Eco-Environment & Health 5 (2026) 100210

Contents lists available at ScienceDirect

Eco-Environment & Health

journal homepage: www.journals.elsevier.com/eco-environment-and-health

Original Research Article

Serum perfluoroalkyl and polyfluoroalkyl substances and the risk of cardiometabolic diseases: Unraveling the mediating role of inflammatory markers

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ARTICLE INFO

Keywords:
Perfluoroalkyl and polyfluoroalkyl substances (PFASs)
Cardiometabolic diseases (CMDs)
Inflammatory markers
High-sensitivity C-Reactive protein (hs-CRP)
Serum ferritin (SF)

ABSTRACT

The persistence and biotoxicity of perfluoroalkyl and polyfluoroalkyl substances (PFASs) have raised concerns about cardiometabolic diseases (CMDs). Inflammation is thought to underlie the pathology of various CMDs. We aimed to comprehensively assess the risk of CMDs associated with PFASs and quantify the mediating effects of two kinds of inflammatory markers. Nine PFASs, a direct marker (high-sensitivity C-reactive protein [hs-CRP]), and an indirect marker (serum ferritin [SF]) were analyzed. A total of 12 CMDs of five types were defined based on 15 cardiometabolic biomarkers. The PFAS mixture had significant adverse effects on hypercholesterolemia (HC; OR = 1.20, 95% CI: 1.03–1.39), high low-density lipoprotein cholesterol (high LDL-C; OR = 1.13, 95% CI: 1.01–1.30), hypertension (OR = 1.10, 95% CI: 1.03–1.19), and hyperuricemia (OR = 1.31, 95% CI: 1.16–1.48) in the quantile-based g-computation (QGC) model, with PFNA and PFTrDA contributing the most. PFHxS was found to significantly impact all five types of CMDs simultaneously. The exposure-response analysis exhibited complex nonlinear patterns, with significant heterogeneity across diseases. Both inflammatory markers significantly mediated the effects of multiple PFASs on CMDs, with SF contributing a higher proportion of the mediating effects for obesity, dyslipidemia, and hyperuricemia. The highest mediation proportion reached 85.78% for abdominal obesity (FDR = 0.024). These results suggest that inflammation may serve as a key pathological mechanism linking PFAS exposure to CMDs, highlighting the potential value of SF as an iron status and indirect inflammatory marker in assessing PFAS-related cardiometabolic health risks.

1. Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFASs) have emerged as global environmental pollutants due to their widespread use in industrial applications and consumer products [1–3]. Their strong carbon–fluorine bonds confer exceptional chemical stability, resulting in persistent environmental contamination and bioaccumulation in human tissues, with biological half-lives spanning decades [4]. As a prominent class of endocrine-disrupting chemicals (EDCs) [5], PFASs have drawn increasing attention for their capacity to disrupt metabolic regulation.

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https://doi.org/10.1016/j.eehl.2025.100210
Received 16 April 2025; Received in revised form 10 October 2025; Accepted 15 December 2025
Available online 24 December 2025
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Through mechanisms such as fatty acid mimicking, nuclear receptor binding, and activation of various biological pathways, PFASs may contribute to the development of cardiometabolic diseases (CMDs), including obesity, dysglycemia, dyslipidemia, hypertension, and hyperuricemia [6]. Emerging evidence has examined the association between PFAS exposure and CMD risk [7–15]. However, existing epidemiological findings remain inconsistent. For instance, different analyses of data from the National Health and Nutrition Examination Survey (NHANES) reported opposite associations between PFAS exposure and obesity risk, reflecting the complexity and heterogeneity of PFAS-related health effects.

Despite rising concerns, no large-scale studies have systematically examined the association between PFAS exposure and CMDs in the general Chinese population. Existing research has been limited by small sample sizes, examination of only a few PFAS compounds, and a focus solely on specific populations (e.g., only males) [16–18]. Moreover, because individuals are typically exposed to multiple PFAS congeners concurrently, it is critical to assess the combined or interactive effects of PFAS mixtures on CMDs. Nevertheless, few studies have adopted mixture-based approaches or addressed the intricate exposure-response relationships involved. A systematic investigation is thus urgently needed to clarify which cardiometabolic outcomes are most affected by PFASs, identify the key PFAS congeners driving these associations, and provide robust evidence to inform targeted regulatory actions. Furthermore, the complexity of environmental mixed exposures and health outcomes demands the use of advanced statistical models capable of capturing joint and interactive effects, thereby enhancing the accuracy and relevance of exposure-health assessments in real-world settings.

Effectively assessing cardiometabolic health remains a significant challenge, necessitating the identification of alternative biomarkers to reliably evaluate the risk of various CMDs. Inflammation is a pivotal pathological mechanism in chronic diseases. Numerous inflammatory markers have been widely adopted in clinical practice. Among these, high-sensitivity C-reactive protein (hs-CRP) is a direct inflammatory marker that has been established as a predictor of initial cardiovascular events [19]. A cross-sectional study demonstrated that young participants stratified into a high-inflammatory-risk group based on hs-CRP levels exhibited significantly higher prevalence rates of obesity, hypertension, and dyslipidemia [20]. Additionally, serum ferritin (SF) is well recognized in clinical practice as a biomarker for assessing iron status, but it also serves as an indirect indicator of inflammation [21]. An epidemiological study conducted in a Chinese population revealed that elevated SF levels significantly increased the prevalence of hyperuricemia [22]. However, the mediating role of inflammatory markers in the association between PFASs and CMDs remains unclear.

In this study, we conducted a systematic investigation of the association between PFASs and five types of CMDs using a nationally representative sample from the China Health and Nutrition Survey (CHNS) to identify PFAS-related CMDs and key PFAS homologs, and clarify the exposure association patterns between PFASs and CMDs. Additionally, one direct inflammatory marker (hs-CRP) and one indirect marker (SF) were used to quantify the mediating effects in the relationships between PFASs and cardiometabolic outcomes.

2. Materials and methods

2.1. Study population

CHNS is an ongoing population-based cohort study covering residents from 15 provinces in China [23,24]. For the 2015 survey, 8100 individuals were recruited for PFAS and cardiometabolic measurement (limited access data). After excluding 282 underage participants and 34 self-reported cardiovascular disease (CVD) patients identified through the community-based questionnaire, subsequent analyses were conducted on 7784 participants (age range: 18–94; age < 65, n = 6101; age ≥ 65, n = 1683; Fig. S1). Informed consent was obtained from all participants. This survey was approved by the ethics committee of the National Institute for Nutrition and Health, Chinese Center for Disease Control and Prevention (No. 201524).

According to our study purposes, two study populations were identified in the two-phase cross-sectional analysis (Fig. S1). The first population (association analysis), comprising 6697 to 7581 participants who have complete PFAS exposure and cardiometabolic measurement data, was used to explore the association between PFASs and CMDs. These participants were divided into five subgroups based on the five types of CMDs: obesity, dysglycemia, dyslipidemia, hypertension, and hyperuricemia. The second population (mediation analysis), comprising 6176 to 6938 participants after further excluding participants with missing data on hs-CRP and SF across the five subgroups, was used to explore the potential mediating role of inflammatory markers in the relationship between PFASs and CMDs.

