 (41.51)	2459 (42.35)	907 (39.42)	
High intensity	2564 (31.62)	2046 (35.23)	518 (22.51)	

Data are shown as mean ± SD or n (%).
Abbreviations: MetS, metabolic syndrome; BMI, body mass index; SD, standard deviation.

Table 2
Distribution of serum perfluoroalkyl substances (PFAS) among 8108 participants from NHANES 2007–2018.

PFAS (ng/mL)	Mean ± SD	P5	P25	P50	P75	P95
PFHxS	2.13 ± 2.83	0.07	0.8	1.4	2.5	5.9
PFNA	1.15 ± 1.14	0.07	0.5	0.9	1.4	2.87
PFOA	3.00 ± 2.78	0.27	1.4	2.35	3.8	7.3
PFOS	11.53 ± 11.68	0.53	4.2	7.95	14.1	33.1

Abbreviations: SD, standard deviation; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid.

Table 3
Serum perfluoroalkyl substances associated with metabolic syndrome.

Variables	Unadjusted model	Adjusted model
	OR (95 % CI)	OR (95 % CI)
PFHxS		
Q1	1.00	1.00
Q2	1.38 (1.20–1.59)	1.24 (1.01–1.52)
Q3	1.53 (1.34–1.76)	1.34 (1.10–1.64)
Q4	1.60 (1.39–1.84)	1.40 (1.14–1.72)
P for trend	<0.001	0.008
Continuous (ln-transformed)	1.21 (1.15–1.27)	1.16 (1.08–1.26)
PFNA		
Q1	1.00	1.00
Q2	1.28 (1.11–1.47)	1.09 (0.88–1.36)
Q3	1.14 (0.99–1.31)	0.95 (0.76–1.19)
Q4	1.44 (1.26–1.66)	1.36 (1.09–1.70)
P for trend	<0.001	0.001
Continuous (ln-transformed)	1.18 (1.11–1.25)	1.17 (1.06–1.29)
PFOA		
Q1	1.00	1.00
Q2	1.06 (0.92–1.22)	0.93 (0.75–1.15)
Q3	1.10 (0.96–1.26)	1.02 (0.82–1.26)
Q4	1.28 (1.12–1.47)	1.26 (1.00–1.58)
P for trend	<0.001	0.005
Continuous (ln-transformed)	1.11 (1.04–1.18)	1.13 (1.02–1.25)
PFOS		
Q1	1.00	1.00
Q2	1.26 (1.09–1.46)	1.19 (0.96–1.48)
Q3	1.55 (1.34–1.78)	1.38 (1.11–1.72)
Q4	1.94 (1.69–2.23)	1.50 (1.19–1.88)
P for trend	<0.001	0.002
Continuous (ln-transformed)	1.27 (1.20–1.34)	1.15 (1.06–1.25)

Abbreviations: OR, odds ratio; CI, confidence interval; Q, quartile; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid.
Model adjusted for survey cycle, age, sex, race/ethnicity, education, marital status, drinking and smoking status, physical activity, sleep problems and body mass index were controlled.
P values for trend test were calculated by fitting median scores for quartiles as continuous variables in generalized linear models.

2. Methods

2.1. Study participants

NHANES is a series of nationally representative cross-sectional surveys conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). A complex, multistage, stratified, clustered probability design was used to assess the health and nutrition status of U.S. civilians (https://www.cdc.gov/nchs/nhanes/index.htm). Data were collected from personal structured interviews at home, health examinations at mobile examination centers, and specimen analyses in laboratories.

In the present study, data from NHANES, 2007–2018 incorporating 8108 participants aged ≥18 years with complete information on serum PFAS concentrations and MetS were finally analyzed. The conduct of NHANES was approved by the Institutional Review Board of the National Center for Health Statistics. Written consent was obtained from all study participants.

Table 4
Serum perfluoroalkyl substances associated with metabolic syndrome by sex.

