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Associations of exposure to individual polyfluoroalkyl substances and their mixtures with vitamin D biomarkers in postmenopausal women

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ABSTRACT

The potential impact of polyfluoroalkyl substances (PFAS) on vitamin D status in postmenopausal women remains unexplored. This study examined the effects of individual PFAS and their combined exposures on vitamin D biomarkers among 2114 postmenopausal women utilizing data from the National Health and Nutrition Examination Survey (NHANES) spanning 2003–2018. The serum levels of four PFAS compounds, including perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS), and perfluorononanoic acid (PFNA), were assessed alongside the 25-hydroxyvitamin D [25(OH)D] level. Our findings indicated that elevated log-transformed PFAS concentrations were significantly associated with reduced 25(OH) D levels (β_{PFOS}: −15.969, 95 % CI: −19.154, −12.785; β_{PFOA}: −17.288, 95 % CI: −22.446, −12.131; β_{PFNA}: −8.510, 95 % CI: −12.148, −4.871; β_{PFHxS}: −4.056, 95 % CI: −7.003, −1.110) and increased odds of vitamin D deficiency (OR_{PFOS}: 2.495, 95 % CI: 1.685, 3.694; OR_{PFOA}: 3.146, 95 % CI: 1.823, 5.429; OR_{PFNA}: 1.906, 95 % CI: 1.357, 2.677; OR_{PFHxS}: 1.480, 95 % CI: 1.109, 1.976). These associations were modified by race, the family income—poverty ratio and the survey cycle. Notably, non-Hispanic White individuals presented a stronger inverse association between PFOS exposure and 25(OH)D levels. Bayesian kernel machine regression and weighted quantile sum analyses demonstrated that the effects of exposure to mixtures of the four studied PFAS were consistent with the effects of exposure to individual PFAS. These findings indicate that exposure to individual PFAS, particularly PFOA and PFOS, and their four mixtures may adversely affect serum 25(OH)D concentrations in postmenopausal women, underscoring the need for further investigation into the potential impact of PFAS on vitamin D status in this population.

1. Introduction

Polyfluoroalkyl substances (PFAS) are resilient endocrine disrupting chemicals that are extensively used in industrial and consumer products (Bečanová et al., 2016; Herzke et al., 2012). Owing to their persistence and widespread use, PFAS are classified as emerging contaminants of concern (Wang et al., 2024a). Four specific PFAS compounds—perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS), and perfluorononanoic acid (PFNA) —were detected in over 98 % of the serum samples from a representative general population in the U.S., and these compounds were responsible for the majority of human PFAS exposure (Costello et al., 2022; Tian et al., 2022). Animal studies have shown that these compounds cause multiorgan toxicity, including damage to the skeletal system and reproductive organs (Ding et al., 2022). Additionally, emerging evidence suggests that exposure to PFAS is associated with hormonal disruptions and various health issues in women, including menstrual irregularities, disturbances in thyroid function and adverse pregnancy outcomes (Aimuzi et al., 2020; Rickard et al., 2022a; Y et al., 2023).

Vitamin D, a crucial steroid hormone for numerous physiological functions, is key to preserving healthy mineralized skeletons by regulating phosphate and calcium homeostasis (Chen et al., 2020; Ko and Kim, 2020; Lee et al., 2008). Notably, one-third of the population in the

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U.S. suffers from insufficient vitamin D levels, with a higher prevalence among African Americans (Etzel et al., 2019). Since the active form of vitamin D, 1,25-hydroxyvitamin D (25(OH)D), shares structural similarities with classic steroid hormones (Pike and Meyer, 2010), its metabolism may be disrupted by PFAS. PFAS are known endocrine disruptors that can potentially interfere with the vitamin D receptor (VDR), induce the expression of the vitamin D-metabolizing enzyme CYP24A1, or cause broader endocrine disruption, affecting calcium and phosphate balance (Azhagiya Singam et al., 2023; Norman, 2008).

Research investigating the association between PFAS exposure and vitamin D status remains limited and inconsistent (Chang et al., 2021; Etzel et al., 2019; Khalil et al., 2018). Two population-based studies revealed that several PFAS compounds, including PFHxS, PFOS and PFOA, are associated with serum 25(OH)D levels (Chang et al., 2021; Etzel et al., 2019). However, another study failed to establish such an association (Khalil et al., 2018). These discrepancies may stem from differences in study design, population demographics, and exposure assessment methods. The inconsistencies in the current literature underscore the need for further investigation into the relationship between PFAS exposure and vitamin D status, particularly in populations that are vulnerable to PFAS exposure.

Owing to hormonal status modifications, postmenopausal women may be particularly susceptible to PFAS (Rickard et al., 2022b). The cessation of menstruation, a key pathway for PFAS elimination (El Khoudary et al., 2020; Wise et al., 2022), possibly leads to higher PFAS concentrations in postmenopausal women than in premenopausal women (Wong et al., 2014). Nevertheless, the specific impact of PFAS exposure on vitamin D status among postmenopausal women remains unknown. Moreover, individuals are typically exposed to multiple PFAS simultaneously (Braun and Gray, 2017), but previous studies have predominantly examined exposure to individual PFAS, neglecting the potential cumulative effects of exposure to PFAS mixtures. To address these research gaps, we conducted this study utilizing data from the National Health and Nutrition Examination Survey (NHANES) to examine the associations of exposure to individual and multiple PFAS with vitamin D status among postmenopausal women.

2. Materials and methods

2.1. Study design and population

The NHANES is a biennial population-based national survey conducted by the U.S. Centers for Disease Control and Prevention (CDC). Through physical examinations, interviews and biospecimen collection, this survey assesses the nutritional and health conditions of the noninstitutionalized U.S. population (Wang et al., 2021). All participants provided written informed consent, and the survey protocols were approved by the Ethical Review Committee of the National Center for Health Statistics (NCHS) (Cheng et al., 2023). Comprehensive details about the NHANES are available at http://www.cdc.gov/nchs/nhanes.