2.2. Serum PFAS measurement

Participants were required to fast overnight before providing 12 mL of fasting blood, distributed across three 4 mL tubes, and subsequently stored at −86 °C for further study. The extraction, measurement, and quality control methods for serum samples have been described elsewhere [25]. Briefly, serum PFAS concentrations were measured using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS). PFASs with detection rates below 50% were excluded, and concentrations below the detection limit were replaced with a limit of quantification divided by the square root of two. Finally, nine PFASs, including perfluorooctanoic acid (PFOA), perfluorodecanoic acid (PFDA), perfluorononanoic acid (PFNA), perfluoroundecanoic acid (PFUnDA), perfluorohexanesulfonate (PFHxS), perfluoro-n-pentanoic acid (PFPeA), perfluorooctanesulfonate (PFOS), perfluorododecanoic acid (PFDoDA), and perfluorotridecanoic acid (PFTrDA), were included in the analysis.

2.3. Cardiometabolic outcomes and inflammatory markers

The primary outcomes of this study included 12 CMDs: general obesity, abdominal obesity, waist-height ratio (WHtR) obesity, body fat percentage (BFP) obesity, type 2 diabetes (T2DM), insulin resistance (IR), hypertriglyceridemia (HTG), hypercholesterolemia (HC), low high-density lipoprotein cholesterol (low HDL-C), high low-density lipoprotein cholesterol (high LDL-C), hypertension, and hyperuricemia, which were categorized into five study subgroups (Table 1). The 15 cardiometabolic biomarkers, obtained through anthropometric methods and standard biochemical analyses (Supplementary Methods 1.2), were used to define these 12 diseases. The inflammatory markers, including direct marker (hs-CRP) and indirect marker (SF), were also measured using standard biochemical analyses. All samples were subjected to strict quality control at the Beijing National Center Laboratory.

2.4. Covariates

The adjusted covariates were as depicted in the directed acyclic graph (Fig. S2), including age (continuous), sex (male or female), residence (urban or rural), education (junior high school and below, technical school or high school, and university and above), annual household income (<30,000, 30,000–75,000, 75,000–120,000, and ≥120,000 yuan), tobacco use (no or yes), alcohol use (no or yes), physical activity (continuous), total daily energy intake (continuous), total daily fat intake (continuous), total daily cholesterol intake (continuous). Models for outcomes except obesity were further adjusted for body mass index (BMI, continuous), and models for hyperuricemia were further adjusted for BMI and serum creatinine (continuous). Detailed information regarding the collection and definition of covariates is provided in Supplementary Methods 1.3.

Table 1
The definition of 12 cardiometabolic diseases (CMDs) according to 15 cardiometabolic biomarkers for the five study subgroups.

	CMDs	Definition
Obesity study (n = 7396)	General obesity	Participants with a BMI ≥ 28 kg/m^2.
	Abdominal obesity	Participants with a WC ≥ 90 cm for males, and ≥ 85 cm for females.
	WHtR obesity	Participants with a WHtR > 0.5.
	BFP obesity	Participants with a BFP ≥ 25 cm for males, and ≥ 35 cm for females.
Dysglycemia study (n = 6697)	T2DM	Participants with FBG ≥ 7.0 mmol/L or HbA1c ≥ 6.5%, or those who report a diabetes diagnosis or are taking antihyperglycemic medications.
	IR	Participants with a HOMA-IR ≥ 2.69.
Dyslipidemia study (n = 7439)	HTG	Participants with TG ≥ 2.3 mmol/L.
	HC	Participants with TC ≥ 6.2 mmol/L.
	Low HDL-C	Participants with HDL-C < 1.0 mmol/L.
	High LDL-C	Participants with LDL-C ≥ 4.1 mmol/L.
Hypertension study (n = 7541)	Hypertension	Participants with SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, or those who report a hypertension diagnosis or are taking antihypertensive medications.
Hyperuricemia study (n = 7581)	Hyperuricemia	Participants with SUA levels ≥ 420 μmol/L for males, and ≥ 360 μmol/L for females.

BFP, body fat percentage; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; FINS, fasting insulin; HbA1c, glycated hemoglobin; HC, hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; High LDL-C, high low-density lipoprotein cholesterol; HOMA-IR, the homeostasis model assessment of insulin resistance; HTG, hypertriglyceridemia; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; Low HDL-C, low high-density lipoprotein cholesterols; SBP, systolic blood pressure; SUA, serum uric acid; T2DM, type 2 diabetes; TC, total cholesterol; TG, triglycerides; WC, waist circumference; WHtR, waist-height ratio.

2.5. Statistical analysis

2.5.1. Statistical description

The demographic characteristics, inflammatory and cardiometabolic measurements, and PFAS concentrations were described with mean (standard deviations, SD), median (interquartile ranges, IQR), n (%), and tested with *t*-test, Wilcoxon rank sum test, and the Chi-square test as appropriate. Spearman correlation analysis was used to explore the potential relationships among nine PFASs. All PFASs, hs-CRP, triglycerides (TG), insulin, and several covariates (physical activity, total energy intake, total fat intake, and total cholesterol intake) were natural logarithm (ln) transformed to minimize the impact of outliers. Additionally, all nine PFASs and 15 cardiometabolic biomarkers were standardized (converted to *z*-scores) to facilitate the comparison of model coefficients across parameters with different units of measurement. We assumed that the missing covariate data were missing at random and employed random forest multiple imputation to impute the missing values.

2.5.2. Mixed-exposure association analysis

The quantile-based g-computation (QGC) model was employed to evaluate the combined effects of nine PFASs on cardiometabolic outcomes [26], which is a novel environmental mixture analysis method integrating weighted quantile sum (WQS) regression and g-computation approaches. The WQS model combines highly correlated exposure variables into a weighted additive index through bootstrap sampling of training datasets (random subsets), with mixture effects estimated using validation sets [27]. This yields two primary outputs: 1) a WQS index representing the exposure mixture, incorporated into generalized linear models (GLM) with covariates to estimate health outcome associations, and 2) component weights (summing to one) identifying important mixture constituents via maximum likelihood estimation. The WQS formulation is:

$$g(\mu) = \beta_0 + \beta_1 \left(\sum_{i=1}^{c} w_i q_i \right) + z\varphi$$

$$\mathrm{WQS} = \sum_{i=1}^{c} w_i q_i$$

Where, c exposure components are converted to quartiles ($q_i = 0,1,2,3$), w_i denotes component weights, β_0 is the intercept, β_1 represents the regression coefficient for the weighted quartile sum (interpretable as outcome change per quartile increase in mixture exposure), z is the covariate matrix, and φ contains covariate coefficients. The link function $g(\cdot)$ accommodates various GLM specifications. The WQS model mitigates overfitting and multicollinearity by aggregating mixture effects, but it has three main limitations: the assumption of linear additive effects, which can lead to false positives in high-dimensional exposures; the restriction of unidirectional effects; and the need for predefined effect directionality.

To address these limitations, researchers developed the QGC model, which overcomes key constraints of the WQS model by permitting heterogeneous effect directions across exposure components while accommodating nonlinear and non-additive effects for both individual and mixture exposures, thereby providing more robust estimates of complex health effects associated with multi-pollutant exposures. In the QGC framework, the coefficient β_1 corresponds to the g-computation estimator derived from marginal structural models, quantifying the change in outcomes associated with each quartile increase in exposure levels. The analytical procedure follows three key steps parallel to WQS regression: 1) quantile transformation of exposure variables, 2) generalized linear model specification, and 3) estimation of component weights. Notably, QGC eliminates the restrictive directional homogeneity assumption by allowing the sum of positive and negative weights to each equal one. To enhance statistical reliability, both QGC and WQS models (see Section 2.5.6) implemented in this study employed an extensive bootstrap procedure with $B = 10{,}000$ iterations.

