The pan-immune-inflammation value is associated with all-cause and cardiovascular mortality among individuals with diabetes

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Submitted: 11 January 2026; **Accepted:** 18 April 2026
Online publication: 18 August 2026

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/220758

Abstract

Introduction: Diabetes is a major global health burden, with chronic inflammation playing a central role in its progression and complications. The pan-immune-inflammation value (PIV) is a novel composite biomarker reflecting systemic immune inflammation. However, its prognostic value for mortality in individuals with diabetes remains unclear.

Material and methods: We conducted a retrospective cohort analysis using the nationally representative National Health and Nutrition Examination Survey (NHANES) data, including participants aged ≥ 20 with available PIV data. PIV was calculated using a validated equation and then log-transformed (ln) before analysis. Multivariable Cox regression models were employed to evaluate this association. We further explored the dose-response relationship using restricted cubic splines (RCS) and threshold analysis to identify potential non-linear effects. The robustness of findings was confirmed through subgroup and sensitivity analyses, and the potential mediating role of estimated glomerular filtration rate (eGFR) was investigated.

Results: During a median follow-up of 94.9 months, 2,549 deaths were recorded, including 727 attributable to cardiovascular diseases. Elevated lnPIV levels were strongly associated with increased all-cause and cardiovascular mortality. Critical thresholds were identified at lnPIV values of 5.056 for all-cause mortality and 5.586 for cardiovascular mortality. These core associations were stable across all subgroup and sensitivity analyses. Furthermore, mediation analysis estimated that eGFR accounted for 5.1% and 6.4% of the lnPIV-associated risk for all-cause and cardiovascular mortality, respectively.

Conclusions: Pan-immune-inflammation value was found to be independently associated with increased risks of all-cause and cardiovascular mortality in individuals with diabetes, characterized by a nonlinear association and a distinct threshold effect. These findings suggest that PIV could serve as a practical biomarker for risk stratification, potentially identifying patients who may benefit from more intensive management of both inflammation and renal function.

Key words: pan-immune-inflammation value, diabetes, mortality, estimated glomerular filtration rate, cardiovascular risk.

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia and a spectrum of microvascular and macrovascular complications. It constitutes a major global health burden, imposing substantial morbidity, mortality, and economic costs on healthcare systems worldwide. The International Diabetes Federation's latest Global Diabetes Atlas estimated that approximately 589 million adults aged 20–79 years were living with diabetes in 2024 [1, 2]. The overall and cardiovascular mortality rates among diabetic individuals vary across different populations and regions, influenced by factors such as healthcare accessibility, socioeconomic status, and the quality of diabetes management. In the majority of developing nations, limited availability of effective diabetes management and care exacerbates the cardiovascular mortality burden among diabetics. Therefore, it is necessary to strengthen diabetes monitoring and management, so as to reduce the rate of readmission and mortality of patients.

Research has demonstrated that individuals with systemic inflammatory disorders have a substantially higher risk of developing all-cause and cardiovascular mortality than healthy individuals, suggesting that inflammatory parameters can be used as prognostic indicators for cardiovascular disease and long-term survival among patients with diabetes [3–5]. Recently, combined prognostic score-based hematological indices from peripheral blood counts have attracted great interest as indirect measures of cancer-related inflammatory responses [6–8]. PIV is a novel comprehensive inflammatory biomarker that incorporates lymphocyte, neutrophil, monocyte, and platelet counts [9], and its potential applications have not been extensively investigated since its first proposal. PIV has been shown to be effective in assessing the risk and prognosis of many malignancies, such as colorectal, breast, and laryngeal tumors. It is also beneficial in monitoring and acts as an indication of human immunological response and inflammation [10–13]. Inflammatory factors are known to mediate a cascade of metabolic disturbances and immune responses in the development of diabetes [14, 15]. However, the relationship between PIV and risk of mortality among individuals with diabetes is currently unclear, as is the subsequent dose-response relationship.

Therefore, using a nationally representative dataset from NHANES 1999–2018, we performed a retrospective cohort analysis to examine the relationship between PIV and risk of mortality among participants with diabetes and to further determine the prognostic role of PIV in the management of diabetes.