Our study utilized publicly accessible data from the NHANES cycles between 2003 and 2018, including complete serum PFAS and 25(OH)D concentration data from 2114 postmenopausal women. The detailed selection process is depicted in Figure S1.

2.2. Menopausal status

Menopausal status was assessed through responses to questions concerning reproductive health. The participants were initially asked "Have you had at least one menstrual period in the past 12 months? (excluding bleeding due to medical conditions, hormone therapy, or surgeries)". Those who answered "No" were then asked, "What is the reason that you have not had a period in the past 12 months?". Participants who responded "Menopausal" were defined as postmenopausal women (Shi et al., 2023).

2.3. Measurement of PFAS concentrations

Serum PFAS concentrations were quantified via online solid-phase extraction-high-performance liquid chromatography-turbo ion spray-tandem mass spectrometry, and the detailed laboratory methodology is available in the NHANES manual (Zhang et al., 2023). Using data from the 2003–2018 cycles, this study focused on four highly detectable PFAS compounds: PFOA, PFOS, PFHxS, and PFNA. Because PFOS and PFOA were measured in linear and branched isomers separately after the 2011–2012 cycles, they were summed in the 2013–2018 cycles. Table S1 details the limit of detection (LOD) for the examined PFAS, and a concentration below the LOD was substituted with the LOD divided by the square root of 2.

2.4. Measurement of vitamin D status

Serum 25(OH)D levels serve as biomarkers of vitamin D status. For the 2003–2006 cycles, the DiaSorin assay kit was used to measure the levels of serum 25(OH)D (Herrick et al., 2019). Beginning with the 2007–2008 cycles, liquid chromatography—tandem mass spectrometry (LC—MS/MS) was used for measurement. To account for methodological differences, serum 25(OH)D levels from the 2003–2006 cycles were converted to equivalent measurements via the standardized LC—MS/MS approach in accordance with official guidelines and best practices (Herrick et al., 2019). In addition to treating serum 25(OH)D levels as a continuous variable, vitamin D status was classified into a binary variable according to the recommendations of the World Health Organization (WHO): (1) deficiency ($<$50 nmol/L) and (2) normal status ($\geq$50 nmol/L) (Etzel et al., 2019).

2.5. Covariates

Based on previous studies (Chang et al., 2021; Etzel et al., 2019; Wang et al., 2021), the subsequent variables were identified as potential confounding factors: race, age, the family income—poverty ratio (PIR; low income: $<$1.30, intermediate income: 1.30–1.85, and high income: $>$1.85), education level (less than high school, high school graduate, or more than high school), body mass index (BMI) (normal: $<$25 kg/m^2, overweight: 25–30 kg/m^2, and obesity $\geq$30 kg/m^2) (Wang et al., 2024a), smoking status (current, never and former), alcohol consumption status (current, never and former), vitamin D supplement (yes and no), time since menopause, physical activity (active and inactive), diabetes (yes and no) and hypertension (yes and no). Alcohol consumption status was categorized as nondrinker (having $<$12 drinks in a lifetime), former drinker (having $\geq$12 drinks in 1 year but not drinking last year, or not drinking last year but having $\geq$12 drinks in a lifetime), or current drinker (having $\geq$12 drinks in 1 year and drinking last year) (Mukamal et al., 2010). Participants who reported engaging in vigorous or moderate physical activity were categorized as physically active, whereas those who did not report engaging in vigorous or moderate physical activity were categorized as physically inactive (Yin et al., 2023). Vitamin D supplement use was assessed according to the dietary supplement questionnaire (Etzel et al., 2019). The time since menopause was calculated by subtracting the age at the last menstrual period from the current age for postmenopausal women (Taylor et al., 2014). Hypertension and diabetes were defined on the basis of self-reported information.

2.6. Statistical analyses

Descriptive data were used to summarize participant characteristics, with continuous variables presented as the means (standard deviations, SDs) or medians (interquartile ranges, IQRs) and categorical variables presented as counts (percentages). One-way analyses of variance (ANOVAs) were performed to compare continuous variables with a normal distribution between groups, whereas the Kruskal—Wallis H test was used for variables with skewed distributions. The χ^2 test was used to compare group differences for categorical variables. To address the skewed distribution, PFAS concentrations were transformed into natural logarithmic continuous variables for subsequent analyses.

Survey-weighted linear regression models and binary logistic regression models were used to assess the associations of serum 25(OH) D levels and vitamin D deficiency risk with serum PFAS concentrations categorized into quartiles and as continuous variables. Two models were employed to adjust for confounding factors in all analyses. Model 1 was unadjusted, whereas Model 2 was adjusted for age, education level, race, smoking status, BMI, vitamin D supplement, alcohol consumption status, the PIR, time since menopause, physical activity, hypertension and diabetes. Subgroup analysis was conducted to evaluate the consistency of the results across different subgroups stratified by race, age, alcohol consumption status, smoking status, and the PIR. Interactions were tested by conducting likelihood ratio tests to compare multivariable models with and without interaction terms. To further assess the impact of time trends on the results, we included the survey cycle as a binary variable in the subgroup analysis.