Variables	Sex		*P*-interaction
	Female	Male	
PFHxS			
Q1	1.00	1.00	<0.001
Q2	1.23 (0.95–1.58)	0.94 (0.66–1.34)	
Q3	1.43 (1.10–1.87)	0.93 (0.67–1.30)	
Q4	1.80 (1.36–2.39)	0.82 (0.59–1.15)	
PFNA			
Q1	1.00	1.00	0.002
Q2	1.31 (0.97–1.76)	0.80 (0.57–1.11)	
Q3	1.07 (0.78–1.45)	0.69 (0.49–0.96)	
Q4	1.70 (1.24–2.32)	0.88 (0.63–1.24)	
PFOA			
Q1	1.00	1.00	0.001
Q2	0.86 (0.65–1.14)	0.88 (0.63–1.23)	
Q3	1.21 (0.90–1.62)	0.70 (0.50–0.98)	
Q4	1.46 (1.07–1.98)	0.84 (0.59–1.19)	
PFOS			
Q1	1.00	1.00	<0.001
Q2	1.20 (0.91–1.57)	0.92 (0.63–1.34)	
Q3	1.33 (1.00–1.77)	1.04 (0.73–1.49)	
Q4	1.87 (1.38–2.54)	0.95 (0.65–1.37)	

Abbreviations: OR, odds ratio; CI, confidence interval; Q, quartile; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid.
Data are presented as OR (95 % CI) calculated in multivariable models after adjusting for survey cycle, age, sex, race/ethnicity, education, marital status, drinking and smoking status, physical activity, sleep problems and body mass index.

2.2. Serum PFASs

Serum concentrations of PFASs were measured using solid phase extraction coupled to High Performance Liquid Chromatography-Turbo Ion Spray ionization-tandem Mass Spectrometry (SPE-HPLC-TIS-MS/MS) [18]. The laboratory procedures and quality control methods for serum PFAS measurements have been described elsewhere [19].

In this study, four PFASs including perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluoromethylheptane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), were included. The linear and branched isomers of PFOA and PFOS were detected separately in NHANES 2013–2018, and were added together for further analysis. The four PFASs under study have been proven to be effective in reflecting total PFAS exposure in humans, and have been widely assessed in prior studies [20,21].

2.3. Definition of MetS

According to the National Cholesterol Education Program's Adult Treatment Panel III criteria (NCEP-ATP III), MetS was defined as having three or more of the following five components: (i) central obesity: waist circumference >88 cm for females or >102 cm for males; (ii) high triglycerides: triglycerides ≥150 mg/dL or taking anti-lipid medications; (iii) low HDLC: HDLC <50 mg/dL for females or <40 mg/dL for males; (iv) high blood pressure (BP): systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg or taking anti-hypertensive medications; (v) high fasting glucose: fasting glucose ≥110 mg/dL or taking antidiabetic medications.

2.4. Assessment of covariates

Demographic characteristics and lifestyle factors were obtained through standardized questionnaires. Race/ethnicity was classified as non-Hispanic Whites, non-Hispanic Blacks, Mexican Americans, and others. Education was classified as less than high school, high school or equivalent, and college or above. Marital status was classified as married, separated, and never married. Smoking status was classified as non-smokers and smokers according to whether participants had smoked 100 cigarettes during their lifetime. Drinking alcohol status was classified as non-drinkers and drinkers based on the question "Have you had at least 12 drinks of any type of alcoholic beverage in any one year?" Sleep problems were assessed by the question "Have you ever told a doctor or other health professional that you have trouble sleeping?" Type, frequency and duration of physical activity were obtained from the Physical Activity questionnaire (PAQ). Participants were divided into none physical activity, low intensity physical activity, and high intensity physical activity based on metabolic equivalent (MET) [22].

2.5. Statistical analyses

Baseline characteristics of study participants according to MetS were compared using one-way ANOVA tests, Kruskal-Wallis test,

Table 5
Association of weighted quantile sum (WQS) regression index with metabolic syndrome.