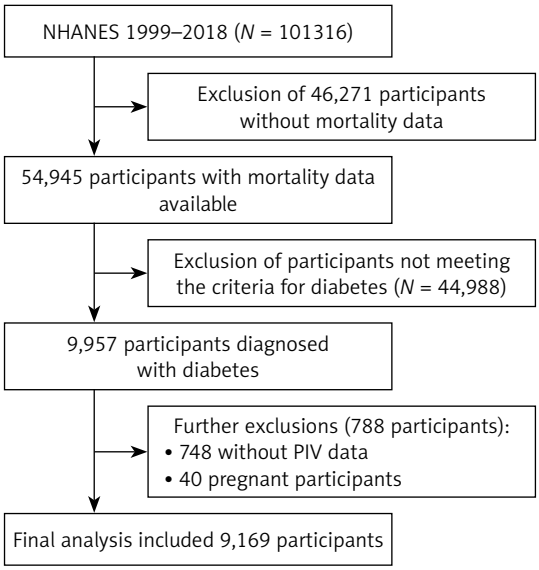


Figure 1. Flowchart of participants' selection for this study

Material and methods

Study population

We collected data from 1999-2018 cycles of the NHANES database, a nationally cross-sectional study administered by the Centers for Disease Control and Prevention (CDC) designed to evaluate the health and nutrition status of the American population. All participants in this research provided their written informed consent and took part in the NHANES survey according to the protocol, thereby ensuring adherence to rigorous ethical principles. Detailed methodological protocols and access to the NHANES dataset are available through the official portal of the CDC. From an initial sample of 101,316 individuals, we excluded those aged < 20 years or with unavailable mortality data (n = 46,271), those without diabetes (n = 44,988), and those with missing data for PIV or who were pregnant (n = 788). Diabetes status was defined according to the American Diabetes Association guidelines, incorporating both biochemical measures and clinical history. Specifically, individuals meeting at least one of the following criteria were considered diabetic: self-reported diagnosis, active use of diabetes medication, a fasting glucose level ≥ 7.0 mmol/l, a 2-hour post-load glucose level ≥ 11.1 mmol/l, or an HbA1c value ≥ 6.5%. The final analytical cohort comprised 9,169 eligible adults (Figure 1).

Assessment of mortality and follow-up

To ascertain all-cause and cardiovascular mortality among study participants, their data were merged with statistics sourced from the National Death Index (NDI). Based on NDI information, par-

ticipants were categorized as deceased or surviving, with follow-up duration calculated from the enrollment date to December 31, 2019. Employing the Tenth Revision of the International Classification of Diseases (ICD-10), the primary causes of death were clearly defined. In particular, cardiovascular mortality was defined based on ICD-10 codes I00-I09, I11, I13, and I20-I51 [16].

Calculation of PIV

The NHANES mobile examination center is equipped with the Beckman Coulter DxH 800 device, which not only generates complete blood count (CBC) reports for blood samples but also conducts a comprehensive analysis of blood cellular components for all individuals involved. The PIV metric is derived from carefully tested blood samples, following strict standardized collection methods to ensure the accuracy and consistency of the collected data. This PIV calculation is primarily based on the results of the CBC assessment. Specifically, the counts of platelets, neutrophils, and lymphocytes are precisely determined at a concentration of 1,000 cells per microliter. The calculation of PIV follows a precise equation: PIV= platelet count × neutrophil count × monocyte count/lymphocyte count [17].

