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The Association Between the Mixed Exposure of PFASs and Hypertension in Overweight and Obese Populations: NHANES 2009 – 2018

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Abstract: Per- and polyfluoroalkyl substances (PFASs), recognized for their environmental stability and suspected health risks, have become a focal point in environmental health research. This study evaluated the potential link between combined PFASs exposure and hypertension development. Utilizing 2009-2018 NHANES data, we performed a cross-sectional analysis. Multivariate logistic regression, restricted cubic spline (RCS), and weighted quantile sum (WQS) regression models were employed to evaluate both individual and joint effects of PFASs exposure on hypertension. Among 2,086 participants, higher serum PFOA levels were significantly associated with hypertension after adjusting for covariates (OR: 1.104; 95% CI: 1.023,1.191, $P < 0.05$). A non-linear relationship was observed ($P = 0.0167$). The WQS model further indicated that mixed PFASs exposure positively correlated with hypertension prevalence (β: 0.245; 95% CI: 0.049–0.440; $P = 0.0141$). Among overweight and obese individuals, cumulative PFAS exposure is linked to an increased risk of hypertension. Further investigation is necessary to confirm this relationship and clarify its biological pathways.

Keywords: Hypertension, Perfluoroalkyl and polyfluoroalkyl substances, Weighted quantile sum regression, NHANES

1. Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are a series of synthetic compounds, mainly including perfluorooctane sulfonate (PFOS), perfluorohexane sulfonic acid (PFHxS), perfluorooctanoic acid (PFOA), perfluorooctanoic acid (PFNA), etc. Because of its high stability and durability, it is commonly used in every aspect of life, such as fire foam, food packaging, industry and other fields [1]. Due to the extensive use of PFASs and its difficulty in biodegradation, PFASs are widely accumulated in the environment, like soil, air, surface waters and ground waters [2]. In addition, PFASs may bioaccumulate in the human body[3], and even higher concentrations of PFASs have been noticed in pregnant women and embryonic / fetal tissues [4]. Previous studies have shown that PFASs have neurotoxicity[5, 6], genotoxicity [7, 8], reproductive toxicity[9] and developmental toxicity[10], which seriously threaten human health and have attracted widespread attention.

Hypertension, a pervasive non-communicable disease, arises from complex interactions between biological predisposition and environmental exposures. As the primary modifiable risk factor for cardiovascular diseases, it imposes a staggering global health burden [11]. The World Health

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Organization (WHO) published its comprehensive Global Report on Hypertension in September 2023[12], hypertension affects 33% of adults aged 30-79 years worldwide. Beyond its direct cardiovascular consequences such as stroke, and heart failure, hypertension frequently co-occurs with and exacerbates other chronic conditions like diabetes and chronic kidney disease [13, 14], further exacerbating health risks. In recent years, environmental pollutants is likely to play an increasingly significance part in the occurrence and development of hypertension. For example, an investigation utilizing the National Health and Nutrition Examination Survey (NHANES) data revealed a notably positive association between brominated flame retardant (BFRs) exposure and the incidence of hypertension[15]; In addition, the American Heart Association pointed out that sustained environmental exposure to fine particulate matter (PM2.5) can notably increase the incidence and mortality of cardiovascular disease[16]. Additionally, another piece of research also confirmed that the risen concentration of PM2.5 was firmly associated with the escalated risk of being hospitalized for cardiovascular diseases[17]. These results suggest that environmental pollutants may be one of the important potential triggers of hypertension. However, whether PFASs have an effect on hypertension is still controversial. A cross-sectional analysis identified significant associations between perfluorooctanoic acid (PFOA), a synthetic PFASs compound, and elevated hypertension risk. [18]. Another analysis confirmed hypertension associations for limited PFAS variants (notably PFOA), whereas the majority showed no epidemiological relevance[19]. Nevertheless, a separate analysis failed to establish significant associations between PFOA exposure and hypertension risk [20], and another study reported that perfluorodecanoic acid (PFDA) concentration was positively correlated with the prevalence of hypertension[21]. Existing studies predominantly examine the effects of single PFASs compounds, and rarely consider the possible joint effects of mixed exposure of multiple PFASs. Given that PFASs in the environment usually exist in the form of mixtures, and there may be synergistic or antagonistic effects between different compounds, evaluating the hypertensive effects of PFAS co-exposure represents a critical research priority in environmental epidemiology. Epidemiological studies have consistently established obesity as an independent predictor of hypertension development [22]. Moreover, the cardiotoxic effects of environmental pollutants may be potentiated by this factor.