WQS index	OR (95 % CI)[a]
Q1	1.00
Q2	1.32 (1.08–1.61)
Q3	1.45 (1.18–1.78)
Q4	1.58 (1.26–1.97)
Per 1 unit increment in WQS index	1.23 (1.10–1.38)

Abbreviations: OR, odds ratio; CI, confidence interval.
[a] Adjusted for survey cycle, age, sex, race/ethnicity, education, marital status, drinking, smoking, physical activity, sleep problems, and body mass index.

and χ^2 test, where appropriate. In view of deviations from normal distributions, four PFASs under study were ln-transformed. PFASs were also categorized into quartiles. Spearman correlation on four ln-transformed PFASs concentrations was conducted. Univariate and multivariable logistic regression models were used to derive odds ratio (OR) and 95 % confidence interval (CI) for the association of serum PFASs with MetS. Confounders under adjustment included survey cycle, age, sex, race/ethnicity, education, marital status, drinking status, smoking status, physical activity, sleep problems, and body mass index (BMI). Testing for trends was conducted by fitting the median score of quartiles of each PFAS as a continuous variable in logistic regression models. Given the different susceptibility to MetS between female and male, stratified analyses were performed according to sex. Testing for interactions was performed by adding the interaction term in logistic regression models.

Weighted quantile sum (WQS) regression was used to explore the association of mixed PFAS exposure and MetS. WQS index comprised of weighted sums of each PFAS, and was calculated using package "gWQS" in the R coding platform version 4.4.0.

Mediation effect of albumin on the association of single and multiple PFASs with MetS risk was evaluated using the package "mediation" in the R coding platform. Total effect of PFASs on MetS was divided into indirect and direct effects. Total, indirect, and direct effects were computed by combining albumin and MetS model with adjustment for all covariates in logistic regression models.

All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA) and R coding platform version 4.4.0 (R Foundation for Statistical Computing). Statistical significance was defined as 2-sided *P* value was less than 0.05.

3. Results

3.1. Characteristics of study participants

Table 1 showed the baseline characteristics of study participants. Of 8108 participants, the average age (± standard deviation or SD) was 49.04 ± 18.06 years and average of BMI (±SD) was 29.18 ± 6.93 kg/m^2. Nearly half participants were males (49.12 %), and 40.48 % of participants were non-Hispanic White. There were 2301 participants were reported to have MetS, with its prevalence of 28.38 %. Notable variations between participants without and with MetS were observed in age, sex, race/ethnicity, education, marital status, smoking, drinking, physical activity, sleep problems, and BMI.

3.2. Correlation analyses

The median concentrations (in ng/mL) of PFHxS, PFNA, PFOA and PFOS were 1.40, 0.90, 2.35, and 7.95 in all participants, respectively (Table 2). The Spearman correlation of four serum PFASs was illustrated in Supplementary Fig. 1. The four PFASs had a moderate to high correlation with each other (Spearman correlation coefficients ranged from 0.47 to 0.73).

3.3. Single PFASs and MetS

Shown in Table 3 was the association of serum PFASs in quartiles and ln-transforms with MetS risk. Comparing the highest quartile with the lowest quartile, the multivariable-adjusted OR (95 % CI) was 1.40 (1.14–1.72) for PFHxS, 1.36 (1.09–1.70) for PFNA, 1.26 (1.00–1.58) for PFOA and 1.50 (1.19–1.88) for PFOS when associating MetS. In both crude and adjusted models, higher concentrations of serum PFHxS, PFNA, PFOA and PFOS were associated with greater risk of MetS in a dose-response manner (all *P* for trends <0.001). Moreover, per unit increment in natural ln-transformed PFHxS, PFNA, PFOA, and PFOS concentrations was significantly associated with 16 %, 17 %, 13 %, and 15 % increased risk of MetS, respectively.

The dose-response association between ln-transformed PFASs and MetS was displayed in Supplementary Fig. 2. The association of ln-transformed PFHxS, PFNA and risk of MetS tended to be linear (*P* for non-linear >0.05), and that of ln-transformed PFOA, PFOS and risk of MetS tended to be non-linear (*P* for non-linear <0.05)

The association of serum PFASs in quartiles with MetS components was provided in Supplementary Table 1. All PFASs were significantly associated with high blood pressure and high triglycerides. No hint of significance was noted for high fasting glucose, low HDLC, and central obesity. The association between ln-transformed PFASs and metabolic related factors was also displayed in Supplementary Fig. 2.