2.5.3. Single-exposure association analysis

Logistic regression and linear regression models were performed to examine the relationships between nine PFASs and 12 CMDs, as well as 15 cardiometabolic biomarkers. To account for potential nonlinear exposure-response relationships, we analyzed the exposure variables after quartile transformation. Each PFAS concentration was categorized into four groups: Quartile 1 (Q1), Quartile 2 (Q2), Quartile 3 (Q3), and Quartile 4 (Q4), with odds ratios (OR) and 95% confidence intervals (CI) calculated relative to the Q1 reference group.

2.5.4. Exposure-response analysis

We employed two analytical strategies to examine the exposure-response relationship: the Bayesian Kernel Machine Regression (BKMR) model for mixed exposures and the restricted cubic splines (RCS) model for single exposures. The BKMR model integrates Bayesian theory with statistical methodology and estimates high-dimensional exposure-response functions through iterative kernel-based techniques

[28]. Its fundamental mathematical expression is as follows:

$$Y_i = h(z_i) + x_i^T \beta + \epsilon_i$$

Here, Y_i denotes the health outcome, $z_i = (z_{i1}, \ldots, z_{iM})^T$ represents a vector of M exposure variables, and x_i is the matrix of potential covariates (assuming a linear relationship between covariates and outcomes). The term β denotes the regression coefficients, and $h(\cdot)$ is the high-dimensional exposure-response function to be estimated, which may incorporate nonlinearities or interactions among the exposure variables. The core assumption is that individuals with similar exposure characteristics may share similar exposure-response functions $h(\cdot)$. To ensure adequate model fitting, this study implemented 50,000 iterations using a Markov Chain Monte Carlo (MCMC) sampler.

Additionally, the RCS model was used to characterize the exposure-response relationship between individual PFASs and health outcomes. The number of knots was set to four, positioned at the 5th, 35th, 65th, and 95th percentiles of the ln concentrations of the nine PFASs, with the median concentration serving as the reference value.

2.5.5. Mediation analysis

Mediation analysis is a widely used statistical approach to investigate the underlying mechanisms through which an independent variable affects a dependent variable. To explore the pathways linking PFASs and CMDs, we performed mediation analysis to assess the potential mediating role of inflammatory markers. First, the associations among PFASs (X), CMDs (Y), and the inflammatory markers (M) were tested, including X–Y, X–M, and M–Y relationships [29]. Subsequently, we added interaction terms of PFAS*hs-CRP and PFAS*SF to the model to examine potential interactions influencing the mediation pathways [29]. Finally, a non-parametric bootstrap method with 1000 resamples was employed to estimate the total effect (TE), natural direct effect (NDE), natural indirect effect (NIE), and the mediation proportion.

2.5.6. Sensitivity analysis

To ensure the robustness of our findings, several sensitivity analyses were conducted. Firstly, PFAS concentrations were grouped by quartiles. The linear regression model was used to analyze the association between the concentration groups and cardiometabolic biomarkers, with the Q1 group as the reference. Secondly, considering that PFASs have a long biological half-life, there may be a bioaccumulation effect in the human body. The linear sum concentration of nine PFASs (sum PFAS) was calculated, and the GLM was fitted to analyze the association between the sum PFAS and cardiometabolic outcomes. Thirdly, the WQS model was used to verify the health effects of PFAS mixtures on cardiometabolic outcomes. As mentioned earlier (see Section 2.5.2), 40% of the dataset was randomly assigned to the training set, and 60% was assigned to the validation set. The directionality hypothesis for the WQS model was determined based on the association direction of PFAS mixtures with outcomes in the QGC model. Fourthly, considering the impact of dietary factors on PFASs and CMDs, we further adjusted for fish and meat intake in the analytical models. Fifth, serum creatinine, as an indicator of kidney function, was adjusted for in all models. Sixth, acknowledging the influence of liver disease on CMDs, we further adjusted for the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD, the specific definition is detailed in Supplementary Methods 1.3). Seventh, dietary iron intake was adjusted for in the mediation analysis models concerning serum ferritin to account for its potential influence on serum ferritin levels. Eighth, we conducted age and sex stratification of the study participants to explore the heterogeneity in the health effects of PFASs.

More details on statistical analysis are described in the Supplementary Materials. All statistical analyses were conducted using R (version 4.3.1). QGC, mediation analysis, WQS, and BKMR were implemented using the qgcomp, mediation, gWQS, and bkmr packages, respectively. All reported results underwent false discovery rate (FDR) correction to account for multiple testing. A two-sided P value or FDR < 0.05 was considered statistically significant.

Table 2
Characteristics of the adult participants, China Health and Nutrition Survey (CHNS) 2015.

	Total (n = 7818)
Age, years	53.80 (13.51)
Female, n (%)	4406 (56.4)
Rural, n (%)	5009 (64.1)
Education, n (%)	
Junior high school and below	3871 (49.5)
Technical school or high school	1625 (20.8)
University and above	2322 (29.7)
Average annual household income, yuan (%)	
<30,000	2862 (36.6)
30,000–75,000	2674 (34.2)
75,000–120,000	1085 (13.9)
≥120,000	1197 (15.3)
Tobacco user, n (%)	1968 (25.2)
Alcohol user, n (%)	2160 (27.6)
Physical activity, MET h/week	112.34 [49.52, 213.21]
Total energy intake, kcal	1911.38 [1521.29, 2415.05]
Total fat intake, g	72.52 [51.03, 101.38]
Total cholesterol intake, mg	213.56 [109.64, 349.14]
Serum creatinine, μmol/L[e]	85.94 (19.69)
BMI, kg/m^2 [a]	24.25 (3.48)
WC, cm[a]	84.68 (10.31)
WHtR	0.53 (0.06)
BFP, %	29.16 (8.78)
FBG, mmol/L[b]	5.23 (0.76)
HbA1c, mg/dL[b]	5.56 (0.50)
FINS, μU/mL[b]	5.80 [4.10, 8.30]
HOMA-IR	1.33 [0.91, 1.98]
TG, mmol/L[c]	1.22 [0.82, 1.80]
TC, mmol/L[c]	4.93 (1.00)
HDL-C, mmol/L[c]	1.28 (0.33)
LDL-C, mmol/L[c]	3.14 (0.89)
SBP, mmHg[d]	128.42 (18.61)
DBP, mmHg[d]	81.34 (10.85)
SUA, μmol/L[e]	289.80 (85.52)

[a] Obesity study (n = 7417).
[b] Dysglycemia study (n = 6728).
[c] Dyslipidemia study (n = 7434).
[d] Hypertension study (n = 7563).
[e] Hyperuricemia study (n = 7615).
Data are presented as mean (SD) for normally distributed variables, median [P25, P75] for skewed variables, and number (percentage) for categorical variables.

3. Results

3.1. Participant characteristics and PFAS concentrations

A total of 7784 adult participants aged 18 years or older were included in this study, with a mean age of 53.8 years (Table 2). The proportion of women was slightly higher than that of men (56.4% vs 43.6%). A higher proportion of participants were rural residents (64.2%) and had an education level of junior high school and below (49.6%). The average annual household income followed a right-skewed distribution, with a higher proportion of low-income participants (36.6%).