Weighted quantile sum (WQS) regression was used to estimate the combined effect of exposure to the four PFAS on serum 25(OH)D levels and vitamin D deficiency risk. Briefly, this method involves performing a mixture effect analysis by calculating the WQS index to assess the impact of multiple exposures on an outcome, with weights assigned to reflect the contribution of each exposure (Wang et al., 2024b). Specifically, the WQS index was constructed on the basis of the quartiles of PFAS, indicating the average change in serum 25(OH)D levels and the odds ratio (OR) of vitamin D deficiency risk for each increasing PFAS mixture quartile. The samples were split into two groups at random: 40 % for training and 60 % for validation, with 10,000 bootstraps conducted to evaluate PFAS weights. Given that the direction of the association between PFAS exposure and serum 25(OH)D levels was unclear, we performed separate analyses constrained in both the positive and negative directions to assess the effects of the PFAS mixture on 25(OH)D levels. The same approach was also used to analyze the association between PFAS exposure and vitamin D deficiency risk.

Bayesian kernel machine regression (BKMR) was further applied to explore the joint effects of the four PFAS compounds (Bobb et al., 2018), including the nonlinear relationships and interactions. The BKMR approach estimates a nonparametric high-dimensional exposure—response function in a flexible and efficient manner by combining Bayesian and statistical learning methods, allowing for the assessment of potential antagonistic and synergistic effects among the mixture components and visualization of the exposure—response associations for each component. In this study, 10,000 iterations were performed using the Markov chain Monte Carlo algorithm.

Several sensitivity analyses were conducted to validate the robustness of the results. (1) Adjustments were made for the six-month period and the blood sample collection session to account for the potential influences of time and season on the results. (2) In this study, missing covariate values were addressed using multiple imputations by chained equations (MICE), a method that assumes that data are missing at random and provides more accurate and reliable estimates than single imputation methods (Aris et al., 2022). (3) Given that dietary vitamin D intake is a significant factor influencing vitamin D levels, we conducted a sensitivity analysis using data from the 2007—2018, adjusting for dietary vitamin D intake. This period was selected because detailed data on dietary vitamin D intake were unavailable prior to 2007. Similarly, data on vitamin D supplement dosage were also only available from 2007 to 2018. To better capture the impact of supplementation on serum 25(OH)D levels, we also included vitamin D supplement dosage as a continuous variable rather than a binary variable (https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2007/DataFiles/DR1TOT_E.htm).

R statistical software (version 4.3.3) was used for all of the statistical analyses. The WQS and BKMR analyses were conducted utilizing the "gWQS" and "bkmr" packages. A two-tailed significance threshold of $P < 0.05$ was applied for the tests.

3. Results

3.1. Participant characteristics

The characteristics of the selected participants (n = 2114) are presented in Table 1. The mean age of the participants was 63.97 years (SD = 10.68). More than half of the participants were never smokers (58.75 %), were physically active (54.59 %), and were current drinkers (53.36 %). Approximately 65 % of the participants had hypertension, and fewer than one-third had diabetes. All four PFAS compounds had high detection rates among the participants (Table S1), with median PFHxS, PFNA, PFOA, and PFOS concentrations of 1.40, 0.90, 3.02 and 11.40 ng/mL, respectively. Compared with those in the normal group, participants in the vitamin D deficiency group presented significantly elevated levels of PFNA, PFOA and PFOS.

3.2. Associations of individual PFAS exposure with serum 25(OH)D levels and vitamin D deficiency risk

The individual effects of the four PFAS compounds on serum 25(OH) D levels and vitamin D deficiency risk are shown in Tables 2 and 3. According to the fully adjusted model, all four studied PFAS levels were associated with decreased serum 25(OH)D levels and increased odds of vitamin D deficiency. Specifically, for each unit increase in PFHxS, PFNA, PFOS and PFOA levels, the serum 25(OH)D level decreased by 4.056 (95 % CI: −7.003 to −1.110), 8.510 (95 % CI: −12.148 to −4.871), 15.969 (95 % CI: −19.154 to −12.785) and 17.288 (95 % CI: −22.446 to −12.131) nmol/L, respectively. The OR for vitamin D deficiency increased to 1.480 (95 % CI: 1.109–1.976) for PFHxS, 1.906 (95 % CI: 1.357–2.677) for PFNA, 2.495 (95 % CI: 1.685–3.694) for PFOS and 3.146 (95 % CI: 1.823–5.429) for PFOA. Similar associations were also identified when PFAS levels were divided into quartiles (Tables 2–3).

3.3. Associations of mixed PFAS exposure with serum 25(OH)D levels and vitamin D deficiency risk

WQS regression analysis revealed a negative association between coexposure to all four PFAS and serum 25(OH)D levels, along with a positive association between coexposure and vitamin D deficiency risk in the fully adjusted model (Table S2). A quartile change in the WQS index was correlated with a decrease of 4.807 nmol/L in serum 25(OH)D levels (95 % CI: −6.283 to −3.330) and approximately 30 % greater odds of vitamin D deficiency (OR: 1.271, 95 % CI: 1.085–1.487). Figure S2 presents the estimated weights for the four PFAS, with PFOS exerting the greatest influence on both vitamin D deficiency risk (61.6 %) and serum 25(OH)D concentrations (67.8 %).

The BKMR model results demonstrated trends similar to those observed in the WQS regression analysis. The overall associations of multiple PFAS exposures with serum 25(OH)D levels and vitamin D deficiency risk are illustrated in Fig. 1 and were consistent with those demonstrated in the WQS regression analysis. Fig. 1 also shows the associations of exposure to individual PFAS with serum 25(OH)D concentrations and the risk of vitamin D deficiency when the concentrations of other PFAS were fixed at different percentiles. We observed negative associations between the levels of PFOS and PFOA and serum 25(OH)D concentrations, which was aligned with the outcomes derived from linear regression analyses. Interestingly, a positive correlation between the PFHxS concentration and the serum 25(OH)D concentration was detected, which was not identified in the linear regression model. Nonlinear effects of PFHxS, PFOS and PFOA concentrations on serum 25 (OH)D concentrations and of PFOA and PFOS concentrations on vitamin D deficiency risk were observed (Fig. 2). Moreover, several interactions of PFNA with PFOA and PFHxS, as well as associations of PFOA and

Table 1
Characteristics of the study participants.