Given this evidence gap, our investigation specifically examines the relationship between PFASs mixture exposure and hypertension prevalence in overweight/obese individuals using NHANES data.

2. Methods

2.1. Participant population

This study analyzed data from five consecutive cycles (2009-2018) of NHANES, which is a nationally representative cross-sectional survey carried out by the National Center for Health Statistics (NCHS) under the Centers for Disease Control and Prevention (CDC). The initial study population comprised 4,105 participants, and after applying strict exclusion standards, 2,086 eligible research subjects was determined. Exclusion criteria included: missing PFAS data (n=143), non-standardized blood pressure measurements (n=229), age <20 years (n=809), BMI <25 or missing BMI data (n=838), and missing key biochemical indicators (n=9) (Figure 1). The research protocol got approval from the NCHS Institutional Review Board, and all subjects signed the informed consent forms. The datasets can be freely accessed on the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/).

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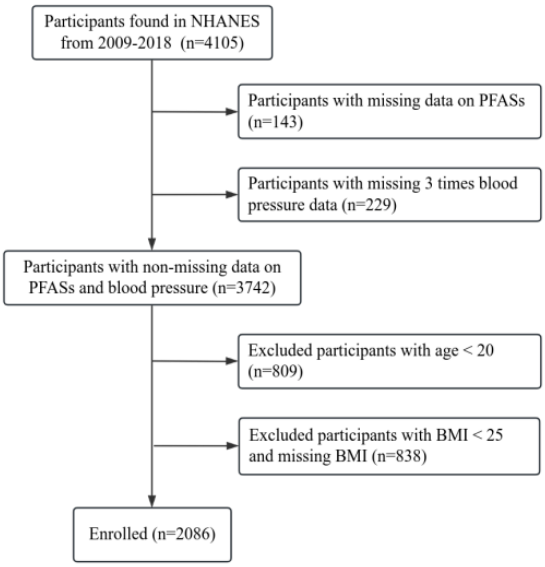


Figure 1: Subjects selection flowchart from NHANES 2009-2018; PFASs, Perfluoroalkyl and polyfluoroalkyl substances

2.2. Exposure variables

To reduce variability and bias from lipid adjustment, we analyzed serum PFAS concentrations as exposure biomarkers. We used online SPE-HPLC-TIS-MS/MS, a proven method for detecting PFAS in biological samples, for quantification. Detailed laboratory protocols can be found in the NHANES Laboratory Procedures Manual. Based on NHANES data from 2009 to 2018, this study selected seven PFAS compounds detected across five survey cycles as exposure factors: Perfluorohexane sulfonic acid (PFHxS), Perfluorononanoic acid (PFNA), 2-(N-methyl-perfluoroctane sulfonamido) acetic acid(Me-PFOSA-AcOH), Perfluoroundecanoic acid (PFUA), perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), Perfluorodecanoic acid (PFDA). All PFAS concentrations were treated as continuous variables. For data below the limit of detection (LOD), we used LOD/$\sqrt{2}$ to fill in the values.