In the first-phase analysis (association analysis), after excluding cases with missing data on PFAS and cardiometabolic biomarkers in the corresponding study subgroups, 7396 participants were included in the obesity study, 6697 in the dysglycemia study, 7439 in the dyslipidemia study, 7541 in the hypertension study, and 7581 in the hyperuricemia study. The prevalence of CMDs in each study subgroup was shown in Tables S1–S12. In the second-phase analysis (mediation analysis), participants with missing inflammatory marker data were further excluded within each study subgroup. Consequently, 6775 participants were

included in the obesity study, 6176 in the dysglycemia study, 6809 in the dyslipidemia study, 6902 in the hypertension study, and 6938 in the hyperuricemia study (Fig. S1).

The detection rates and concentration distributions of the nine PFASs are presented in Table S13. All PFASs exhibited right-skewed distributions, with PFOA showing the highest detection rate and being detected in 100% of all populations. PFOS had the highest concentration, with geometric means ranging from 4.845 to 4.946 ng/mL in the five subgroups. Strong correlation coefficients were observed among eight PFASs, ranging from 0.45 to 0.94, while PFPeA showed a notably lower correlation with other PFASs (Fig. S3).

3.2. The results of the mixed-exposure analysis

3.2.1. Association between PFAS exposure and CMDs in the mixed-exposure analysis

The QGC model indicated that exposure to PFAS mixture may affect the risk of various CMDs, with dyslipidemia, hypertension, and hyperuricemia being the most significant (Fig. 1A). In the dyslipidemia study, a quartile increase in PFAS mixture was associated with a 20% increase in the risk of HC (OR = 1.20, 95% CI: 1.03–1.39) and a 13% increase in high LDL-C (OR = 1.13, 95% CI: 1.01–1.30). In the hypertension study, a quartile increase in PFAS mixture was associated with a 10% increase in the risk of hypertension (OR = 1.10, 95% CI: 1.03–1.19). In the hyperuricemia study, a quartile increase in PFAS mixture was associated with a 31% increase in the risk of hyperuricemia (OR = 1.31, 95% CI: 1.16–1.48). Within this mixture, PFTrDA contributed most to the increased risk of HC (44.65%), high LDL-C (47.39%), and hypertension (46.47%), whereas PFNA contributed most to the increased risk of hyperuricemia (47.33%) (Fig. 1B). However, the QGC model did not identify any significant effects of PFAS mixture on other CMDs.

3.2.2. Association between PFAS exposure and cardiometabolic biomarkers in the mixed-exposure analysis

The QGC model also indicated that exposure to the PFAS mixture has significant effects on five types of cardiometabolic biomarkers (Fig. S4A). In the obesity study, a quartile increase in PFAS mixture was significantly associated with a 0.063 SD increase in BMI levels (β = 0.063, 95% CI: 0.028–0.096) and a 0.068 SD increase in waist circumference (WC) levels (β = 0.068, 95% CI: 0.035–0.102). In the dysglycemia study, a quartile increase in PFAS mixture was associated with a 0.095 SD decrease in fasting blood glucose (FBG) levels (β = −0.095, 95% CI: 0.130 to −0.060), but with a 0.052 SD increase in glycated hemoglobin (HbA1c) levels (β = 0.052, 95% CI: 0.017–0.088). In the dyslipidemia study, a quartile increase in PFAS mixture was associated with a 0.095 SD increase in total cholesterol (TC) levels (β = 0.095, 95% CI: 0.053–0.136) and a 0.068 SD increase in low-density lipoprotein cholesterol (LDL-C) levels (β = 0.068, 95% CI: 0.027–0.109), but with a 0.070 SD decrease in TG levels (β = −0.070, 95% CI: 0.108 to −0.033). In the hypertension study, a quartile increase in PFAS mixture was associated with a 0.036 SD increase in systolic blood pressure (SBP) levels (β = 0.036, 95% CI: 0.003–0.069) and a 0.062 SD increase in diastolic blood pressure (DBP) levels (β = 0.062, 95% CI: 0.029–0.096). In the hyperuricemia study, a quartile increase in PFAS mixture was associated with a 0.083 SD increase in serum uric acid (SUA) levels (β = 0.083, 95% CI: 0.050–0.116). Consistently, PFTrDA contributed most to the increase in TC (40.71%), LDL-C (46.66%), SBP (49.20%), and DBP (47.10%) levels, whereas PFNA contributed most to the increase in SUA (44.20%) levels (Fig. S4B).

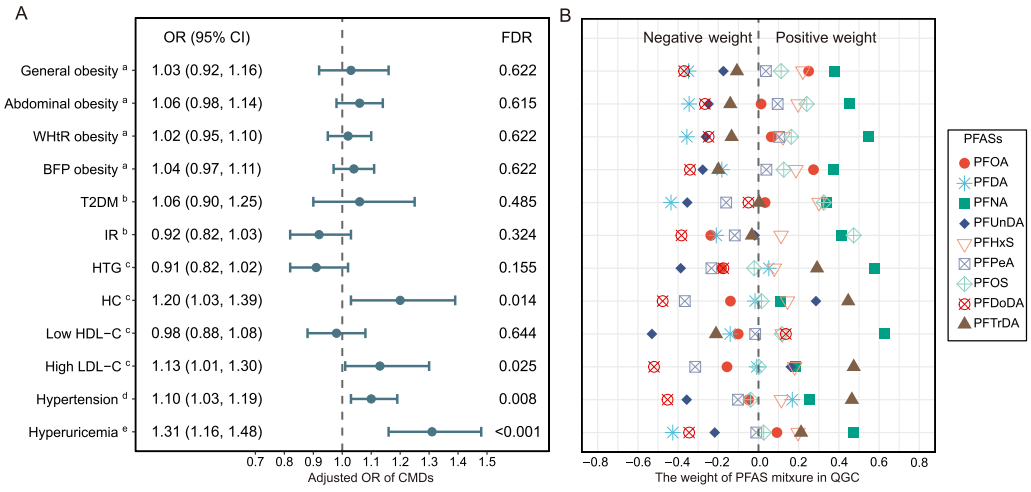

Fig. 1. The association between PFAS mixture and 12 cardiometabolic diseases (CMDs) and the weight of PFAS mixture in the QGC model for the five study subgroups. (A) The adjusted OR of CMDs. (B) The weight of PFAS mixture in QGC. Models were adjusted for age, sex, residence, education, household income, tobacco use, alcohol drinking, physical activity, total energy intake, total fat intake, and total cholesterol intake. Models for outcomes except obesity were further adjusted for body mass index (BMI). Models for hyperuricemia were further adjusted for BMI and serum creatinine. [a] Obesity study (n = 7396). [b] Dysglycemia study (n = 6697). [c] Dyslipidemia study (n = 7439). [d] Hypertension (n = 7541). [e] Hyperuricemia study (n = 7581). FDR, false discovery rate; OR, odds ratio; PFASs, perfluoroalkyl and polyfluoroalkyl substances;PFOA, perfluorooctanoic acid; PFDA, perfluorodecanoic acid; PFNA, perfluorononanoic acid; PFUnDA, perfluoroundecanoic acid; PFHxS, perfluorohexanesulfonate; PFPeA, perfluoro-n-pentanoic acid; PFOS, perfluorooctanesulfonate; PFDoDA, perfluorododecanoic acid; PFTrDA, perfluorotridecanoic acid; QGC, quantile-based g-computation.