Definition of covariates

To minimize confounding bias in our analysis, we pre-specified and adjusted for potential confounding variables. At the socio-demographic level, our research included age distribution of participants, gender, race, body mass index (BMI) classification (< 24.9, 25–29.9, and ≥ 30 kg/m^2), educational degrees (classified as incomplete high school, high school and above), and quantification of household economic status, using the household poverty to income ratio (PIR) as an indicator. The specific ranges are ≤ 1.35, 1.35–1.85, and > 1.85. For laboratory tests, we focused on several crucial biomarkers, such as fast blood glucose, hemoglobin A1c (HbA1c), homeostatic model assessment of insulin resistance (HOMA-IR), albumin, eGFR, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride levels. The presence of hypertension, coronary heart disease (CHD), stroke, bronchitis, or cancer was determined by self-reported physician diagnosis. We followed the standard definition of smoking history that individuals were considered as smokers if their lifetime cigarette consumption exceeded 100 cigarettes. Alcohol consumption was categorized as follows: non-drinkers are individuals who report consuming fewer than 12 alcoholic drinks in their entire lifetime, light-to-moderate drinkers are defined as those who consume less than one drink per day for women and up to two drinks per day for men, heavy drinkers are individuals who exceed the thresholds for light-to-moderate consumption, and former drinkers are individuals who have consumed 12 or more alcoholic drinks in their lifetime but report not drinking alcohol in the past year [18]. Detailed methodology and covariate criteria are described in the CDC NHANES guidelines, available at www.cdc.gov/nchs/nhanes/.

Statistical analysis

Statistical analysis was performed using R software (version 4.4.2) and EmpowerStats (version 5.2). The criterion of statistical significance was established at $p < 0.05$. The PIV data are unevenly distributed and their values were log-transformed (ln) before conducting statistical analysis. Participants were divided into four groups based on quartiles (Q1–Q4) of the lnPIV index. Continuous data are presented as mean ± SD, while categorical data are presented as percentages. The categorical variables were compared using the χ^2 test, while the association between continuous variables was analyzed through a linear regression model. To further explore the association between PIV and mortality, we constructed three multivariate Cox regression models: model 1 (a model adjusted only for gender, age, race, education and PIR), model 2 (further adjusted for BMI, smoking history, drinking status and history of hypertension, CHD, stroke, bronchitis, cancer and diabetes medication), and model 3 (fully adjusted, including all potential confounding factors). To explore the threshold effects of PIV and mortality, we employed a two-piecewise linear regression model with an RCS analysis to assess non-linear associations and identify the inflection point value. In addition, we conducted a subgroup analysis stratified by gender, race, age, PIR, BMI, smoking history, drinking status, diabetes medication, as well as the presence or absence of hypertension, CHD, stroke, bronchitis and cancer, to examine in detail the differences and similarities in different settings. Subsequently, we performed interaction tests to assess whether there were significant differences in effects among these subgroups. To examine the stability of the models, we finally performed the sensitivity analysis by excluding participants with follow-up shorter than 2 years or with missing data for any variable used in the primary analyses, and we further excluded individuals with a history of hypertension, CHD, stroke, bronchitis, or cancer, as well as participants with extreme lnPIV values (defined as mean ± 3 SD). We conducted a mediation analysis to examine the extent to which the association between PIV and mortality was mediated through the pathway

of eGFR. All missing values for variables were imputed using the "mice" package.

Results

Baseline characteristics

The baseline characteristics of the participants are summarized in Table I. This study incorporated 9169 participants with an average age of 61.37 ±13.77 years, including 4706 (51.33%) males and 4463 (48.67%) female. Participant characteristics exhibited significant variation across lnPIV quartiles. Higher lnPIV quartiles were associated with increasing age and a higher proportion of Non-Hispanic White individuals, active smokers, and individuals with an educational attainment

Table I. Baseline characteristics of selected individuals according to lnPIV quartiles

