Journal of Orthopaedic Surgery and Research

RESEARCH ARTICLE Open Access

The study findings demonstrated a significant association between C-reactive protein levels and trabecular bone score : NHANES 2005–2008

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Abstract

Objectives The association between C-reactive protein and bone density has been primarily investigated in previous studies, with little to no research investigating its relationship with total bone trabecular score.

Methods Data from the NHANES database (500 males and 633 females) were utilized in this study to perform a multiple weighted linear regression analysis to estimate this relationship of CRP and TBS. Subsequently, population characterization, univariate logistic regression analysis, subgroup and interaction analysis were in progress.

Results Upon covariate adjustment, the analysis revealed a notable negative correlation between CRP and TBS(β=-0.0081,95% CI (-0.0142, -0.0019), *P* = 0.009). Furthermore, no interactions were detected within any subgroups.

Conclusion This finding enhances our comprehension of the relationship in inflammation and bone health, offering the novel research outlook for the treatment and prevention of osteoporosis and osteoporotic fractures.

Keywords Total TBS, C-reactive protein, Inflammation

Introduction

Osteoporosis is a systemic bone disease resulting from the imbalance between bone formation and resorption. Key features include reduced bone density, microstructural deterioration, culminating in heightened bone fragility and fracture susceptibility [1, 2]. Osteoporotic fractures, deemed severe complications of this condition, are associated with elevated rates of mortality and disability, profoundly affecting patient well-being and imposing considerable economic strain on society [3–5].

Trabecular bone score (TBS) is calculated from standard dual X-ray absorptiometry (DXA) bone mineral density (BMD) scans of the lumbar spine, offering an evaluation of bone microarchitecture that is associated with the mechanical characteristics of bone tissue [6, 7]. Due to many individuals who sustain fractures may have normal or slightly reduced BMD, leading to an underestimation of fracture risk if relying only on BMD [7, 8]. TBS contributes to more effectively assess the fracture risk in patients with normal or mildly reduced bone density who may be at risk of low-energy fractures, as well as in patients with known microstructural damage to the bones [7]. Thus, TBS plays a crucial role in identifying

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individuals at high risk of fractures by assessing bone microstructure and quality [9].

Persistent low-grade inflammation or immune responses are linked to reduced bone mass and a heightened risk of fractures [10, 11]. osteoporosis and fragility fractures are more common in specific inflammatory diseases like systemic lupus erythematosus and rheumatoid arthritis [12–14]. Furthermore, as individuals age, there is a typical age-related pro-inflammatory state that leads to an increase in circulating levels of C-reactive protein (CRP) as the liver responds to interleukin-6 (IL-6) and various cytokines [15]. Consequently, it has been established that older individuals tend to gain lower bone mass and a higher risk in fractures [12, 16]. While some research have examined the link between CRP and BMD [17, 18], the association between CRP and TBS has been rarely reported. In order to investigate this relationship, we analyzed data from 2005 to 2008 in the National Health and Nutrition Examination Survey (NHANES). Through rigorous inclusion criteria and adjustment for covariates, we aimed to elucidate the correlation of CRP and total TBS.

Methods

Data extraction and variable selection

The NHANES database includes demographic details, physical measurements, survey responses, and laboratory test results, using complex sampling techniques. It is a national cross-sectional survey. Its primary objective is to offer comprehensive insights into the wealth of information about the overall health and nutritional status of American population [19]. Information from NHANES can be accessed via the official website(https://www.cdc.gov/nchs/nhanes/index.htm), and the National Center for Health Statistics (NCHS) ethics review committee has approved this data .

The study employed latex-enhanced turbidimetry to measure CRP levels through antigen or antibody binding. Measurements were conducted using a Behring turbidimeter, and the data was processed through signal subtraction employing the logit-log function. The dependent variable analyzed was Total TBS, representing a texture index derived from assessing grayscale variations in lumbar spine DXA scans. Spine scans were obtained using the Hologic QDR-4500 A fan beam densitometer, followed by TBS software (version 2.1.0.2) from Med-IMAP SA TBS calculator for estimating total TBS scores in adults aged 20 and above. CRP levels were divided into four groups based on quartile levels: first quartile (Q1): 0.01–0.08 mg/dL, second quartile (Q2): 0.09–0.19 mg/dL, third quartile (Q3): 0.20–0.44 mg/dL, fourth quartile (Q4): 0.45–17.5 mg/dL.