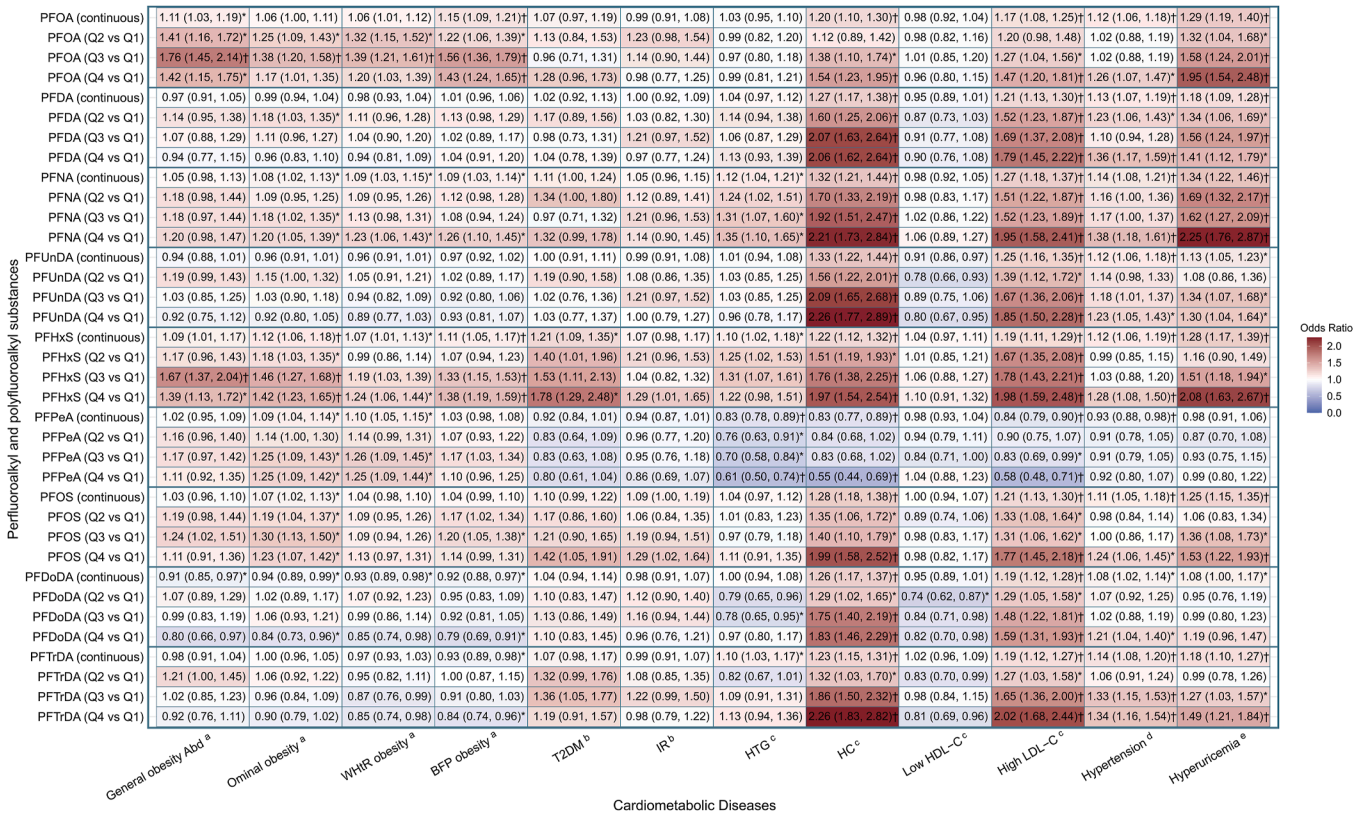

Fig. 2. The association between nine ln-transformed PFAS exposures and 12 cardiometabolic diseases (CMDs) in the logistic regression models. Model covariates are as specified in Fig. 1. † FDR < 0.01, * FDR < 0.05.

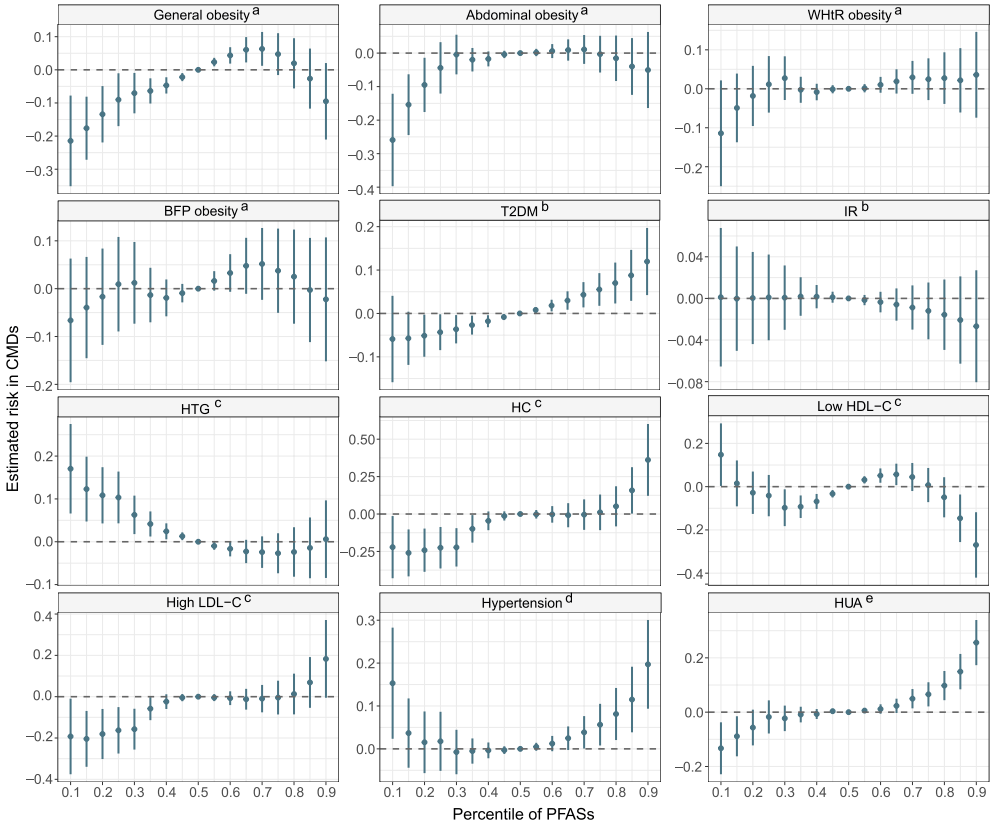

Fig. 3. The exposure-response relationship between PFAS mixture and cardiometabolic diseases (CMDs) in BKMR models. Model covariates are as specified in Fig. 1.