Characteristics	Overall (n = 2114)	Vitamin D deficiency (n = 617)	Normal (n = 1497)	P value
Age, years, mean (SD)	63.97 (10.68)	62.39 (10.45)	64.63 (10.71)	**< 0.001**
Race, n (%)				**<0.001**
Mexican American	325 (15.37)	135 (21.88)	190 (12.69)	
Non-Hispanic Black	384 (18.16)	199 (32.25)	185 (12.36)	
Non-Hispanic White	1066 (50.43)	208 (33.71)	858 (57.31)	
Other Race	339 (16.04)	75 (12.16)	264 (17.64)	
Education level, n (%)				**<0.001**
Less than high school	607 (28.71)	216 (35.01)	391 (26.12)	
High school graduate	534 (25.26)	150 (24.31)	384 (25.65)	
More than high school	973 (46.03)	251 (40.68)	722 (48.23)	
PIR, n (%)				**<0.001**
Low income	646 (30.56)	230 (37.28)	416 (27.79)	
Intermediate income	295 (13.95)	96 (15.56)	199 (13.29)	
High income	1173 (55.49)	291 (47.16)	882 (58.92)	
BMI, n (%)				**<0.001**
Normal	559 (26.44)	97 (15.72)	462 (30.86)	
Overweight	630 (29.80)	172 (27.88)	458 (30.60)	
Obesity	925 (43.76)	348 (56.40)	577 (38.54)	
Smoking status, n (%)				**<0.001**
Never	1242 (58.75)	319 (51.70)	923 (61.66)	
Former	553 (26.16)	159 (25.77)	394 (26.32)	
Current	319 (15.09)	139 (22.53)	180 (12.02)	
Alcohol consumption status, n (%)				**0.001**
Never	494 (23.27)	158 (25.61)	336 (22.44)	
Former	492 (23.37)	169 (27.39)	323 (21.58)	
Current	1128 (53.36)	290 (47.00)	838 (55.98)	
Physical activity, n (%)				**<0.001**
Active	1154 (54.59)	276 (44.73)	878 (58.65)	
Inactive	960 (45.41)	341 (55.27)	619 (41.35)	
Diabetes, n (%)				**0.003**
Yes	555 (26.25)	190 (30.79)	365 (24.38)	
No	1559 (73.75)	427 (69.21)	1132 (75.62)	
Hypertension, n (%)				0.267
Yes	1372 (64.90)	412 (66.77)	960 (64.13)	
No	742 (35.10)	205 (33.23)	537 (35.87)	
Vitamin D supplement, n (%)				**<0.001**
Yes	1037 (49.05)	120 (19.45)	917 (61.26)	
No	1077 (50.95)	497 (80.55)	580 (38.74)	
Time since menopause, year, mean (SD)	18.10 (11.77)	17.62 (11.62)	18.29 (11.84)	0.238
Serum 25(OH) D, nmol/L, mean (SD)	68.19 (30.19)	35.46 (9.21)	81.69 (25.05)	**< 0.001**
PFHxS, ng/mL, median (IQR)	1.40 (0.80, 2.60)	1.43 (0.80, 2.50)	1.40 (0.80, 2.60)	0.606
PFNA, ng/mL, median (IQR)	0.90 (0.50, 1.50)	1.07 (0.65, 1.70)	0.90 (0.50, 1.40)	**< 0.001**
PFOA, ng/mL, median (IQR)	3.02 (1.90, 4.80)	3.40 (2.00, 4.90)	2.90 (1.87, 4.70)	**0.004**
PFOS, ng/mL, median (IQR)	11.40 (6.10, 20.70)	14.00 (7.40, 23.50)	10.70 (5.70, 19.00)	**< 0.001**

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; PIR, family income—poverty ratio; PFAS, perfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid.

PFOS with serum 25(OH)D levels, were identified (Fig. 2).

3.4. Subgroup and sensitivity analyses

Stratifying by age, race, smoking status, alcohol consumption status, the PIR and survey cycle revealed similar inverse associations between PFAS exposure and serum 25(OH)D levels and positive relationships with vitamin D deficiency risk (Table S3). These associations were modified by race, the PIR and the survey cycle. Compared with other races, a stronger association between PFOS exposure and lower 25(OH) D levels was observed among non-Hispanic whites (*P* for interaction <0.001). Significant interactions were found between the three PFAS (PFNA, PFOA and PFOS) and the PIR concerning the risk of vitamin D deficiency, with participants with high incomes exhibiting greater vitamin D deficiency risk than those with low or intermediate incomes (all *P* values for interactions <0.05). Moreover, we also observed a stronger negative association between PFNA exposure and serum 25 (OH)D levels in the 2003–2010 cycle than in the 2011–2018 cycle (*P* for interaction =0.037).

In sensitivity analyses, the associations between individual PFAS exposure and serum 25(OH)D levels and vitamin D deficiency risk remained robust when (1) the dietary vitamin D intake covariates and the vitamin D supplement (continuous variable) were included (Tables S4-S5 and Figure S3), (2) the survey period and blood sample collection session covariates were included (Tables S4-S5 and Figure S4), and (3) imputing missing covariates (Tables S4-S5 and Figure S5) were included.