Drawing from previous research and clinical insights, we have included essential covariates that could impact the relationship between Total Trabecular Bone Score and C-reactive protein in our study. These covariates encompass categorical variables such as education, race, smoking, drinking status, and income-to-poverty ratio. The income-to-poverty ratio serves as a gauge of a family's financial status, calculated by dividing their income by the poverty guidelines set by the Department of Health and Human Services (HHS). It is further classified into three categories: "low" (<1.99), "moderate" (1.99–3.49), and "high" (>3.49). Among the continuous covariates considered in this analysis are age, cholesterol, total calcium, blood urea nitrogen, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, serum uric acid, albumin, direct high-density lipoprotein cholesterol (HDL-C), hemoglobin, CRP low-density lipoprotein cholesterol (LDL-C), body mass index (BMI in kg/m^2).

Statistical analyses

Prior to conducting statistical analysis, a normality test was conducted in whole continuous variables. Generalized weighted linear regression was employed for analyzing continuous variables, and (mean ± standard deviation) was used to show the result. While a weighted chi-square test was used for analyzing categorical variables, presented as percentages. Following covariate adjustments, three multiple weighted linear regression models were developed: Model 1 with no covariate adjustments, Model 2 adjusting for certain covariates such as gender, race, and age, and Model 3 incorporating all covariates. Subgroup analysis and analysis of subgroup interactions were also performed.

R software (version 4.3.0) is a programming software, and it is used for all data analysis. When $P<0.05$ (two-tailed), it is considered to be statistically significant.

Results

The exclusion and inclusion process of research objects

For the particular study, data was got from 20,497 individuals within NHANES, and after stringent inclusion and exclusion criteria were applied, 1133 individuals were selected for analysis. The inclusion criteria: individuals whose age is greater than or equal to 20 years old. The Exclusion criteria: 1.individuals whose data for total tbs and CRP is missing. 2. Exclude individuals with missing values in other variables. 3. Exclude individuals with cancer and diabetes. The specific screening process is outlined in Fig. 1.

Characteristics of the study population

The study involved 1133 individuals in total, with an average age of 45.230 ± 16.654 years. CRP was categorized into quartiles, and the corresponding demographic and population characteristics are presented in Table 1