3.3. The results of the single-exposure analysis

3.3.1. Association between PFAS exposure and CMDs in the single-exposure analysis

A broader association between PFAS exposure and CMDs was found in the single-exposure models (Fig. 2). Specifically, six PFASs (PFOA, PFDA, PFNA, PFHxS, PFPeA, and PFOS) were associated with CMD risks in the obesity study, one PFAS (PFHxS) was associated with CMD risks in the dysglycemia study, eight PFASs (PFOA, PFDA, PFNA, PFHxS, PFPeA, PFOS, PFDoDA, and PFTrDA) were associated with CMD risks in the dyslipidemia study and hypertension study, seven PFASs (PFOA, PFDA, PFNA, PFHxS, PFPeA, PFOS, and PFTrDA) were associated with CMD risks in the hyperuricemia study.

Notably, PFHxS significantly impacted all five types of CMDs simultaneously. The Q4 of ln(PFHxS) was significantly associated with higher risk of general obesity (OR = 1.39, 95% CI: 1.13–1.72), abdominal obesity (OR = 1.42, 95% CI: 1.23–1.65), WHtR obesity (OR = 1.24, 95% CI: 1.06–1.44), BFP obesity (OR = 1.38, 95% CI: 1.19–1.59), T2DM (OR = 1.78, 95% CI: 1.29–2.48), HC (OR = 1.97, 95% CI: 1.54–2.54), high LDL-C (OR = 1.98, 95% CI: 1.59–2.48), hypertension (OR = 1.28, 95% CI: 1.08–1.50), and hyperuricemia (OR = 2.08, 95% CI: 1.63–2.67) compared to the Q1. Additionally, we found that some PFASs (PFPeA, PFDoDA, and PFTrDA) were negatively associated with the risk of CMDs.

3.3.2. Association between PFAS exposure and cardiometabolic biomarkers in the single-exposure analysis

In analyzing the associations between 9 PFAS congeners and 15 cardiometabolic biomarkers, results similar to those observed with CMDs were noted (Fig. S5). However, we discovered that several PFASs (PFOA, PFUnDA, and PFPeA) exhibited opposing effects on the levels of FBG and HbA1c. Specifically, PFOA exposure was significantly negatively associated with FBG levels ($\beta = -0.043$, 95% CI: 0.068 to −0.018), but positively associated with HbA1c levels ($\beta = 0.039$, 95% CI: 0.015–0.063). PFPeA exposure was negatively associated with FBG levels ($\beta = -0.050$, 95% CI: 0.073 to −0.027), but positively associated with HbA1c levels ($\beta = 0.026$, 95% CI: 0.004–0.048).

3.4. The results of the exposure-response analysis

The BKMR model indicated that the exposure-response curves between the PFAS mixture and CMDs are mostly nonlinear (Fig. 3). Except for the monotonically increasing association between PFAS mixture and the risk of T2DM, high LDL-C, and hyperuricemia, other typical relationships included an inverse "U"-shaped association with general obesity and abdominal obesity, an "S"-shaped association with low HDL-C, and a "U"-shaped association with hypertension. The exposure to PFAS mixture showed an inverse "U"-shaped association with BMI, WC, and BFP levels, an "S"-shaped association with FBG, HbA1c, TC, HDL-C, LDL-C, and SUA levels, an inverse "U"-shaped association with fasting insulin (FINS) and the homeostasis model assessment of insulin resistance (HOMA-IR) levels, and an approximately linear association with TG, SBP, and DBP levels (Fig. S6). The results of the RCS analysis were similar to those of the mixed-exposure analysis, also revealing complex nonlinear associations between PFAS congeners and CMDs (Fig. S7–S18).

3.5. The results of mediation analysis

Before conducting the mediation analysis, an association analysis was performed between the inflammatory markers (M) and PFASs (X), as well as the cardiometabolic outcomes (Y) (Tables S14–S17). The X–M–Y associations that met the criteria for mediation analysis were included in the model, and significant interaction terms (X*M) were specified (Tables S18–S19). The mediation model showed that hs-CRP and SF significantly mediated the effects of multiple PFASs on various cardiometabolic outcomes, and several cardiometabolic outcomes were simultaneously mediated by both inflammatory markers (Fig. 4).

Emerging evidence indicates significant differences between hs-CRP and SF in mediating the cardiometabolic effects of PFASs. Hs-CRP primarily mediated the effects of PFNA and PFHxS on obesity, dyslipidemia, and hyperuricemia. In contrast, SF demonstrated a broader mediating role, acting as an indirect inflammatory marker in the associations of eight PFASs (excluding PFPeA) with obesity, dysglycemia and dyslipidemia, and hyperuricemia (Tables S20–S21). Specifically, in the

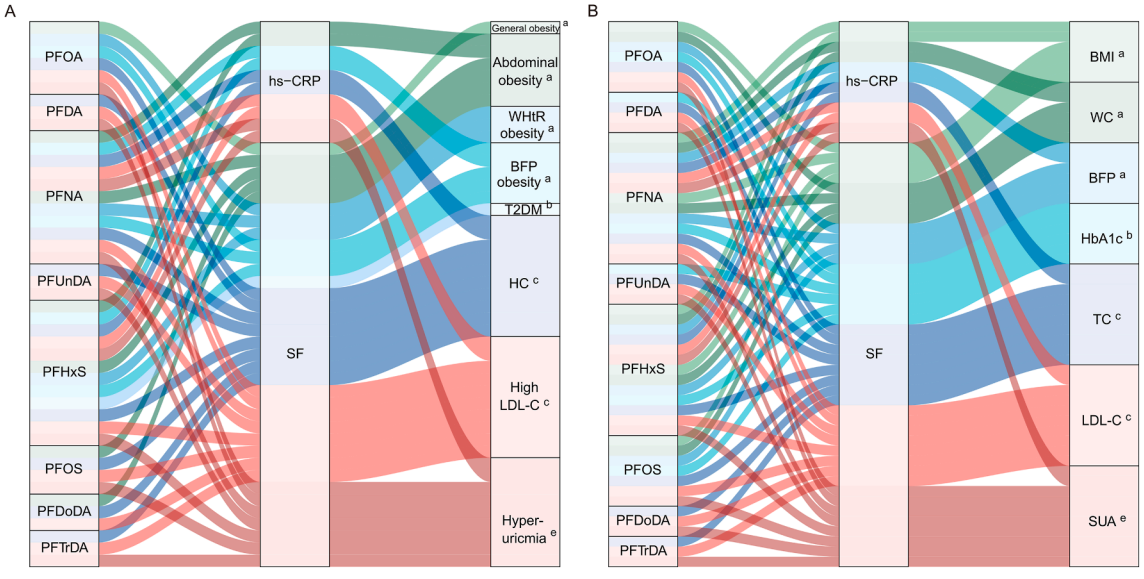

Fig. 4. The mediation effects of high-sensitivity C-reactive protein (hs-CRP) and serum ferritin (SF) in the association between ln-transformed PFAS exposures and cardiometabolic outcomes. (A) The CMDs outcomes. (B) The cardiometabolic biomarker outcomes. Model covariates are as specified in Fig. 1. CMDs, cardiometabolic diseases; HbA1c, glycated hemoglobin; hs-CRP, High-sensitivity C-reactive protein; SF, serum ferritin; SUA, serum uric acid; TC, total cholesterol; WC, waist circumference.

obesity study, hs-CRP significantly mediated the effect of PFNA on general obesity (mediation prop. = 33.84%, FDR = 0.008) and BMI levels (mediation prop. = 23.62%, FDR < 0.001). SF, however, showed stronger mediating effects, particularly on abdominal obesity and WC levels, with the highest mediation proportion reaching 85.78% for abdominal obesity (mediation prop. = 85.78%, FDR = 0.024). In the dysglycemia study, only SF significantly mediated the effect of PFHxS on T2DM (mediation prop. = 32.18%, FDR = 0.018) and HbA1c levels (mediation prop. = 11.27%, FDR < 0.001). In the dyslipidemia study, both hs-CRP and SF were involved in mediating the effects, but SF demonstrated higher mediation proportions for the effect of PFHxS on elevated TC and LDL-C levels (ranging from 38.53% to 41.31%, FDR < 0.001). In the hyperuricemia study, the mediating effect of hs-CRP was minimal (less than 6%), whereas SF significantly mediated the effects of eight PFASs on uric acid outcomes. For instance, SF mediated the effect of PFUnDA on hyperuricemia (mediation prop. = 53.84%, FDR = 0.003) and SUA levels (mediation prop. = 43.10%, FDR < 0.001).