Parameter	Total (*n* = 9169)	Q1 (*n* = 2292)	Q2 (*n* = 2292)	Q3 (*n* = 2292)	Q4 (*n* = 2293)	*P*-value
Age [years]	61.37 ±13.77	60.47 ±12.89	61.05 ±13.58	61.62 ±13.96	62.35 ±14.53	< 0.001
Gender (%)						0.314
Male	4706 (51.33%)	1161 (50.65%)	1151 (50.22%)	1184 (51.66%)	1210 (52.77%)	
Female	4463 (48.67%)	1131 (49.35%)	1141 (49.78%)	1108 (48.34%)	1083 (47.23%)	
Race (%)						< 0.001
Mexican American	1828 (19.94%)	425 (18.54%)	540 (23.56%)	468 (20.42%)	395 (17.23%)	
Other Hispanic	837 (9.13%)	212 (9.25%)	217 (9.47%)	218 (9.51%)	190 (8.29%)	
Non-Hispanic White	3391 (36.98%)	547 (23.87%)	756 (32.98%)	947 (41.32%)	1141 (49.76%)	
Non-Hispanic Black	2239 (24.42%)	838 (36.56%)	568 (24.78%)	450 (19.63%)	383 (16.70%)	
Other race or multi-racial	874 (9.53%)	270 (11.78%)	211 (9.21%)	209 (9.12%)	184 (8.02%)	
Educational degree (%)						0.007
Incomplete high school	3372 (36.78%)	881 (38.44%)	891 (38.87%)	821 (35.82%)	779 (33.97%)	
High school	2088 (22.77%)	501 (21.86%)	517 (22.56%)	512 (22.34%)	558 (24.33%)	
Above high school	3709 (40.45%)	910 (39.70%)	884 (38.57%)	959 (41.84%)	956 (41.69%)	
PIR (%)						0.069
≤ 1.35	3471 (37.86%)	884 (38.57%)	883 (38.53%)	818 (35.69%)	886 (38.64%)	
> 1.35, ≤ 1.85	1246 (13.59%)	304 (13.26%)	280 (12.22%)	343 (14.97%)	319 (13.91%)	
> 1.85	4452 (48.55%)	1104 (48.17%)	1129 (49.26%)	1131 (49.35%)	1088 (47.45%)	
BMI [kg/m^2]	32.03 ±7.45	31.19 ±6.84	31.72 ±6.99	32.46 ±7.41	32.75 ±8.37	< 0.001
Cigarette consumption > 100 (%)						< 0.001
Yes	4608 (50.26%)	1048 (45.72%)	1086 (47.38%)	1178 (51.40%)	1296 (56.52%)	
No	4561 (49.74%)	1244 (54.28%)	1206 (52.62%)	1114 (48.60%)	997 (43.48%)	
Drinking status						< 0.001
Never	1651 (18.01%)	409 (17.84%)	467 (20.38%)	417 (18.19%)	358 (15.61%)	
Mild-to-moderate	2761 (30.11%)	697 (30.41%)	634 (27.66%)	717 (31.28%)	713 (31.09%)	
Heavy	1941 (21.17%)	518 (22.60%)	499 (21.77%)	464 (20.24%)	460 (20.06%)	
Former	2816 (30.71%)	668 (29.14%)	692 (30.19%)	694 (30.28%)	762 (33.23%)	
History of diseases						
Hypertension (%)						< 0.001
Yes	5855 (63.86%)	1411 (61.56%)	1419 (61.91%)	1472 (64.22%)	1553 (67.73%)	
No	3314 (36.14%)	881 (38.44%)	873 (38.09%)	820 (35.78%)	740 (32.27%)	

Table I. Cont.