2.3. Definition of outcomes

This study considered incident/prevalent hypertension as its core outcome variable. In the NHANES survey, professionally trained staff measured blood pressure following a standard protocol. Once the subjects had rested for five minutes in a tranquil environment, a mercury sphygmomanometer was used to take three blood pressure measurements, with a 30 - second gap between each reading. The final outcome was calculated as the mean of the three blood pressure measurements, and the systolic as well as diastolic blood pressure values were noted down separately. Standardized medical questionnaires were used in the questionnaire survey for various health problems. Participants were asked the question: "Has any doctor or medical professional ever informed you that you have hypertension or diagnosed you with hypertension?" Those who replied "yes" were categorized as having hypertension, whereas those who replied "no" were categorized as not having hypertension. In addition, subjects need to answer whether they had taken antihypertensive drugs in the past month. Hypertension is defined as fulfilling at least one of the following criteria: (1) Physician-diagnosed hypertension as self-reported; (2) The current use of antihypertensive medications; (3) A measured blood pressure of ≥140/90 mmHg.

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2.4. Covariates

Referring to previous research [22, 23], potential confounders included gender, age, race, education level, the family income to poverty ratio (PIR), marital status, alcohol consumption, smoking, vigorous work activity, diabetes and BMI. Standardized questionnaires and Mobile Examination Center (MEC) protocols were utilized by trained personnel to systematically collect and manage demographic characteristics, lifestyle factors, medical history, physical examination data, and laboratory test results. Demographic characteristics included gender, age, race, marital status, education level, and PIR which is computed as the proportion of reported annual family income to the federal poverty guideline specific to both the household's size and its state of residence during the survey year. Lifestyle includes drinking and physical activity. Smoking status was divided into three groups: current smokers, former smokers, and non-smokers. The classification was based on two factors: the total number of cigarettes smoked over their lifetime (more than 100 or not) and if they were still smoking now. Alcohol use is divided into drinkers and non-drinkers based on whether they have consumed 12 or more alcoholic beverages in any year or at least one alcoholic beverage per month. Physical activity was defined according to "Are there vigorous activities in your work that lead to a marked increase in your breathing and heart rate, such as continuously lifting heavy objects, engaging in excavation or construction work for at least 10 minutes?"(yes/no). We defined diabetes as self-reported diabetes diagnosis, a fasting blood glucose (FPG) level $\geq$ 7.0 mmol/L, a glycated hemoglobin level > 6.5%, or the use of oral hypoglycemic drugs or insulin. The body mass index (BMI) was determined as weight (kg) divided by the square of height (m^2). Based on the WHO definition of overweight and obesity, those with BMI $\geq$ 25 are defined as overweight people, and those with BMI $\geq$ 30 are defined as obese people.

2.5. Statistical analysis

We compared the baseline characteristics of hypertensive and non-hypertensive participants. Continuous variables were analyzed by t-tests, and categorical variables by χ^2 tests. For continuous variables with a normal distribution, we used mean ± standard deviation for representation. For non-normally distributed variables, we reported the median (interquartile range). Categorical variables were presented as frequency (percentage). Following NCHS guidelines, we applied MEC sampling weights to address NHANES' complex, multistage sampling design.[24]. We used weighted multivariate logistic regression to analyze the links between individual PFAS levels and hypertension prevalence. Three models were utilized. Model 1 was a basic, unadjusted model. Model 2 took age, race and sex into account. Model 3 made additionally adjustments for gender, age, race, education level, marital status, the family income to poverty ratio, alcohol use, smoking, vigorous work activity, BMI, history of diabetes. We made use of restricted cubic splines (RCS) featuring three knots in order to illustrate the potential nonlinear association of hypertension with PFASs within the overweight and obese populations. Wald χ^2 test was used to test the nonlinearity in the associations. Weighted quantile sum (WQS) regression analysis was implemented to evaluate the joint association of multiple PFASs exposures with hypertension. With the help of a weighted index, WQS regression assessed the total influence of all predictors on the outcome, where each predictor's influence was determined by its relative importance. The analysis involved randomly splitting the data, with 40% allocated to the estimation set (for training) and the remaining 60% assigned to the validation set. Bootstrap resampling (1000 iterations) facilitated the estimation of model parameters [25]. SPSS software (version 25) was used for multivariate logistic regression, and R software (version 4.4.2) was employed for statistical analysis of RCS model and WQS regression model. If the two-tailed P value was lower than 0.05, it was deemed to be statistically significant.