Stratified analyses were done for the association between serum PFASs and MetS according to sex. The sex-specific association

Table 6
Serum perfluoroalkyl substances, individually and as a whole, associated with metabolic syndrome mediated by serum albumin.

Variables	Total effect				Natural direct effect				Natural indirect effect				Proportion eliminated	*P*
	β	Lower	Upper	*P*	β	Lower	Upper	*P*	β	Lower	Upper	*P*		
PFHxS	0.005	0.0006	0.009	0.02	0.005	0.0009	0.009	0.02	−0.0003	−0.0005	−0.0001	0.002	7.0 %	<0.001
PFNA	0.01	0.002	0.02	0.02	0.01	0.003	0.02	0.01	−0.0009	−0.001	−0.0003	0.001	5.3 %	<0.001
PFOA	0.005	0.0001	0.009	0.04	0.005	0.0005	0.01	0.03	−0.0006	−0.001	−0.0002	0.006	13.3 %	<0.001
PFOS	0.001	0.0002	0.002	0.02	0.001	0.0002	0.002	0.01	−0.00008	−0.0001	−0.00002	0.007	2.4 %	<0.001
WQS index	0.03	0.02	0.04	<0.001	0.03	0.02	0.05	<0.001	−0.003	−0.005	−0.002	<0.001	8.1 %	<0.001

Abbreviations: PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid. Effect-size estimates were calculated in multivariable models after adjusting for survey cycle, age, sex, race/ethnicity, education, marital status, drinking, smoking, physical activity, sleep problems, and body mass index.

between serum PFASs in quantiles and MetS was presented in Table 3. Significant differences in effect-size estimates were seen for PFHxS, PFNA, PFOA, and PFOS, and the association with MetS was reinforced in females.

3.4. Mixed PFASs and MetS

Besides single PFASs, the mixed impact of serum PFASs on MetS and its components were also explored by using WQS regression analyses (Table 4 and Supplementary Table 3). The WQS index was generated, and it represented the mixture of four PFASs. After adjusting for potential confounders, each unit mixture (WQS index) increment in PFASs was associated with a 23 % increase in MetS risk (OR = 1.23, 95 % CI: 1.10–1.38, $P < 0.001$; Table 5).

3.5. Mediation analyses

Further analysis was conducted to assess whether the association between PFASs and MetS was mediated by serum albumin, as shown in Table 6. For single PFASs, the proportion mediated by serum albumin ranged from 2.4 % (for PFOS) to 13.3 % (for PFOA). When treating four PFASs as a whole, serum albumin was estimated to interpret 8.1 % of the association with MetS.

4. Discussion

In this study, we aimed to explore the association of serum PFASs with MetS, and examine the mediating role of serum albumin in this association among 8108 US adults from NHANES, 2007–2018. Our key findings are that PFASs were found to be significantly and independently associated with MetS, especially in females, and importantly they acted in a dose-dependent manner. It is also worth noting that an estimated 8.1 % of the observed association between PFASs and MetS was mediated through serum albumin.

A growing number of epidemiologic studies have investigated the association of serum PFASs with MetS and its components [23–28], however, the results are thus far inconclusive. Among 148 Chinese male adults, Yang et al. reported that high PFAS concentrations were associated with the significant risk of MetS and its components [29]. This association was also supported by Liu et al. who analyzed 1871 adults from NHANES, 2013–2014 [13]. However, Zare et al. among 15,876 young Italian adults did not support the consistent association between PFASs and MetS [30], in line with the results of another study among 397 residents aged 55–75 years from Taiwan [26]. Studies focusing on different PFASs may yield disparate results due to inherent differences in the compounds themselves. Studies with lower exposure levels may fail to detect any significant signals. Discrepant results should be viewed with caution, and may reflect the complex nature of PFAS exposure. Besides the differences in races or participant characteristics, some previous studies aforementioned have inadequate statistical power or the association between PFASs and MetS was restricted to relatively small subgroups. Therefore, more large-scale, well-designed studies are warranted.