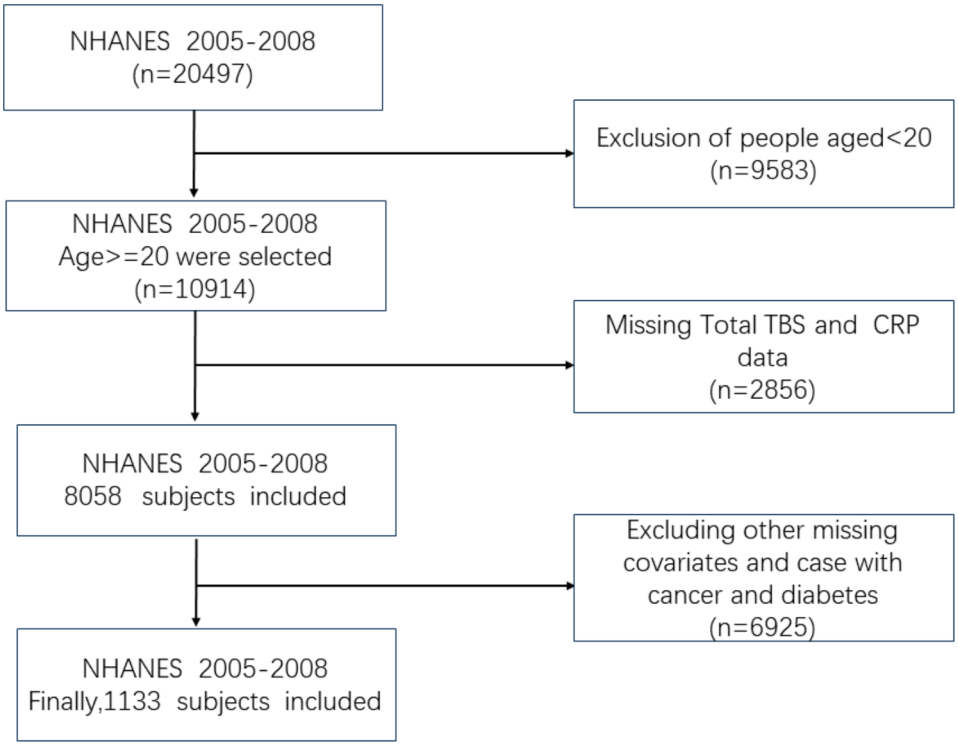

Fig. 1 Inclusion and exclusion flowchart

(Please find Table 1 at the end of this document). Our analysis revealed that variables such as alanine aminotransferase, blood urea nitrogen, total protein, race, poverty-income ratio, education level, and smoking history did not show significant associations with the baseline characteristics of CRP quartiles. However, other variables exhibited significant associations. Specifically, HDL-C, albumin, and trabecular bone score were significantly higher in the CRP (Q1, Q2) groups compared to the CRP (Q4) group. Conversely, males and BMI were significantly higher in the CRP (Q4) group compared to the CRP (Q1, Q2) groups.

Univariate analysis

In the weighted univariate linear regression analysis (Supplementary S1 at the end of this document), we identified variables that exhibited significant association with Total TBS. These variables include Non-Hispanic Black ethnicity, a high income-to-poverty ratio, more than high school, age, alanine aminotransferase, cholesterol levels, C-reactive protein, blood urea nitrogen, serum uric acid, HDL-C, serum albumin, LDL-C, and BMI. Conversely, no significant correlations were observed for the other variables.

Relationship between CRP and total TBS

As shown in the Table 2, through weighted multiple linear regression, significant negative associations with Total TBS were found in all three models.Model1 (β = -0.0258, 95% CI -0.0405, -0.0109),Model 2 (β = -0.0235, 95% CI -0.0377, -0.0094), Model 3 (β = -0.0081, 95% CI -0.0142, -0.0019).The Model 3 including all variables, for a one-unit increase in CRP, Total TBS will decrease by 0.0081. However, when CRP was categorized into quartiles, a significant association between CRP and Total TBS was not found. Furthermore, all trend test P-values were <0.05, suggesting a significant decreasing trend in Total TBS with higher CRP levels.

In the subgroup and interaction analyses, all variables were adjusted for except CRP, Total TBS, and the relevant stratification variables. A significant correlation between CRP and Total TBS could not be found among Mexican Americans, Other Hispanics, Other/multiracial individuals, those with a high school education or lower, smokers, and non-drinkers. Additionally, no significant interactions were detected in any subgroup (P for interaction >0.05). The results are illustrated in Fig. 2.

Discussion

This study examined the relationship of CRP and TBS by analyzing health data of adults aged 20 and older in the NHANES database from 2005 to 2008. A significant negative correlation between CRP and TBS was observed overall. Nonetheless, this correlation was not significant in subgroups including Mexican Americans, Other Hispanics, Other/multiracial individuals, those with a high

