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Association Between Perfiluoroalkyl and Polyfluoroalkyl (PFAS) Substances Mixture Exposure and Diabetes in U.S. Adults: Results from NHANES 2015-2018

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Abstract. Perfluoroalkyl and polyfluoroalkyl substances (PFAS), recognized as endocrine-disrupting chemicals, persist in the environment and pose significant health risks. Their association with a wide range of human diseases has been established. This study specifically seeks to investigate the correlation between PFAS exposure factors and diabetes. For our analysis, we utilized data from the National Health and Nutrition Survey (NHANES) spanning from 2015 to 2018. To assess the comprehensive effects of PFAS exposure factors on diabetes, we employed a logistic model, RCS regression analysis, and WQS regression.This study analyzed data from 221 individuals aged 18 years or older, among whom 37 had diabetes. After adjusting for potential confounders, significant associations were observed between diabetes and PFOSA (OR: 15.31, 95% CI: 1.78-130.93), PFUnDA (OR: 3.50, 95% CI: 1.25-11.82), PFOS (OR: 1.16, 95% CI: 1.08-1.28), and SmPFOS (OR: 1.44, 95% CI: 1.06-1.97). None of these associations exhibited a nonlinear correlation. Additionally, in the Weighted Quantile Sum Regression analysis (β: 1.5081, P=0.002), PFAS exposure demonstrated a positive correlation with diabetes prevalence.Our findings suggest a positive correlation between PFAS exposure and diabetes in the studied population. However, further research is necessary to confirm this association and elucidate its underlying mechanisms.

Keywords: Diabetes, perfluoroalky1 and polyfluoroalky1 substances, NHANES, logistic model, Weighted Quantile Sum Regression.

1. Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFASs) encompass a range of synthetic compounds, including perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), and others[1]. These compounds are widely utilized in various industries, such as food packaging, fire-fighting foam, and other industrial applications, due to their remarkable stability and durability[2]. However, the widespread use of PFAS and their resistance to biodegradation have led to their accumulation in the environment, including air, soil, surface water, and groundwater[3]. Epidemiological studies have linked PFAS exposure to an elevated risk of thyroid dysfunction, liver injury, and testicular cancer. Furthermore, PFAS can be transmitted through the placenta and breast milk, resulting in fetal growth

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retardation and a weakened immune response in children, thus posing a serious threat to human health[4, 5].

Diabetes, particularly type 2 diabetes, which accounts for over 90% of cases, is a prevalent chronic metabolic disease[6]. Its pathogenic factors are diverse, including genetics, lifestyle choices, and environmental exposures[7]. Recently, the issue of environmental pollution has gained increasing attention due to its potential impact on human health. Studies have demonstrated that pollutants like heavy metals and certain air contaminants can significantly affect human health, with diabetes being one of the outcomes closely associated with such exposures.

Among the various environmental pollutants, the relationship between PFAS—a new class of persistent organic pollutants—and diabetes remains highly debated. While some studies have suggested an association between PFAS exposure and diabetes, others have yielded conflicting results. Notably, gender differences and complex molecular mechanisms may play crucial roles in influencing the relationship between PFAS and diabetes[8, 9]. Currently, research often focuses on the effects of individual PFAS compounds, overlooking the potential combined effects of exposure to multiple PFAS. Given that PFAS typically occur as mixtures in the environment, assessing the impact of their co-exposure on diabetes is of utmost importance.

Therefore, this study aims to explore the potential link between PFAS and diabetes, specifically seeking to clarify the relationship between mixed PFAS exposures and diabetes through rigorous research methods. By doing so, we hope to provide novel insights and a stronger foundation for the prevention and management of diabetes.