4. Discussion

Our study revealed that individual exposure to four PFAS (including PFHxS, PFNA, PFOA and PFOS) was associated with greater odds of vitamin D deficiency and reduced serum 25(OH)D levels in post-menopausal women. A significant interaction between PFOS exposure and race regarding the levels of serum 25(OH)D was detected, with a stronger inverse association in non-Hispanic White individuals. Moreover, the combined effects of the four PFAS compounds were inversely associated with serum 25(OH)D levels and positively correlated with the odds of vitamin D deficiency.

Research regarding the relationship between PFAS exposure and vitamin D levels remains sparse and contradictory. One cross-sectional study revealed a negative relationship between PFOS concentrations

Table 2
Associations between PFAS exposure and serum 25(OH)D levels (weighted).

PFAS	Model 1		Model 2	
	β (95 % CI)	*P* value	*β* (95 % CI)	*P* value
PFHxS				
Quartile 1 (n = 573)	Ref		Ref	
Quartile 2 (n = 505)	−3.292 (−8.556, 1.972)	0.218	−2.847 (−6.859, 1.164)	0.162
Quartile 3 (n = 528)	−1.098 (−6.870, 4.673)	0.707	−2.138 (−6.711, 2.435)	0.356
Quartile 4 (n = 508)	−3.010 (−8.462, 2.442)	0.277	−5.679 (−10.343, −1.016)	**0.018**
Continuous (Log-transformed)	−2.356 (−5.814, 1.102)	0.180	−4.056 (−7.003, −1.110)	**0.007**
PFNA				
Quartile 1 (n = 546)	Ref		Ref	
Quartile 2 (n = 519)	−7.082 (−12.239, −1.924)	**0.008**	−5.761 (−9.973, −1.548)	**0.008**
Quartile 3 (n = 533)	−7.988 (−13.523, −2.453)	**0.005**	−7.018 (12.256, −1.781)	**0.009**
Quartile 4 (n = 516)	−11.097 (−16.352, −5.841)	**< 0.001**	−10.663 (−15.597, −5.728)	**< 0.001**
Continuous (Log-transformed)	−9.358 (−13.175, −5.540)	**< 0.001**	−8.510 (−12.148, −4.871)	**< 0.001**
PFOA				
Quartile 1 (n = 539)	Ref		Ref	
Quartile 2 (n = 519)	−0.307 (−5.506, 4.893)	0.907	−3.470 (−7.724, 0.783)	0.109
Quartile 3 (n = 544)	−7.322 (−12.062, −2.582)	**0.003**	−10.240 (−14.425, −6.055)	**< 0.001**
Quartile 4 (n = 512)	−11.438 (−16.258, −6.618)	**< 0.001**	−14.652 (−19.212, −10.092)	**< 0.001**
Continuous (Log-transformed)	−12.230 (−17.751, −6.709)	**< 0.001**	−17.288 (−22.446, −12.131)	**< 0.001**
PFOS				
Quartile 1 (n = 535)	Ref		Ref	
Quartile 2 (n = 524)	−4.456 (−10.202, 1.290)	0.127	−3.149 (−8.273, 1.974)	0.225
Quartile 3 (n = 531)	−13.639 (−18.333, −8.945)	**< 0.001**	−13.611 (−17.345, −9.877)	**< 0.001**
Quartile 4 (n = 524)	−19.650 (−23.994, −15.307)	**< 0.001**	−16.989 (−20.879, −13.099)	**< 0.001**
Continuous (Log-transformed)	−17.190 (−20.922, −13.451)	**< 0.001**	−15.969 (−19.154, −12.785)	**< 0.001**

Abbreviations: PFAS, perfluoroalkyl substances; PFHxS, perfluorohexane sulfonic acid; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid.
Model 1 was an unadjusted model.
Model 2 was adjusted for age, race, education level, the family income—poverty ratio, smoking status, physical activity, vitamin D supplementsupplementation, body mass index, alcohol consumption status, time since menopause, diabetes and hypertension.

Table 3
Associations between PFAS exposure and vitamin D deficiency risk (weighted).

PFAS	Model 1		Model 2	
	OR (95 % CI)	*P* value	*OR* (95 % CI)	*P* value
PFHxS				
Quartile 1 (n = 573)	Ref		Ref	
Quartile 2 (n = 505)	1.137 (0.808, 1.601)	0.459	1.085 (0.708, 1.663)	0.705
Quartile 3 (n = 528)	1.278 (0.844, 1.934)	0.244	1.461 (0.929, 2.298)	0.100
Quartile 4 (n = 508)	1.337 (0.923, 1.937)	0.123	1.598 (1.050, 2.432)	**0.029**
Continuous (Log-transformed)	1.245 (0.969, 1.600)	0.086	1.480 (1.109, 1.976)	**0.008**
PFNA				
Quartile 1 (n = 546)	Ref		Ref	
Quartile 2 (n = 519)	1.608 (1.149, 2.252)	**0.006**	1.548 (1.055, 2.271)	**0.026**
Quartile 3 (n = 533)	1.692 (1.161, 2.465)	**0.007**	1.716 (1.121, 2.628)	**0.013**
Quartile 4 (n = 516)	1.968 (1.425, 2.716)	**< 0.001**	2.193 (1.472, 3.268)	**< 0.001**
Continuous (Log-transformed)	1.763 (1.338, 2.322)	**< 0.001**	1.906 (1.357, 2.677)	**< 0.001**
PFOA				
Quartile 1 (n = 539)	Ref		Ref	
Quartile 2 (n = 519)	1.065 (0.750, 1.514)	0.721	1.337 (0.887, 2.015)	0.164
Quartile 3 (n = 544)	1.826 (1.260, 2.648)	**0.002**	2.631 (1.737, 3.983)	**< 0.001**
Quartile 4 (n = 512)	1.778 (1.234, 2.561)	**0.002**	2.583 (1.669, 3.997)	**< 0.001**
Continuous (Log-transformed)	1.889 (1.227, 2.910)	**0.004**	3.146 (1.823, 5.429)	**< 0.001**
PFOS				
Quartile 1 (n = 535)	Ref		Ref	
Quartile 2 (n = 524)	1.283 (0.878, 1.874)	0.196	1.270 (0.837, 1.926)	0.258
Quartile 3 (n = 531)	2.080 (1.424, 3.038)	**< 0.001**	2.536 (1.667, 3.860)	**< 0.001**
Quartile 4 (n = 524)	2.709 (1.900, 3.864)	**< 0.001**	2.834 (1.902, 4.224)	**< 0.001**
Continuous (Log-transformed)	2.380 (1.658, 3.414)	**< 0.001**	2.495 (1.685, 3.694)	**< 0.001**