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3. Results

3.1. Baseline characteristics

Table 1 summarizes the features of the study population (n=2086), including 1196 hypertensive and 890 non-hypertensive subjects. Hypertensive patients were older, more frequently non-Hispanic, married, and diabetes prevalence than non-hypertensive individuals. Notable differences ($P < 0.05$) were also observed between group in PIR, smoking status, physical activity, and BMI.

Table 1: Characteristics of the study population

Variable	Overall (n=2086)	Non-hypertension (n=1196)	Hypertension (n=890)	χ^2	P value
Gender, n (%)				6.076	0.1163
Male	1023 (52.3)	621(54.4)	402 (48.9)		
Female	1063 (47.7)	575(45.6)	488 (51.1)		
Age, years, n (%)				261.923	< 0.001***
20-39	561 (29.3)	476 (40.1)	85 (12.1)		
40-64	993 (47.7)	556 (46.4)	437 (50.0)		
≥65	532 (22.9)	164 (13.5)	368 (37.9)		
Race, n (%)				38.461	< 0.001***
Mexican American	369 (9.7)	267 (12.5)	102 (5.2)		
Other Hispanic	243 (6.2)	148 (7.0)	95 (5.0)		
Non-Hispanic White	842 (66.0)	463 (63.7)	379 (69.8)		
Non-Hispanic Black	449 (11.9)	211 (10.5)	238 (14.1)		
Other Race	183 (6.1)	107 (6.2)	76 (5.9)		
Marital status, n (%)				88.877	< 0.001***
Married	1148 (58.9)	643 (56.8)	505 (62.4)		
Widowed	154 (5.6)	48 (3.1)	106 (9.4)		
Divorced	229 (10.6)	110 (9.5)	116 (9.4)		
Separated	60 (1.7)	36 (1.8)	24 (1.5)		
Never married	332 (15.2)	240 (19.4)	92 (8.4)		
Living with partner	166 (8.0)	119 (9.3)	47 (5.9)		
Education level, n (%)				5.129	0.1317
<High school	527 (15.9)	325 (17.3)	202 (13.8)		
High school	462 (24.2)	250 (23.8)	212 (24.9)		
>High school	1095 (59.8)	619 (58.9)	476 (61.4)		
PIR, n (%)				11.668	0.0503
≤1	406 (13.4)	251 (14.7)	155 (11.2)		
1-3	771 (31.9)	445 (33.4)	326 (29.6)		
>3	671 (46.1)	445 (43.7)	307 (49.8)		
unknown	238 (8.7)	136 (8.2)	102 (9.4)		
Alcohol use, n (%)				8.624	0.0666
≥12 drinks	1254 (65.8)	749 (67.2)	505 (63.6)		
<12 drinks	662 (27.5)	341 (25.4)	321 (30.9)		
unknown	170 (6.7)	106 (7.4)	64 (5.6)		
Diabetes, n (%)				158.009	< 0.001***
Yes	470 (17.2)	156 (9.0)	314 (30.3)		
No	1614 (82.7)	1039 (90.9)	575 (69.5)		

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Table 1: (continued)

unknown	2 (0.1)	1 (0.0)	1 (0.1)		
Smoking Status, n (%)				54.285	< 0.001***
Current Smokers	382 (17.0)	247 (19.6)	135 (12.9)		
Former Smokers	545 (27.5)	252 (22.1)	293 (36.3)		
Non-smokers	1157 (55.4)	692 (58.3)	462 (50.8)		
unknown		2 (0.0)			
Vigorous work activity, n (%)				18.782	< 0.001***
Yes	434 (23.2)	285 (26.4)	149 (18.2)		
No	1650 (76.7)	910 (73.6)	740 (81.8)		
unknown	0 (0.0)	1 (0.0)	1 (0.0)		
BMI, kg/m²	30.46 (27.70-34.90)	30.0 (27.3-34.2)	31.1 (28.2-36.3)		< 0.001***
BMI, kg/m², n (%)				15.86	< 0.01**
25-29.9	928 (46.3)	574 (49.8)	354 (40.8)		
≥30	1158 (53.7)	622 (50.2)	536 (59.2)		