2. Method

2.1. Study population

The research population of the data in this study all came from NHANES, NHANES (National Health and Nutrition Examination Survey) The National Health and Nutrition Survey (NCHS) is an important public health survey project conducted by the National Center for Health Statistics (NCHS) under the Centers for Disease Control and Prevention (CDC) of the United States. This project aims to assess the health and nutritional status of adults and children in the United States. NHANES database https://www.cdc.gov/nchs/nhanes) is a global public health and nutrition research one of the most important data resource, contains data related to health. The NHANES research protocol was approved by the NCHS Research Ethics Review Committee, and participants provided written informed consent at the time of enrollment. This study initially included 1,686 adult individuals from two consecutive periods from 2015 to 2018. A total of 86 subjects with missing PFAS data, 41 patients whose diabetes could not be determined, and 1,338 individuals with missing covariate data were excluded. Finally, 221 subjects were included in the research analysis.

Exposure variables

To avoid the additional variability and potential bias introduced by lipid adjustment, we use serum PFAS concentrations to reflect individual exposure levels. According to the serum data provided by NHANES, to ensure the reliability of the study, perfluorooctane sulfonamide (PFOSA), perfluorundecanoic acid (PFUnDA), n-perfluorooctane sulfonic acid (PFOS), and monomethyl perfluorooctane sulfonic acid (Sm-PFOS) were included as exposure factors in this study.

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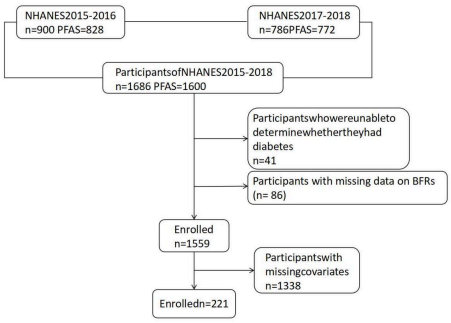


Figure 1: Flowchart of research participants.NHANES，National Health and Nutrition Inspection Survey; PFAS，Perfluoroalkyl and polyfluoroalkyl substances

2.2. Outcome definition

In this study, diabetes status was the primary outcome. We analyzed the NHANES database, focusing on participants' responses to the self-reported questionnaire item: "Has a doctor ever told you that you have diabetes?" Affirmative responses were taken as indications of a diabetes diagnosis, while negative answers suggested no such diagnosis. Additionally, the questionnaire inquired about the use of diabetes medications or insulin. We conducted morning examinations of fasting blood glucose, glycated hemoglobin, and the Oral Glucose Tolerance Test (OGTT) for all participants, excluding pregnant women. Multiple indicators were used to cross-verify diabetes status. The criteria for defining diabetes included any of the following: (1) Fasting blood glucose (GLU) $\geq$ 7.0 mmol/L; (2) 2-hour OGTT > 11.1 mmol/L; (3) Random blood glucose $\geq$ 11.1 mmol/L; (4) Glycated hemoglobin (HbA1c) > 6.5%; (5) Reported use of diabetes medications or insulin; (6) Self-reported diagnosis of diabetes by a medical professional.

2.3. Covariates

Drawing from prior literature, our study encompassed numerous potential variables (detailed in Table 1), such as age, gender, race, BMI, recent smoking habits, and alcohol consumption frequency. We gathered comprehensive data from the NHANES database, spanning demographics, diet, physical examinations, laboratory tests, and questionnaires. Specifically, we considered age groups (under and over 65), gender (male and female), and racial backgrounds (including Mexican American, other Hispanic, non-Hispanic white, non-Hispanic Black, and other races). BMI served as a proxy for body mass, categorized as normal (BMI < 25 kg/m^2), overweight (25 $\leq$ BMI < 30), and obese (BMI $\geq$ 30). Smoking habits were gauged by the average daily cigarette consumption over the past month, with participants grouped based on whether they smoked less than 10, between 10 and 20, or more than 20 cigarettes daily. Alcohol consumption frequency was assessed through a survey question inquiring about drinking habits over the past year, and participants were subsequently divided into two groups based on whether they consumed alcohol less than 5 times or 5 times or more in the past 12 months.