Table 1 Characteristics of the study population

Characteristic	C-reactive protein (mg/dL)					
	Total	***Q1* (0.01–0.08)**	***Q2* (0.08–0.19)**	***Q3* (0.19–0.44)**	***Q4* (0.44–17.5)**	***P-value***
N	1133	311	271	269	282	
Age (years)	45.230± 16.654	40.550± 16.031	45.439± 16.810	48.881± 16.330	46.709± 16.394	*< 0.0001*
Alanine aminotransferase (U/L)	26.689 ± 18.063	23.868± 13.290	29.594± 25.146	27.238± 14.502	26.485± 17.151	*0.0371*
Aspartate aminotransferase (U/L)	26.076± 12.738	25.514± 12.395	27.369± 15.372	25.591± 8.065	25.915± 13.887	*0.529*
Cholesterol (mg/dL)	197.110± 39.651	190.328± 38.083	198.978± 40.018	201.071± 39.728	199.018± 40.205	*0.003*
Serum calcium (mg/dL)	9.447 ± 0.319	9.485± 0.287	9.476± 0.317	9.452± 0.327	9.374± 0.338	*0.0001*
Blood urea nitrogen (mg/dL)	12.273± 4.595	11.781± 3.954	12.523± 4.273	13.178± 5.175	11.712± 4.824	*0.818*
Serum uric acid (mg/dL)	5.460± 1.334	5.060± 1.257	5.446± 1.276	5.765± 1.391	5.621± 1.309	*< 0.0001*
Total protein (g/dL)	7.168± 0.459	7.146± 0.458	7.190± 0.470	7.154± 0.447	7.185± 0.460	*0.2542*
Serum albumin (g/dL)	4.216 ± 0.322	4.348± 0.298	4.272± 0.294	4.202± 0.282	4.027± 0.319	*< 0.0001*
HDL-C(mg/dL)	55.399 ± 15.927	59.369± 16.896	55.830± 14.645	52.940± 14.774	52.950± 16.224	*0.0001*
LDL-C(mg/dL)	115.535± 35.010	108.688± 32.897	117.332± 34.718	119.996± 35.971	117.106± 35.707	*0.0108*
hemoglobin (g/dL)	14.652± 1.539	14.638± 1.522	14.907± 1.371	14.798± 1.517	14.280± 1.659	*0.0085*
Total TBS	1.393± 0.139	1.454± 0.101	1.409± 0.118	1.361± 0.149	1.340± 0.153	*< 0.0001*
BMI (kg/m2)	28.043± 5.897	24.630± 4.164	27.043 ± 4.616	29.508± 5.294	31.370± 6.834	*< 0.0001*
Gender *(%)*						*< 0.0001*
male	44.1	40.51	35.79	43.12	57.09	
female	55.9	59.49	64.21	56.88	42.91	
Race *(%)*						*0.0988*
Mexican American	19.8	19.29	19.93	19.70	20.21	
Other Hispanic	3.9	2.89	4.80	4.83	3.19	
Non-Hispanic White	49.4	49.20	52.40	50.56	45.74	
Non-Hispanic Black	22.4	22.19	18.45	20.82	28.01	
Other/multiracial	4.5	6.43	4.43	4.09	2.84	
Income to poverty ratio (%)						*0.3177*
Low	37.4	42.77	38.75	34.94	32.62	
Middle	38.1	32.48	38.00	37.92	44.68	
High	24.4	24.76	23.25	27.14	22.70	
Education (%)						*0.2145*
Less than high school	24.0	18.65	23.62	29.74	24.82	
High school	24.2	22.51	25.09	23.79	25.53	
More than high school	51.8	58.84	51.29	46.47	49.65	
Smoke(%)						*0.5159*
Yes	51.2	54.98	50.18	45.72	53.19	
No	48.8	45.02	49.82	54.28	46.81	
Drinking status(%)						*0.0001*
Yes	26.3	20.58	23.25	26.02	35.82	
No	73.7	79.42	76.75	73.98	64.18	

Data are presented as weighted mean±standard deviation or percentage (%).BMI: Body Mass Index, HDL-C: High-Density Lipoprotein Cholesterol, LDL-C: Low-Density Lipoprotein Cholesterol, Drinking status (drinking at least 12 drinks per year), Smoke (at least 100 cigarettes smoked in a lifetime)

Table 2 Association of CRP with total TBS

Association of CRP with Total TBS.	Model1	β	(95% CI)	P	Model 2	β	(95% CI)	P	Model 3	β	(95% CI)	P
CRP increase per 1 mg/dL increase		-0.0258	(-0.0405, -0.0109)	< 0.001		-0.0235	(-0.0377, -0.0094)	0.001		-0.0081	(-0.0142, -0.0019)	*0.009*
CRP (quartile)												
Q1 (0.01-0.08 mg/dL)		ref				ref				ref		
Q2 (0.08-0.19 mg/dL)		-0.0395	(-0.0596, -0.0195)	< 0.001		-0.0182	(-0.0362, -0.0001)	0.048		1.6289	(-0.0014, 0.3340)	*0.071*
Q3 (0.19-0.44 mg/dL)		-0.1001	(-0.1255, -0.0747)	< 0.001		-0.0708	(-0.0933, -0.0483)	< 0.001		-1.8994	(-0.0231, 0.0193)	*0.861*
Q4 (0.44-17.5 mg/dL)		-0.1061	(-0.1311, -0.0812)	< 0.001		-0.0902	(-0.1135, -0.0668)	< 0.001		-2.6995	(-0.025, 0.0196)	*0.812*
P for trend		0.0006				0.0011				0.0094		

Model 1: Unadjusted covariates. Model 2: Adjusted for race, gender, and age. Model 3: Adjusted for age, sex, race, Education, Income-to-poverty ratio, BMI, Drinking status, Smoke, serum albumin, Alanine aminotransferase, Aspartate aminotransferase, blood urea nitrogen, serum calcium, cholesterol, total protein, C-reactive protein, HDL-C, LDL-C, hemoglobin

school or lower education, smokers, and non-drinkers. The findings of this study suggest that maintaining lower CRP levels might result in higher TBS levels, potentially contributing to the prevention of osteoporosis and fractures.