***p < 0.001, **p < 0.01,*p < 0.05

3.2. Associations between hypertension and individual PFASs

The initial unadjusted logistic regression analysis (Model 1) indicated significant positive relationships between most PFAS compounds and hypertension, excluding PFUA and PFDA (Table 2). After adjusting for demographic and clinical covariates, PFOA remained significantly associated with hypertension, with a 10.1% increase in odds (95% CI: 1.019–1.189; P < 0.05). RCS model displayed that there was a nonlinear relationship between PFOA and hypertension (nonlinear P = 0.0167), and no significant nonlinear relationship was found for the other six PFASs (nonlinear p> 0.05) (Figure 2.).

Table 2: Multivariate logistic regression of serum PFASs and hypertension

Variable	Model 1			Model 2			Model 3		
	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
PFHxS	1.092	1.016-1.174	< 0.05*	1.054	0.988-1.125	0.1084	1.056	0.989-1.128	0.1038
Me-PFOSA-AcOH	2.029	1.104-3.730	< 0.05*	1.131	0.739-1.731	0.5651	1.193	0.791-1.799	0.3941
PFNA	1.172	1.056-1.301	< 0.01**	1.057	0.933-1.199	0.3780	1.096	0.951-1.263	0.2026
PFUA	1.588	0.972-2.595	0.0645	1.079	0.932-1.250	0.3045	1.163	0.772-1.751	0.4643
PFOA	1.142	1.075-1.212	< 0.001***	1.075	1.005-1.150	< 0.05*	1.101	1.019-1.189	< 0.05*
PFOS	1.029	1.014-1.045	< 0.001***	1.006	0.992-1.020	0.4037	1.008	0.992-1.024	0.3091
PFDA	1.251	0.904-1.733	0.1729	0.961	0.771-1.197	0.7170	1.019	0.795-1.307	0.8781

Model 1: unadjusted model
Model 2: adjusted for gender, age, race
Model 2: adjusted for gender, age, race, diabetes, marital status, BMI, alcohol use, smoking, education level, PIR, vigorous work activity
CI, confidence interval. OR, odd ratio; ***p < 0.001, **p < 0.01,*p < 0.05

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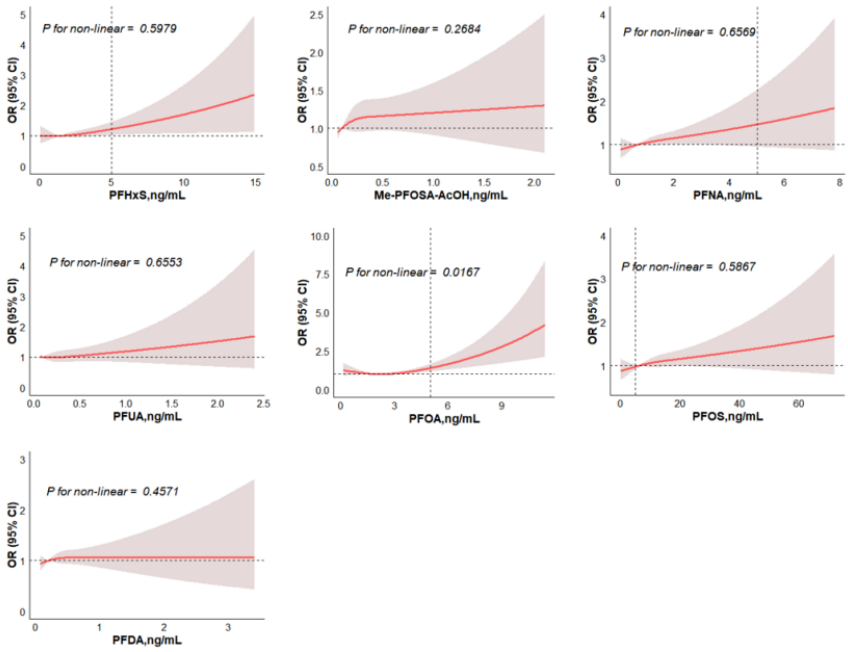