Abbreviations: PFAS, perfluoroalkyl substances; PFHxS, perfluorohexane sulfonic acid; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid.
Model 1 was an unadjusted model.
Model 2 was adjusted for age, race, education level, the family income—poverty ratio, smoking status, physical activity, vitamin D supplement, body mass index, alcohol consumption status, time since menopause, diabetes and hypertension.

and serum 25(OH)D concentrations (Etzel et al., 2019). In contrast, another study involving pregnant women demonstrated that elevated PFAS levels were correlated with higher 25(OH)D concentrations (Chang et al., 2021). Furthermore, a relatively small-sample-size study ($n < 110$) revealed no significant associations between PFAS exposure and vitamin D biomarkers (Khalil et al., 2018). The discrepancies across these studies may be partly explained by differences in the study populations. Chang's study focused on Black women, whereas the majority of participants in our study were White. Additionally, PFAS exposure levels in Chang's study were significantly lower than those in our study, which may have led to inconsistent findings. Our study employed LC—MS/MS for more accurate and specific vitamin D measurements than the immunoassays used in Chang's research (Chang et al., 2021). Moreover, the limited statistical power resulting from the relatively small sample sizes possibly hinders the detection of fully nonmonotonic dose—response relationships or the achievement of statistically significant results, further contributing to the observed differences (Vandenberg et al., 2012). Our study is the first to explore the associations between serum PFAS and serum 25(OH)D levels in postmenopausal women utilizing a relatively large, nationally