Consistent with the findings of most previous studies, our findings supported the individual contribution of PFHxS, PFNA, PFOA, and PFOS, from the continuous, categorical, dose-dependent, and trending aspects, to MetS risk, as well as high BP and triglycerides. A growing body of studies confirmed the association between serum PFASs and metabolic components. For instance, PFNA was found to be associated with the significant risk of MetS, and PFHxS was positively correlated with elevated triglycerides [31]. Another study observed the positive association between PFOS and low-density lipoprotein cholesterol [26]. A recent meta-analysis revealed that PFNA, PFOA, PFOS, and PFHxS were significantly associated with hypertension, in line with the findings of this study. We thus have reason to speculate that if involved, some PFASs might play a leading role in reprogramming metabolic homeostasis.

The majority of studies to date focused on PFASs individually, despite the toxicity caused by PFASs possibly involves their complex interplays. Given the complex nature of MetS and its components, it seems unlikely that PFASs individually make a considerable contribution, but whether mixed PFAS exposure would enhance risk prediction is of added interest. To achieve this goal, we employed the WQS regression, a penalized regression method that estimates mixture effects using a weighted index [32], and interestingly found that the association with MetS was strongly reinforced after treating PFASs as a composite index. Irrespective of the identification of culprit PFASs and the precise biological link with metabolic dysfunction, it is essential to heed the detrimental attributes of serum PFASs and to attach a high priority to finding effective means to prevent, reduce, and eradicate the sources of PFAS pollution from a public health standpoint.

Some potential mechanisms may explain the association between serum PFASs and MetS. Firstly, exposure to PFASs could activate nuclear receptors, which lead to changes in gene expression patterns that control lipid synthesis [33]. The ePFAS exposure increased levels of oxidative stress and inflammation, which could dysregulate glucose and lipid metabolism [2]. Thirdly, PFAS exposure was associated with gut microbiota [34], which could play a crucial role in the occurrence of MetS [35].

Another important finding of the present study is that the association between serum PFASs and MetS was partly mediated by serum albumin. A literature search failed to reveal any observational evidence on this mediation; however, this finding may be biologically plausible. Serum albumin was identified as the most important carrier protein for PFOS, PFOA, PFHxS, and PFDA in native human plasma [16]. Experimental studies have shown that serum albumin played a dominant role in the accumulation patterns of circulating PFASs [36–38]. Although elucidating the underlying mechanisms of albumin is beyond the scope of this study, this observation should be confirmed physiologically or epidemiologically in large cohorts. Moreover, the associatioin between PFASs and MetS was more evident in females, which leads us to conjecture that estrogen might serve as a mediator or a confounder, a open question that require additional investigations.

Finally, some limitations should be acknowledged in this study. Firstly, our analyses are based on cross-sectional survey data from NHNAES, which precluded comments on the cause-and-effect relationship between PFASs and MetS. Secondly, only four PFASs were

analyzed in this study, and they have been widely used to reflect PFAS exposure in prior studies [17,20,21]. Thirdly, the cross-sectional design of this study could limit the mediating effect of albumin. Our results should be interpreted with caution. Further longitudinal studies are warranted to confirm the findings of this study.

In conclusion, our findings, based on 8108 US adults from NHANES, 2007–2018, indicate the significant and independent association of serum PFASs with MetS. Importantly, this association was dose-dependent, sex-specific, and possibly mediated by serum albumin. Our findings not only emphasize the view that health practitioners and professionals should aware the detrimental effects of PFASs prior to translating into clinical and public health preventive strategies, but also open up more targeted treatment for metabolic dysfunction.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Institutional review board statement

The NHANES was approved by the Institutional Review Board of the National Center for Health Statistics.

Informed consent statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Written consent was obtained from study participants.

Data availability statement

Publicly available dataset was analyzed in this study. NHANES data are publicly available at https://www.cdc.gov/nchs/nhanes/index.htm.

CRediT authorship contribution statement

Jing Wu: Methodology, Conceptualization. **Xiaoqian Zhang:** Methodology, Formal analysis. **Qiong Wang:** Investigation, Formal analysis. **Ning Ma:** Software, Methodology. **Fangjieyi Zheng:** Formal analysis, Data curation. **Kening Chen:** Validation, Software. **Wenquan Niu:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36894.

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