2.4. Statistical analysis

Statistical analysis involved the use of t-tests and $\chi 2$ tests to compare baseline characteristics between participants with and without diabetes. This comparison encompassed both continuous and categorical variables. Variables adhering to a normal distribution were presented as mean (standard

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deviation), while those deviating from normality were expressed as median (first and third quartiles). Categorical variables were represented by percentages. In accordance with NCHS guidelines, MEC weights were applied to reflect the complex, multi-level sampling design inherent in NHANES. The weighted model served as the foundation for multiple logistic regression analysis. To examine the relationship between individual PFAS and diabetes, multivariate logistic regression analysis was conducted, progressing through three models. Model 1 served as an initial exploration, while Model 2 incorporated adjustments for age, race, and gender. Model 3 further accounted for smoking, drinking, and BMI. Restricted cubic splines (RCS) with three knots facilitated visualization of potential nonlinear associations between diabetes and PFASs among people with type 2 diabetes. The nonlinearity of this correlation was tested using the Wald $\chi 2$ test. To assess the combined impact of PFASs mixture exposure on diabetes, quantile-weighted quantile-sum (WQS) regression analysis was employed. This approach utilizes a weighted index, where the relative importance of each predictor determines its overall effect on the outcome. For model parameter estimation, bootstrap resampling (1000 iterations) was performed, with a randomly generated estimation set comprising 50% of the training data and a validation set containing 50% of the data. All statistical analyses were conducted using R software (version 4.4.3), and a bilateral P-value less than 0.05 was deemed statistically significant. This study employed the RCS curve and logistic regression models to assess the impact of the principal variable and covariates on diabetes, comparing the effects of each variable. Weighted models were utilized for multivariate analysis.

3. Result

3.1. Baseline characteristics

Among the 221 participants, 37 were diabetic patients. Our data analysis revealed that diabetes is more prevalent among older participants compared to non-diabetic patients. Additionally, as the number of cigarettes smoked increases beyond 10, the likelihood of developing diabetes also rises. Non-Hispanic whites constituted the largest proportion of patients. Although the prevalence of diabetes was higher among obese individuals than non-obese ones, this difference was not statistically significant (Table 1).

DOI: 10.54254/2753-8818/2025.AU24407

Table 1: Characteristics of the study population

Variable	Non-diabetic(n=184)	Diabetes(n=37)	P value
Age, years			0.297
< 65, n (%)	166(91.2）	30(86.0)	
≥ 65,n (%)	18(8.8）	7(14.0）	
Gender, n (%)			0.712
Female	75(46.7)	15(50.8)	
Male	109(53.3)	22(49.2)	
Race, n (%)			0.059
Mexican American	13(5.6)	6(15.2)	
Other Hispanic	12(3.7)	3(4.8)	
Non-Hispanic White	75(64.8)	8(41.8)	
Non-Hispanic Black	60(15.5)	10(17.2)	
Other Race - Including Multi-Racial	24(10.4)	10(21.0)	
BMI, Kg/m^2			0.243
< 25 Kg/m^2, n (%)	62(34.8)	9(27.0)	
25-29.9 Kg/m^2, n (%)	54(31.6)	7(16.9)	
≥ 30 Kg/m^2, n (%)	68(33.5)	21(56.1)	
An average of a few cigarettes a day for the last 30 days			0.101
<10,n(%)	91(47.6)	17(35.4)	
10-20,n(%)	87(48.7)	17(49.9)	
>20,n(%)	6(3.6)	3(14.7)	
Frequency of drinking in the last 12 months			0.557
<5,n(%)	98(51.5)	19(58.1)	
≥5,n(%)	86(48.5)	18(41.9)	

The relationship between individuals with PFAS and diabetes Multivariate logistic regression analysis indicated a significant positive correlation between PFOS and diabetes in Model 1. After adjusting for all other covariates, we found that PFUnDA, PFOSA, and SmPFOS (95% CI: 1.25, 11.82; P = 0.018; 95% CI: 1.78, 130.93; P = 0.012; 95% CI: 1.06, 1.97; P = 0.020) were also significantly associated with diabetes. However, the RCS model demonstrated no nonlinear relationship between PFAS exposure and diabetes (Figure 2 and Table 2).