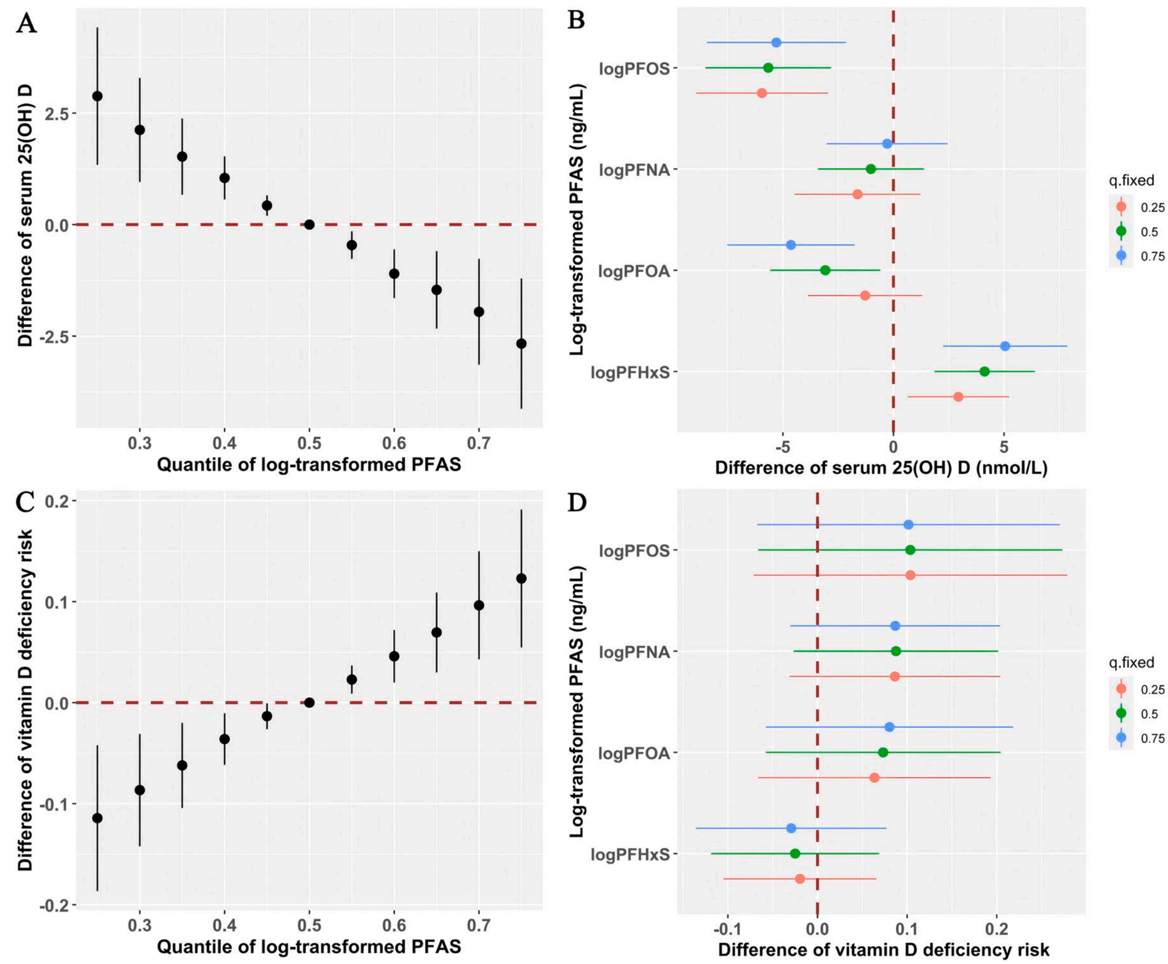

Fig. 1. Joint effects of the four PFAS on serum 25(OH)D levels and vitamin D deficiency risk in BKMR models. (A, C): Overall effect of PFAS mixture at particular percentiles (from 0.25 to 0.75) compared with their 50th percentile; dots represent estimated values of the overall effect, and vertical lines represent the 95 % confidence interval. (B, D): Effects of single PFAS at the 25th to 75th percentiles when other PFAS were fixed at the 25th, 50th, and 75th percentiles; the dots represent the estimates, and the horizontal lines represent the 95 % confidence intervals. Abbreviations: PFAS, perfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; BKMR, Bayesian kernel machine regression. The model was adjusted for age, race, education level, the family income—poverty ratio, smoking status, physical activity, vitamin D supplement, body mass index, alcohol consumption status, time since menopause, diabetes and hypertension.

representative sample. This enhances the robustness of our findings, highlighting the detrimental effects of PFAS exposure, particularly PFOS and PFOA, on vitamin D status among postmenopausal women.

Our study offers novel insights into the influence of PFAS mixtures on vitamin D status, indicating that the combined effects of PFAS are negatively associated with vitamin D biomarkers. This finding reinforces the importance of considering cumulative PFAS exposure and supports our observations regarding the effects of individual PFAS exposure. Moreover, the significant interaction effect between PFOS levels and race on the levels of serum 25(OH)D, particularly in non-Hispanic White individuals, in this study is consistent with previous research (Etzel et al., 2019). These racial disparities may be attributed to different 25 (OH)D concentrations or varying susceptibilities to modified homeostasis of vitamin D (Nelson et al., 2000). Because pigmentation reduces vitamin D production in the skin, African Americans are at a greater risk of vitamin D insufficiency than other racial groups (Thomas et al., 2015). Additionally, most young, healthy Black Americans fail to achieve adequate 25(OH)D levels throughout the year (Harris, 2006). Consequently, non-Hispanic Whites may experience a greater decrease in 25(OH)D levels, as they typically have higher serum 25(OH)D levels than other races do, and they may be less vulnerable to further declines among those with low baseline 25(OH)D levels. These findings collectively indicate that non-Hispanic Whites may have heightened sensitivity to PFAS exposure, influencing vitamin D metabolism.

The biological mechanisms through which PFAS affect vitamin D remain unclear. One potential pathway involves CYP24A1, the primary cytochrome P450 enzyme responsible for inactivating 25(OH)D and 1,25(OH)2D in the liver (Christakos et al., 2016; Hawkes et al., 2017). PFOA has been shown to compete with 1,25(OH)2D for binding to VDRs (Azhagiya Singam et al., 2023), potentially leading to increased expression of CYP24A1 and subsequently decreased levels of 25(OH)D. Additionally, PFAS may alter vitamin D status by exerting endocrine-disrupting effects on other components of the vitamin D endocrine system (Azhagiya Singam et al., 2023; Henry, 2011; Norman, 2008; Rosen Vollmar et al., 2023; Tonelli et al., 2025). For example, PFAS exposure has been associated with changes in parathyroid hormone levels, which influence calcium and phosphorus homeostasis, key factors in vitamin D function (Tonelli et al., 2025). This disruption may have cascading effects on bone health and other physiological processes (Azhagiya Singam et al., 2023). PFAS may also interact with fibroblast growth factors, which are involved in bone health and may influence vitamin D metabolism (Henry, 2011; Rosen Vollmar et al., 2023). Given the limited evidence concerning the effects of PFAS exposure on vitamin D status, further research is necessary to elucidate the potential mechanisms involved.