Figure 2: The link between hypertension and PFASs in overweight and obese populations was modeled using restricted cubic splines (RCS; 3 knots). Hazard ratios (HRs) were adjusted for gender, age, race, alcohol use, marital status, diabetes, smoking, BMI, education level, the family income to poverty ratio, and vigorous work activity. The p-values for nonlinearity were all > 0.05

3.3. Association between hypertension and PFASs in WQS model

We applied WQS regression model to assess the cumulative effect of PFASs co-exposure on hypertension. The adjusted model demonstrated a statistically significantly positive correlation (β = 0.245, 95% CI: 0.049–0.440, P = 0.014), suggesting that combined PFAS exposure elevates hypertension risk (Figure 3A). Component weight analysis (Figure 3B) revealed PFUA as the highest-weighted contributor, with Me-PFOSA-AcOH, PFNA, PFHxS, and PFOA also showing substantial contributions to the observed association

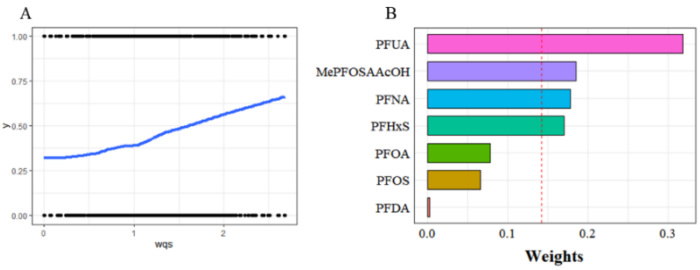


Figure 3: The association between hypertension and PFASs co-exposure using WQS regression. Figure A displays the overall mixture effect, while Figure B presents the weight contributions of single PFAS compounds. The red dashed line indicates the cut-off value (by default, it is equal to the reciprocal of the number of elements in the mixture). The model was adjusted for gender, age, education level, race, PIR, alcohol use,marital status, smoking, diabetes,vigorous work activity, and BMI. wqs, weighted quantile sum. MePFOSAAcOH, Me-PFOSA-AcOH

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4. Discussion

In this study, we selected overweight and obese people and adopted various statistical methods to thoroughly assess the impact of exposure to single and combined PFASs on hypertension. After accounting for potential confounders, this study showed that PFOA was independently related to hypertension prevalence. The association between PFOA and hypertension followed a nonlinear pattern. In the WQS model, PFAS mixtures exhibited a general positive trend with hypertension.