Osteoporosis is a chronic metabolic bone disease characterized by reduced bone density and deterioration of bone microarchitecture [2, 20]. Osteoporotic fractures are severe complications of osteoporosis that have a significant impact on patients' quality of life and can even result in fatalities [3]. While it is widely recognized that bone mineral density (BMD) remains a crucial method for evaluating osteoporosis, BMD primarily indicates bone mass and does not directly assess the deterioration of bone microarchitecture [7, 21]. In many patients with fragility fractures, BMD levels may be marginally low or even fall within the normal range [7], so relying solely on BMD assessment may underestimate the risk of fractures. TBS is a new method that involves extracting bone microstructure evaluations from DXA images [21]. Comparing with BMD, TBS provides a more comprehensive reflection of bone data and is particularly useful in assessing fracture risk in individuals with normal bone density but compromised bone microstructure [8]. Studies have demonstrated that TBS exhibits superior fracture risk prediction capabilities compared to BMD, particularly in individuals with risk factors such as rheumatoid arthritis, primary hyperparathyroidism, and thyroid cancer patients undergoing suppressive therapy with thyroid-stimulating hormone [22–24]. TBS is recognized as an independent risk factor for fractures and has been consistently shown to predict both current and future fragility fractures, regardless of BMD and FRAX assessments [7–9]. The combination of TBS and FRAX can enhance the accuracy of predicting fracture risk [9, 25]. Various factors thought to be linked to TBS, including uric acid, blood cadmium levels, BMI, and diabetes, are becoming the focus of increased research interest [8, 26–28]. Nevertheless, the association between CRP and TBS remains uncertain.

CRP serves as a sensitive indicator reflecting the general inflammatory status [10]. Several studies indicate a link between elevated CRP levels and reduced BMD levels [18, 29, 30]. Some studies have reported that while there may not be a significant link between elevated CRP levels and reduced BMD [31], higher CRP levels are still linked to a greater risk of fractures [13, 32]. This could be due to the limitations of assessing bone quality and changes in bone microstructure based solely on BMD levels. In cases of fragility fractures, many patients may have BMD levels that seem marginally low or even within the normal range [7, 8]. When studies involve a larger population with normal BMD but possibly altered bone microstructure, CRP levels may not correlate with