Table 2: Multivariable logistic regression analysis of PFASs with diabetes

Variable	Model 1			Model 2			Model 3		
	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
PFOSA	4.42	0.66-25.94	0.106	11.4	1.51-83.38	0.016	15.31	1.78-130.93	0.012
PFUnDA	2.29	0.87-6.98	0.097	2.50	0.91-7.47	0.062	3.50	1.25-11.82	0.018
PFOS	1.12	1.05-1.20	0.001	1.136	1.06-1.24	0.001	1.16	1.08-1.28	<0.001
SmPFOS	1.27	0.98-1.62	0.060	1.339	1.00-1.79	0.048	1.44	1.06-1.97	0.020

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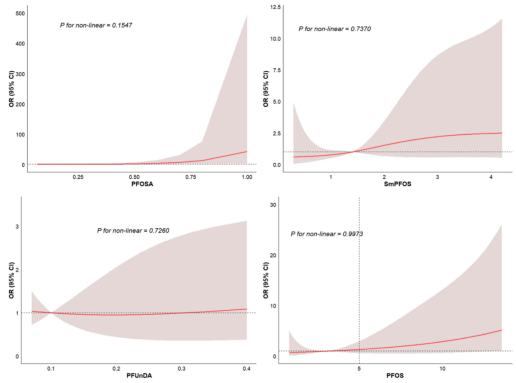


Figure 2: The association between Diabetes and PFASs in overweight and obese populations was modeled using restricted cubic splines (RCS; 3 knots). Hazard ratios (HRs) were adjusted for age, gender, race, alcohol use, smoking, BMI. The p-values for nonlinearity were all > 0.05

3.2. The association between PFAS exposure and diabetes in WQS

This study employs the Weighted Quantile Sum (WQS) regression model to investigate the correlation between PFAS and diabetes. Taking into account various potential confounders, the WQS analysis revealed a positive association between PFAS pollutants and the incidence of diabetes (β: 1.5081, P=0.002). The figure illustrates that PFUnDA has the greatest impact on the diabetes prevalence index, with PFOSA, PFOS, and SmPFOS following in that order(Figure 3).

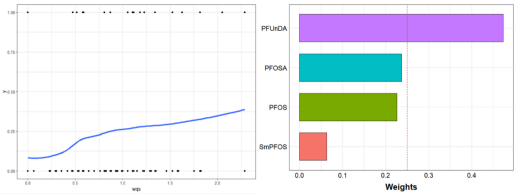


Figure 3: The relationship between PFAS exposure and diabetes was studied through the WQS model. (A) The combined impact of mixed exposure to PFAS. (B) Positive weights of each PFAS in diabetes. The red dotted line represents the cut-off value (by default, it is equal to the reciprocal of the number of elements in the mixture). This model was adjusted according to gender, age, race, alcohol consumption, smoking and BMI

4. Discussion

In our study, we utilized various statistical methods to thoroughly evaluate the effects of exposure to both individual and mixed PFAS on diabetes. After considering potential confounding factors, our findings suggest that PFUnDA, PFOSA, PFOS, and SmPFOS are all independently and positively linked to the occurrence of diabetes. Furthermore, the WQS model revealed an overall positive correlation between PFAS mixtures and diabetes. Epidemiological research on the PFAS-diabetes connection remains divisive. Sung Kyun Park and colleagues observed an association between PFAS exposure and an elevated risk of type 2 diabetes among women, although their study focused primarily on female subjects and did not extend to the general population[10].

Our approach to defining and diagnosing diabetes aligns with numerous previous studies, as do the specific PFASs we investigated. Variations in study populations, time periods, and covariate shifts may account for discrepancies in findings across different studies. Despite these

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inconsistencies, a majority of epidemiological research supports an association between PFAS exposure and insulin resistance as well as abnormal blood glucose levels[9].