3.6. The results of the sensitivity analysis

We conducted six sensitivity analyses to validate the robustness of the main findings, including: 1) PFAS concentrations were categorized into quartiles, and their associations with 15 cardiometabolic biomarkers were consistent with the results from both single-exposure and RCS models (Table S22). 2) A ln(SD) increase in the sum PFAS was significantly associated with increased risks of HC (OR = 1.24, 95% CI: 1.15–1.35), high LDL-C (OR = 1.18, 95% CI: 1.10–1.27), hypertension (OR = 1.16, 95% CI: 1.10–1.23), and hyperuricemia (OR = 1.29, 95% CI: 1.19–1.39), as well as elevated BMI, WC, and some other cardiometabolic biomarker levels (Tables S23–S24). 3) The WQS model revealed that a quartile increase in PFAS mixture was associated with increased risks of HC (OR = 1.52, 95% CI: 1.34–1.72), high LDL-C (OR = 1.42, 95% CI: 1.26–1.58), hypertension (OR = 1.14, 95% CI: 1.04–1.27), and hyperuricemia (OR = 1.45, 95% CI: 1.28–1.65). Additionally, the WQS model identified more significant associations with obesity and T2DM (Tables S25–S26). 4) In all analytical models, after further adjusting for fish and meat intake, serum creatinine, and MASLD prevalence, the conclusions remained largely consistent with the primary analysis (Figs. S19–S33). 5) After adjusting for dietary iron intake, the mediating effect of serum ferritin remained significant, consistent with our primary findings (Table S27). 6) After performing age and sex-stratified analyses of the study participants, we did not observe significant sex differences in the effects of PFASs. However, we found a more pronounced cardiometabolic risk in the younger subgroup (Tables S28–31).

4. Discussion

Based on our large-scale, Chinese population-based study, we found that the PFAS mixture significantly impacted the risk of dyslipidemia, hypertension, and hyperuricemia. Within the PFAS mixture, PFTrDA contributed the most to HC, high LDL-C, and hypertension, whereas PFNA contributed the most to hyperuricemia. Notably, we found that PFHxS had the most extensive impact on all five types of CMDs. Additionally, this study delineated the exposure-response curves for nine PFASs with cardiometabolic outcomes under both mixed- and single-exposure scenarios, revealing differences in exposure patterns among the PFAS homologs. Furthermore, as a surrogate inflammatory marker, SF had a broader and stronger mediating effect than the traditional biomarker hs-CRP in the association of PFASs with CMDs. This research is pioneering in exploring the multifaceted impacts of PFASs on a broad spectrum of CMDs within a national population and elucidating the significant mediating role of inflammation in these relationships.

A major challenge in studying the relationship between PFASs and CMDs is that individuals in real-world scenarios are often exposed to multiple PFASs simultaneously. Consequently, employing mixed models to account for these combined effects is crucial for accurately assessing their overall impact on health. A recent systematic review evaluated the associations between PFASs and CMDs, finding results largely consistent with ours [4]. However, studies assessing the association between PFASs and CMDs using mixed-exposure methods remain sporadic. A cross-sectional study in China indicated that six PFASs (PFOA, PFDA, PFNA, PFUnDA, PFHxS, and PFOS) were positively associated with HC and high LDL-C, while PFUnDA was negatively associated with low HDL-C [30]. Despite numerous studies demonstrating positive associations between multiple PFASs, such as PFOA and PFOS, and hypertension or hyperuricemia [31–34], others have reported null or even negative associations [35–38]. These discrepancies are often attributed to limited sample sizes for evaluating mixed-exposure effects or insufficient covariate adjustment.

Our study comprehensively explored the impact of PFASs on five key CMDs within the large-scale general population, accounting for the effects of obesity on other CMDs by incorporating BMI into models and presenting the most robust conclusions to date. Biologically, PFASs may simultaneously influence the onset of various CMDs through many shared and unique biological mechanisms. Experimental studies suggest that PFASs may activate peroxisome proliferator-activated receptors (PPARs) [39,40], inhibit glycogen synthesis via the serine/threonine protein kinase (AKT) pathway [41], and alter gene expression or DNA methylation linked to lipid metabolism [42]. PFASs also contribute to hypertension and hyperuricemia by upregulating glucocorticoid receptors and interacting with organic anion transporters [43,44]. Given these findings, it is crucial to consider the impact of PFASs on various CMDs in the general population. However, most published studies have focused primarily on specific demographic groups such as pregnant women, children, or highly exposed populations [12,45,46], posing challenges for generalization to the broader population due to varying levels of PFASs and differences in endocrine functions.

Building on the evidence from previous epidemiological studies, we have proposed several new insights. For instance, PFPeA and PFUnDA are identified as negatively associated with a specific lipid profile. One explanation is that these PFASs possess a high oxygen-carrying capacity [47], and high lipid levels increase blood viscosity, affecting blood oxygen transport capacity, which may help explain the negative association between these PFASs in serum and lipid profiles. Furthermore, the evidence on the association of PFASs with dysglycemia is more inconsistent. A study from the NHANES 2013–2014 indicated that specific PFASs were negatively associated with FBG and HbA1c [48], although other studies from Taiwan and Tianjin in China provided conflicting results [49,50]. However, the overall effect of PFASs on dysglycemia remains elusive, with our data indicating opposing effects on FBG and HbA1c. Furthermore, in the age-stratified analysis, we observed that PFASs had a more pronounced impact on cardiometabolic risk in the subgroup aged less than 65 years. This may be attributed to the endocrine system in younger individuals being in a critical developmental and maturation stage, making them more susceptible to endocrine-disrupting chemicals like PFASs [51]. Conversely, the gradual decline in endocrine system function in older adults may result in relatively lower sensitivity to PFASs.

We identified key PFASs specifically associated with certain CMDs, which is crucial for targeted prevention in high-risk populations and for better informing PFAS manufacturing and regulatory decisions. Some mixed-exposure studies also supported our findings, with PFTrDA contributing the most to elevated LDL-C levels [52], while PFNA contributed the most to elevated blood pressure levels [32]. However, another study in China found that the contribution of PFNA to elevated SUA was second only to PFOA [34]. The heterogeneity in this finding may be due to variations in subtypes and quantities of PFASs selected in different studies. Notably, our research is the first to demonstrate that PFHxS significantly impacts all five types of CMDs simultaneously. China, a major producer and consumer of PFASs, has been utilizing these substances since the last century [53]. Given this, concrete steps should be taken to gradually phase out perfluoroalkyl-containing products, reduce PFAS exposure in the population, and enhance occupational

protections among highly exposed individuals, such as carpet manufacturers or firefighters [1,54].