This study has several strengths, including the application of

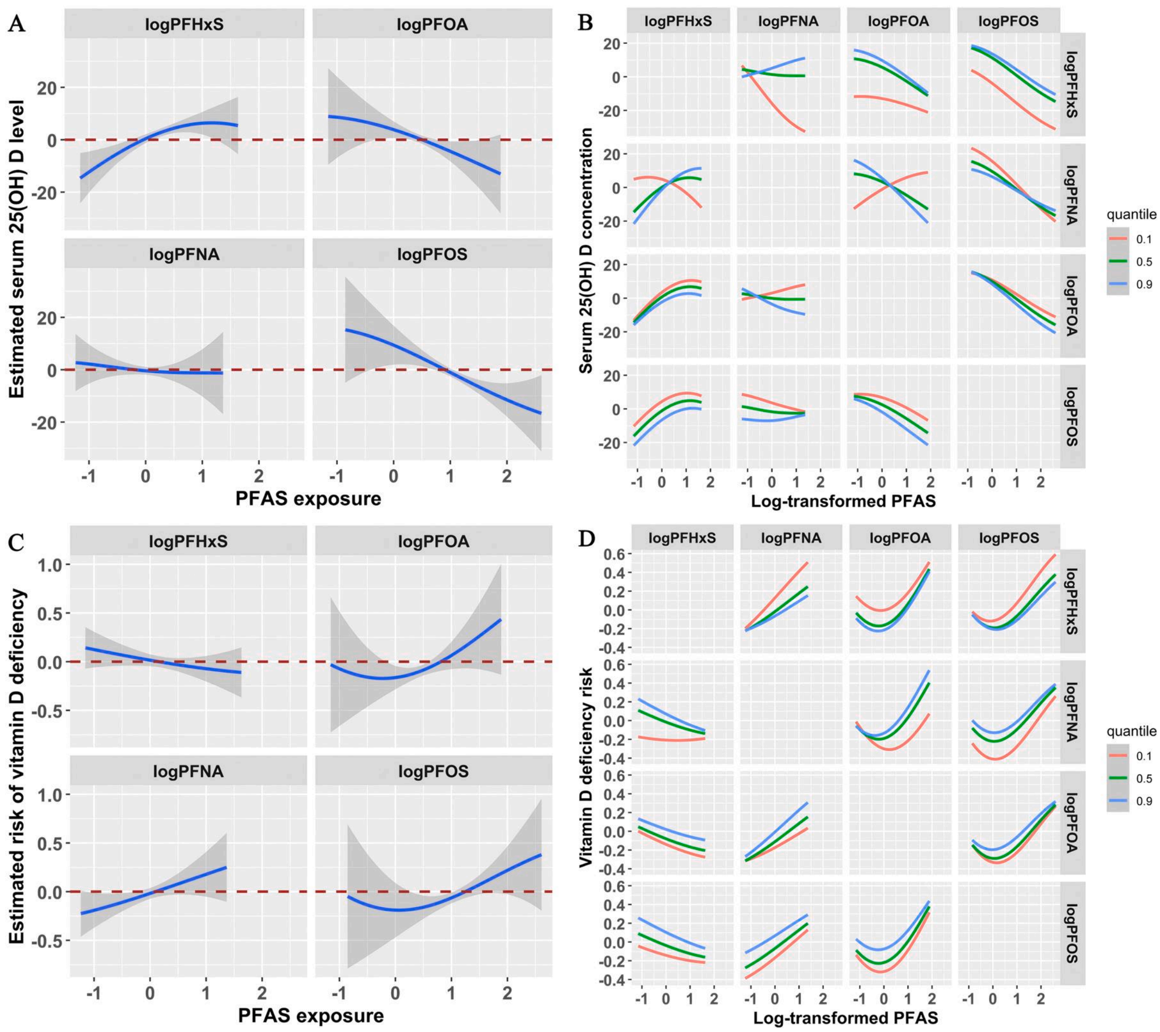

Fig. 2. Univariate exposure–response relationships and bivariate exposure–response relationships for each individual PFAS with the serum 25(OH)D level and vitamin D deficiency risk in BKMR models. (A, C): Univariate exposure—response relationships of single PFAS when other chemicals are fixed at the median. (B, D): The bivariate exposure—response relationships for each individual PFAS are illustrated when the corresponding PFAS on the right longitudinal axis was fixed at the 10th, 50th, and 90th percentiles and other PFAS were held at their 50th percentiles. Abbreviations: PFAS, perfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; BKMR, Bayesian kernel machine regression. The model was adjusted for age, education level, race, the family income—poverty ratio, smoking status, physical activity, vitamin D supplement, body mass index, alcohol consumption status, time since menopause, diabetes and hypertension.

multipollutant effect assessment methods (WQS and BKMR) to examine both individual and joint effects of exposure to PFAS mixtures on vitamin D biomarkers. The inclusion of a nationally representative population sample and adjustment for numerous potential confounders bolster the reliability of our findings. Nevertheless, several limitations should be noted. First, similar to the former NHANES investigation (Tian et al., 2022), survey weights were not applied in the WQS and BKMR models because of their inability to accommodate weighting. Second, a single measurement of PFAS concentrations and vitamin D biomarkers may not adequately represent long-term serum concentrations or reflect dynamic changes in the body. Third, although our study design robustly assesses associations across two distinct survey cycles, temporal changes in PFAS exposure could influence these relationships. Longitudinal studies are needed to further explore these dynamics and substantiate the causality of the observed associations. Finally, the potential for unmeasured confounding factors, such as regional factors, should be considered when interpreting the results. PFAS concentrations and distributions in the environment vary significantly across different regions and are often correlated with industrial activities (Lei et al., 2024). Similarly, vitamin D levels can be influenced by regional factors, such as latitude and sunlight exposure (Al-Musharaf et al., 2018). However, geographic data are not available in the NHANES database, which may bias our results.

5. Conclusion

This study provides evidence of an inverse association between serum 25(OH)D concentrations and exposure to both individual PFAS compounds (PFOS and PFOA) and mixtures of the four studied PFAS compounds among postmenopausal women. These findings contribute valuable epidemiological evidence pertinent to risk assessment among postmenopausal women, potentially facilitating the development of more targeted regulatory policies and interventions to mitigate the adverse health effects of PFAS exposure in these vulnerable populations. Furthermore, future studies are needed to clarify the underlying mechanisms through which PFAS exposure affects 25(OH)D levels.

Ethics and approval

The study protocol (Protocol Number: Protocol #98–12, Protocol

#2005–06, Protocol #2011–17 and Protocol #2018–01) was approved by the NCHS Research Ethics Review Board (ERB), and all participants provided written informed consent prior to participation. (https://www.cdc.gov/nchs/nhanes/irba98.htm).

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CRediT authorship contribution statement

Du Li-Ying: Methodology. **Chen Hao-Jie:** Writing – review & editing. **Ma Jun-Xuan:** Writing – original draft. **Huang Hong-Xuan:** Writing – review & editing, Writing – original draft, Conceptualization. **Kuang Ling:** Writing – review & editing. **Zhang Bing-Yun:** Writing – review & editing. **Xiong Zhi-Yuan:** Software. **Li Hong-Min:** Writing – review & editing. **Liao Dan-Qing:** Methodology. **Lai Shu-Min:** Visualization. **Qiu Cheng-Shen:** Visualization. **Tang Xu-Lian:** Formal analysis, Data curation. **Xu Zi-Hao:** Writing – original draft. **Li Zhi-Hao:** Supervision, Project administration, Conceptualization.

Declaration of Competing Interest

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

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.118103.

Data Availability

Data will be made available on request.

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