Furthermore, our research has contributed to a deeper understanding of health risks associated with PFAS mixtures in relation to diabetes, addressing a critical gap in the existing literature. While numerous studies have focused on individual PFAS compounds, they often overlook the reality of multiple PFAS co-exposure and potential interactions. To address this, our analysis utilized advanced statistical techniques, specifically Weighted Quantile Sum (WQS) regression, to elucidate these complex exposure patterns. Our findings revealed that PFAS mixtures are linked to a heightened risk of diabetes compared to any single compound (Mixture β: 1.5081, P=0.002). Notably, PFUnDA emerged as a primary contributor to these effects, potentially due to its strong binding affinity for crucial biological targets. These results align with emerging evidence suggesting that PFAS mixtures may exhibit synergistic effects through shared mechanisms, such as inducing oxidative stress and amplifying inflammatory responses. Crucially, our study implies that the current risk assessment paradigm, which primarily considers individual compounds, may underestimate the cardiovascular risk in healthy populations. Future research should incorporate mixed analyses to provide a more comprehensive understanding of cumulative exposure effects. Experimental validation of these interactions using common exposure models will further bolster the biological plausibility of our epidemiological insights.

The specific mechanisms underlying the impact of PFAS exposure on diabetes remain elusive, but several hypotheses are worthy of consideration. Firstly, PFAS, particularly PFOS, may activate peroxisome proliferator-activated receptors (PPARα/γ), disrupting fatty acid metabolism, leading to dyslipidemia, reduced insulin sensitivity, and obesity. Our data analysis reveals a higher prevalence of diabetes among overweight individuals[9]. Biological research suggests that PFAS may alter gut microbiota composition and decrease the production of short-chain fatty acids (SCFAs) crucial for maintaining glucose homeostasis, potentially triggering diabetes when glucose levels exceed normal[11, 12]. Hence, PFAS pollutants may influence diabetes through disruptions in fatty acid metabolism and glucose homeostasis. Epidemiological studies further indicate that PFOS exposure in middle-aged women is associated with a 20-30% increased risk of diabetes[10], highlighting a significant association between PFAS pollutants and diabetes prevalence in this population. Previous research has also found that PFAS exposure can compete with thyroid hormone transporters, leading to decreased T3/T4 levels, and may influence the delay of testosterone level decline in males[13, 14]. Clinical trial results suggest that PFOS may elevate the risk of rheumatoid arthritis[15]. In summary, it is postulated that PFAS pollutants may affect diabetes through multiple pathways, including obesity, glucose imbalances, thyroid hormone disruptions, endocrine disturbances, and arthritis diseases. However, comprehensive analysis reveals limited evidence directly linking PFAS to diabetes. The ubiquitous presence of PFAS poses a significant health challenge, and further experimental studies are urgently needed to confirm and investigate the precise association and triggering mechanisms between PFAS exposure and diabetes.

Although this study offers valuable evidence linking PFASs to diabetes in adults, it is important to acknowledge several limitations. The sample size of 221 adults, for instance, is relatively small in the context of epidemiological research, as numerous cases were excluded during the study period due to non-compliance with the inclusion criteria. Additionally, the observational design of the study precludes the establishment of a causal relationship between PFAS and diabetes. While multiple confounding factors were adjusted for, the possibility of residual confounding from unmeasured variables, such as dietary habits and environmental co-exposures, remains. Moreover, the toxicological mechanism underlying the association between PFASs and diabetes is not yet fully

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elucidated in animal and human studies, underscoring the need for further experimental research. Lastly, as our study population consisted of American adults, additional research is necessary to ascertain the generalizability of our findings to other racial groups or those with differing exposure backgrounds. These limitations underscore the importance of future longitudinal studies that incorporate more precise exposure assessments, mechanistic investigations, and diverse populations to validate and extend our findings.

5. Conclusion

In conclusion, our analysis reveals a significant positive correlation between PFAS exposure and diabetes in American adults. Further research is warranted to verify this observation.

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