Few epidemiological studies have explored the link between PFASs and overweight/obesity - related hypertension, and the correlation between PFASs and hypertension remains debated. Research indicates that serum perfluorohexanoic acid (PFHxA) are notably linked to an increased incidence of hypertension[26], moreover, one study showed that an elevation in the overall concentration of PFASs in serum was correlated with a rise in the incidence of hypertension [27]. A meta-analysis indicated that there were significant associations between PFNA, PFOA, PFOS, PFHxA and hypertension[28]. However, another study showed that no meaningful association was found between PFNA, PFHxA and hypertension, and PFOS and PFOA had a positive connection with new onset hypertension in women [29]. Another study found that the link between plasma PFAS levels and blood pressure/hypertension was weak, and most showed no significant relationship [30]. The sample size of this study (n=957) is relatively large for epidemiological studies. The present study features several methodological strengths and limitations. With a substantial sample size of 2,086 participants, we achieved greater statistical power to identify potential associations. Our hypertension assessment protocol and the selection of PFASs analytes followed established methodologies used in comparable studies. However, temporal variations in exposure patterns during the investigation period could have affected the detection rates and concentrations of certain PFASs homologs. Compared to previous research, our analytical approach incorporated a more comprehensive set of covariates, though residual confounding remains possible due to differences in variable selection between studies. Notably, our work provides specific insights into the PFASs-hypertension relationship among overweight and obese populations. First, obesity is a recognized risk factor for hypertension, driven by mechanisms such as chronic inflammation, insulin resistance, and changes in renal sodium[31, 32]. Since PFASs chemicals are known to disrupt lipid metabolism[33], promote lipogenesis[34], and exacerbate oxidative stress[35, 36], their blood pressure regulating effects on obese individuals may be amplified. Second, PFASs compounds are lipophilic and preferentially accumulate in adipose tissue[6], resulting in higher body burden and longer half-life in obese individuals compared with lean populations[37]. This means that there is a possibility of stronger or altered correlation between PFASs and hypertension in this population.

In addition, if the effects are concentrated in metabolically susceptible individuals, previous studies of the general population may mask important heterogeneity. Our population-specific analysis helps to fill this gap and clarify whether the association of PFASs with hypertension varies according to obesity status, which is a key question. Future studies should explore whether weight loss interventions can reduce the cardiovascular risk associated with PFASs in these susceptible populations.

Notably, our study addresses a critical research gap by specifically examining the joint actions of PFAS mixtures on hypertension hazard in overweight and obese populations, thereby advancing understanding of PFAS-related health risks in this vulnerable subgroup. Although a large number of studies have investigated single PFASs compounds, this approach failed to take into account the real exposure scenarios where multiple PFASs coexist and may interact. Our analysis adopted an advanced statistical method (WQS regression) to explain these complex exposure profiles, and the findings demonstrated that PFASs mixture was associated with a higher risk of hypertension than any individual compound (mixture β: 0.245; 95% CI: 0.049, 0.440; P = 0.0141). It is worth noting that

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PFUA, Me-PFOSA-AcOH and PFNA are the main contributors to the observed effects, probably due to their strong binding affinity with key biological targets. These findings are consistent with increasing evidence that PFASs mixtures may synergize through common pathways such as oxidative stress induction and inflammatory response amplification. Importantly, our results suggest that the current risk assessment framework, which mainly evaluates single compounds, may greatly underestimate the cardiovascular risk of overweight / obese people. Future studies should incorporate mixed analysis to better characterize cumulative exposure effects, and regulatory policies may need to consider group based or overall exposure limits to adequately protect this generation of metabolic susceptible subgroups. Experimental validation of these interactions using co-exposure models will further strengthen the biological plausibility of our epidemiological findings.

Although this study provides important proof of the relationship between PFASs and hypertension in overweight/obese people, it should also be acknowledged that there are some limitations. First, as an observational study, this research cannot establish causality between PFASs exposure and hypertension. Second, although serum PFASs concentrations are used as biomarkers of exposure, they may not fully capture individual exposure levels due to the lack of an ideal method for measuring lipophilic chemicals, which may introduce measurement errors. Third, although multiple confounders were adjusted, residual confounders of unmeasured factors (such as dietary patterns, environmental co-exposure) may persist. In addition, the toxicological mechanism between PFASs and hypertension is still not completely clear in animal and human studies, and further experimental studies are needed. Finally, because our study population is composed of American adults, whether the results can be applied to other ethnic groups or people with different exposure backgrounds needs further investigation. These limitations underscore the necessity for future longitudinal investigations incorporating more precise exposure assessments, mechanistic analyses, and diverse population cohorts to validate and expand upon our findings.

5. Conclusion

PFAS exposure was significantly associated with increased hypertension prevalence among overweight/obese individuals, highlighting the need for exposure prevention strategies. Additional studies should confirm these findings and investigate underlying mechanisms.

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