The exposure-response analysis indicates that despite the persistent and chronic nature of human exposure to most compounds, the health effects of mixed PFAS exposure exhibit complex, nonlinear patterns. We identified several distinct patterns through which PFASs may influence cardiometabolic health, including monotonic, inverted "U"-shaped, "U"-shaped, and "S"-shaped associations. Specifically, the association between PFAS exposure and obesity risk primarily exhibited an inverted "U"-shaped pattern, with lower obesity risk at both low and excessively high exposure concentrations of PFASs. One possible explanation is the high lipophilicity of PFASs and other persistent organic pollutants (POPs), which facilitates their sequestration in adipose tissue. At higher exposure levels, this accumulation may reduce the circulating levels of biologically active PFASs, thereby diminishing their metabolic toxicity [55]. Furthermore, elevated PFAS levels can induce mitochondrial dysfunction, oxidative stress, and cytotoxicity, impairing adipocyte function and even triggering apoptosis. This process may hinder the normal proliferation of adipose tissue and its capacity for lipid storage [56]. In contrast, the association between PFAS exposure and hypertension risk exhibited a "U"-shaped pattern. Low doses of PFASs may prevent blood pressure elevation by enhancing vascular endothelial cell function and promoting the release of vasodilatory substances (e.g., nitric oxide) [57,58], while high doses of PFASs further contribute to elevated blood pressure through biological pathways such as upregulation of glucocorticoid receptors, leading to a "U"-shaped curve. Although previous studies have also identified complex non-linear relationships in the health effects of PFASs [30,59], current evidence remains insufficient to comprehensively elucidate these patterns, particularly for certain cardiometabolic indicators. For example, we observed a potential "S"-shaped association between PFAS exposure and low HDL-C risk, suggesting the existence of multiple inflection points or thresholds. However, the underlying mechanisms remain unclear. These findings underscore the need for more precise human exposure measurements and rigorously designed mechanistic studies to further clarify the dose-response dynamics and identify critical risk thresholds for specific PFAS congeners.

Inflammatory responses play a critical mediating role in the association between PFASs and various types of CMDs. PFASs are known to activate immune and inflammatory response pathways, such as the NF-κB pathway [60]. Hs-CRP is a traditional direct marker of inflammation, and some epidemiological studies and animal experiments have linked PFASs with elevated hs-CRP [61,62]. Additionally, data from the NHANES 2003–2012 demonstrated a mediating role of hs-CRP in the association between PFASs and cardiovascular diseases [63]. Furthermore, obesity is characterized as a chronic, low-grade inflammatory state [64]. Our study revealed that hs-CRP, a regulator of fat metabolism [65], can mediate the association between PFASs and obesity risk.

In parallel, SF is often used as an alternative indirect inflammatory marker and has been positively associated with PFASs in epidemiological studies involving patients with uremia [66]. Excess SF can trigger oxidative stress, decrease fatty acid oxidation, and increase lipid transport [67]. Additionally, inflammation may increase xanthine oxidase activity, a key enzyme in purine metabolism involved in synthesizing SUA [68]. Our research further suggests that SF, as an indirect inflammatory marker, offers a more comprehensive and precise reflection of the risk of various CMDs, including obesity, dyslipidemia, and hyperuricemia. Before the onset of cardiometabolic symptoms, assessing inflammatory markers, especially SF, can indicate an individual's potential risk for CMDs.

Our study has several advantages. We utilized national survey data to systematically explore the cardiometabolic risk of PFASs, employing both mixed- and single-exposure methods to enhance the real-world relevance of our findings. Several key PFASs influencing cardiometabolic risk were identified, including homologs with broad impacts on the risk of CMDs (e.g., PFHxS), and those with more specific effects (e.g., PFNA and PFTrDA). This information provides targeted scientific evidence for optimizing PFAS regulatory policies. Additionally, we examined the mediating effects of inflammatory markers between PFASs and the five types of CMDs, shedding light on the biological mechanisms behind PFAS-induced harms. SF can more effectively indicate the individual risk of CMDs compared to hs-CRP, playing a crucial role in the early identification and prevention of CMDs. Despite these strengths, our study also has certain limitations. Firstly, we did not account for exposure routes such as dietary intake and inhalation, as we only measured serum PFASs, which may not fully capture actual exposure levels. Secondly, although we adjusted for known covariates based on extensive literature, unknown confounding factors may still influence our results. Thirdly, the cross-sectional study design precludes establishing causality between PFASs, inflammation, and CMDs. However, given the persistent nature of PFASs, their concentrations in the body likely reflect long-term exposure preceding the onset of CMDs. Fourthly, we considered only one direct marker and one indirect marker of inflammation, excluding other widely recognized inflammatory markers. Finally, to date, there is no comprehensive standard for evaluating cardiometabolic health. We strongly recommend the development of a cardiometabolic risk score that incorporates various lifestyle and biochemical measurements, especially SF levels, to efficiently and accurately predict the individual risk of CMDs.

5. Conclusion

In this nationally representative study, we found the most compelling evidence to date elucidating the cardiometabolic risk associated with PFASs, notably in dyslipidemia, hypertension, and hyperuricemia. Specifically, PFTrDA contributed the most to HC, high LDL-C, and hypertension, while PFNA contributed the most to hyperuricemia. PFHxS significantly impacted all five types of CMDs simultaneously. Although the link between PFASs and dysglycemia still requires further exploration, we have identified some new leads regarding the association of PFASs with obesity and dyslipidemia. Considering the unique properties of PFASs, their ubiquitous environmental exposure, and our findings, targeted regulation of key PFASs should be implemented to minimize population exposure levels. More importantly, we have further quantified the mediating role of two distinct inflammatory markers in the relationship between PFASs and various CMDs. Hs-CRP significantly mediates the association between PFASs and obesity, while SF additionally mediates the association between PFASs and other CMDs, such as dyslipidemia and hyperuricemia, beyond obesity. Inflammation plays a crucial role in the impact of PFASs on CMDs, and inflammatory marker levels can potentially indicate the individual risk of developing CMDs. The detection of inflammatory biomarkers, especially SF, can further assist in the early identification and prevention of CMDs.

CRediT authorship contribution statement

Yongbin Zhao: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Huijun Wang:** Supervision, Methodology, Investigation. **Yanzhen Hu:** Validation, Formal analysis, Data curation. **Zongyao Li:** Validation, Formal analysis, Data curation. **Xi Kang:** Validation, Investigation. **Chang Su:** Resources, Investigation, Funding acquisition, Conceptualization. **Zhenyu Wu:** Writing – review & editing, Validation, Conceptualization. **Tao Zhang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Aidong Liu:** Supervision, Resources, Investigation, Conceptualization.

Data availability

Data were available only on reasonable requests to the corresponding authors.

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.

Acknowledgments

The most important acknowledgment is to the survey team and all China Health and Nutrition Survey participants. This study was supported by the National Natural Science Foundation of China (82222064, 82473730, 82173613, 82373681), the National Key Research and Development Program of China (2019YFC1605100), the National Institutes of Health (R01-HD30880, DK056350, R24-HD050924, R01-HD38700), and the Ministry of Finance of the People's Republic of China (13103110700015005).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eehl.2025.100210.

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