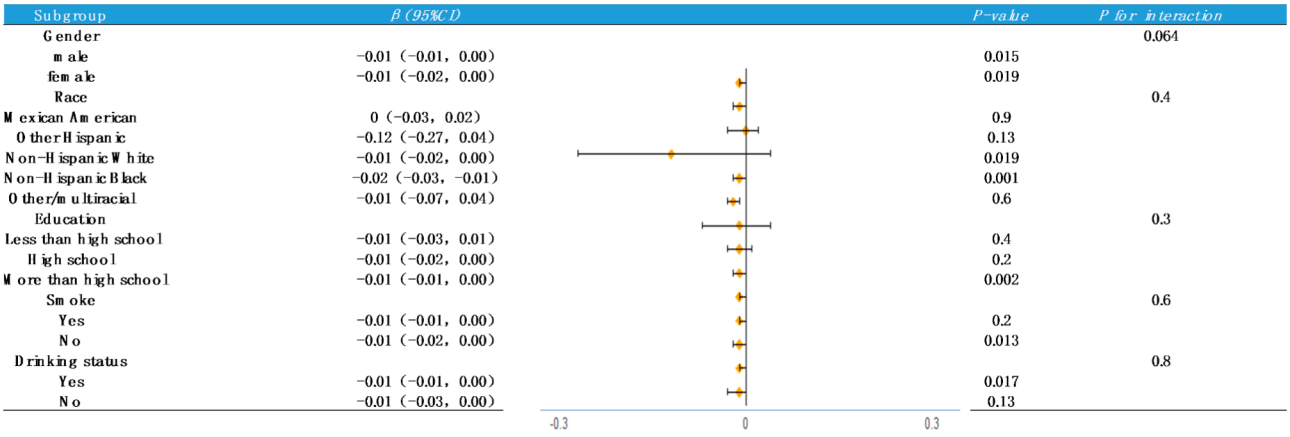

Fig. 2 The subgroup and interaction analyses between CRP and TBS

BMD [31], but could be linked to an increased fracture risk. Our research revealed a notable negative correlation between CRP and TBS, implying that inflammation might contribute to the degradation of bone microstructure. Several potential mechanisms have been proposed to elucidate this association. Elevated CRP levels in the liver can increase the expression of additional inflammatory markers like interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) [33, 34]. IL-6 and TNFα have the ability to enhance osteoclast activity and suppress osteoblast function, resulting in decreased bone mass and structural impairments [35, 36]. NLRP3 is an intracellular multiprotein that plays a critical role in inflammation and immune responses [37]. Fang et al. discovered that CRP can upregulate NLRP3 expression via the FcγRs/NF-κB pathway [38]. NLRP3 can inhibit bone differentiation by inhibiting SIRT1 and inducing bone marrow mesenchymal stem cells (BMSC) differentiation into adipocytes [39], Elevated levels of NLRP3 inflammasome expression can enhance bone resorption [39, 40]. Moreover, inflammation can upregulate the production of ROS (reactive oxygen species); excessive ROS can diminish the quantity and capacity of osteoblasts, leading to impaired bone formation and eventual bone fragility [41].

The association between inflammation and bone health has garnered recent scholarly attention. This study revealed a remarkable negative correlation between CRP and TBS. This correlation remained statistically significant even after adjusting for all covariates. In subgroup analysis, the negative correlation persisted, particularly among non-Hispanic white and black individuals with education beyond high school. CRP measurement can be a valuable adjunct for evaluating bone health in clinical settings. Integrating CRP levels with traditional bone density assessments can offer a more holistic evaluation of fracture risk. Additionally, incorporating TBS into routine bone health screenings may improve the accuracy of fracture risk assessment, assisting clinicians in tailoring personalized treatment strategies.

This study possesses several notable strengths. Firstly, there is a paucity of prior research examining the correlation of CRP and TBS. Secondly, the study employed a multivariable adjustment model to account for confounding variables. Moreover, subgroup analysis helped us to enhance the understanding of the relationship between CRP and TBS across different scenarios. However, this study also exhibits limitations as it is a cross-sectional design, precluding the establishment of a causal relationship between CRP and TBS. Additionally, the study's participants were exclusively from America, which may not be generalizable to other countries or regions. Furthermore, the lack of access to data on other inflammatory markers such as IL-6 and TNFα from the NHANES database could introduce confounding by other inflammatory factors.

Conclusion

In the adult population of America, we found a notable negative correlation in CRP- TBS. CRP serves as a readily available blood marker in clinical settings, and the integration of CRP with BMD can improve the precision of fracture risk assessment. Additionally, we recommend the inclusion of TBS in standard bone health screenings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13018-024-05014-1.

Supplementary Material 1

Acknowledgements

Our sincere gratitude to NHANES for the valuable data provided. We extend our thanks to all study participants and patients. Special appreciation to contributors who guided and aided in the writing of this research.

Author contributions
H.Z and C.H conceptualized and drafted the manuscript; H.Z and H.K conducted data collection and processing; H.Z, H.K, and S.J performed data analysis and engaged in constructive discussions. All authors contributed to the writing and editing of this article and have reviewed and approved the final version for submission.

Funding
This study did not involve any related funding.

Data availability
Sequence data that support the findings of this study have been deposited in the NHANES (https://www.cdc.gov/nchs/nhanes/index.htm.)

Declarations

Ethics approval and consent for participation
NHANES database has got ethical approval from the National Center for Health Statistics (NCHS) to safeguard the data's security and confidentiality. Researchers can request access to the database directly without the requirement for an additional ethical approval process

Competing interests
The authors declare no competing interests.

Received: 6 April 2024 / Accepted: 19 August 2024
Published online: 29 August 2024

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