Parameter	Total (*n* = 9169)	Q1 (*n* = 2292)	Q2 (*n* = 2292)	Q3 (*n* = 2292)	Q4 (*n* = 2293)	*P*-value
Coronary heart disease (%)						< 0.001
Yes	928 (10.12%)	173 (7.55%)	228 (9.95%)	247 (10.78%)	280 (12.21%)	
No	8241 (89.88%)	2119 (92.45%)	2064 (90.05%)	2045 (89.22%)	2013 (87.79%)	
Stroke (%)						< 0.001
Yes	786 (8.57%)	173 (7.55%)	165 (7.20%)	209 (9.12%)	239 (10.42%)	
No	8383 (91.43%)	2119 (92.45%)	2127 (92.80%)	2083 (90.88%)	2054 (89.58%)	
Bronchitis (%)						< 0.001
Yes	812 (8.86%)	159 (6.94%)	178 (7.77%)	205 (8.94%)	270 (11.77%)	
No	8357 (91.14%)	2133 (93.06%)	2114 (92.23%)	2087 (91.06%)	2023 (88.23%)	
Cancer (%)						< 0.001
Yes	1248 (13.61%)	265 (11.56%)	269 (11.74%)	332 (14.49%)	382 (16.66%)	
No	7921 (86.39%)	2027 (88.44%)	2023 (88.26%)	1960 (85.51%)	1911 (83.34%)	
Diabetes treatment						< 0.001
No insulin or drugs	3760 (41.01%)	1031 (44.98%)	918 (40.05%)	935 (40.79%)	876 (38.20%)	
Only drugs	3749 (40.89%)	932 (40.66%)	980 (42.76%)	931 (40.62%)	906 (39.51%)	
Only insulin	799 (8.71%)	158 (6.89%)	192 (8.38%)	187 (8.16%)	262 (11.43%)	
Drugs and insulin	861 (9.39%)	171 (7.46%)	202 (8.81%)	239 (10.43%)	249 (10.86%)	
Laboratory features						
HbA1c	7.17 ±1.74	7.22 ±1.86	7.21 ±1.74	7.18 ±1.76	7.09 ±1.60	0.047
Fasting blood glucose	8.66 ±3.54	8.68 ±3.75	8.72 ±3.62	8.72 ±3.56	8.51 ±3.20	0.137
HOMA.IR	9.15 ±14.42	8.45 ±12.84	8.72 ±13.26	9.88 ±16.07	9.57 ±15.22	0.002
Albumin	41.29 ±3.52	41.62 ±3.48	41.53 ±3.24	41.32 ±3.45	40.68 ±3.79	< 0.001
eGFR	68.38 ±29.21	70.96 ±27.84	70.18 ±29.13	67.44 ±29.15	64.92 ±30.28	< 0.001
Total cholesterol [mg/dl]	190.18 ±46.29	193.00 ±46.17	191.83 ±45.37	190.62 ±47.42	185.30 ±45.84	< 0.001
Triglyceride [mg/dl]	214.89 ±212.78	213.84 ±218.33	214.45 ±212.73	227.10 ±224.05	204.18 ±194.35	0.004
LDL cholesterol [mg/dl]	99.33 ±43.65	101.07 ±43.52	101.03 ±43.18	98.20 ±43.79	97.04 ±43.99	0.002
HDL cholesterol [mg/dl]	48.68 ±15.00	50.03 ±15.53	48.74 ±14.64	47.88 ±14.12	48.08 ±15.57	< 0.001
Lymphocyte count [1000 cells/µl]	2.19 ±1.09	2.34 ±1.68	2.24 ±0.78	2.17 ±0.79	2.00 ±0.79	< 0.001
Monocyte count [1000 cells/µl]	0.58 ±0.21	0.44 ±0.15	0.53 ±0.14	0.60 ±0.15	0.74 ±0.26	< 0.001
Neutrophil count [1000 cells/µl]	4.52 ±1.75	3.03 ±0.93	4.01 ±0.97	4.80 ±1.23	6.24 ±1.84	< 0.001
Platelet count [1000 cells/µl]	245.14 ±72.20	205.46 ±58.68	232.75 ±58.43	254.27 ±61.48	288.07 ±81.03	< 0.001
PIV	338.92 ±292.00	117.04 ±35.25	215.86 ±28.07	331.93 ±42.48	690.69 ±386.01	< 0.001
lnPIV	5.58 ±0.70	4.70 ±0.38	5.37 ±0.13	5.80 ±0.13	6.45 ±0.37	< 0.001
All-cause death	2549 (27.80%)	489 (21.34%)	568 (24.78%)	649 (28.32%)	843 (36.76%)	< 0.001
Cardiovascular death	727 (7.93%)	148 (6.46%)	157 (6.85%)	178 (7.77%)	244 (10.64%)	< 0.001

Mean ± SD for continuous variables: the p-value was calculated by a linear regression model. % for categorical variables; the p-value was calculated by a χ^2 test. PIV – pan-immune-inflammation value, PIR – poverty income ratio, BMI – body mass index, HbA1c – hemoglobin A1c, HOMA.IR – homeostatic model assessment of insulin resistance, eGFR – estimated glomerular filtration rate, HDL – high-density lipoprotein.

above high school level. Similarly, the proportions of individuals diagnosed with hypertension, CHD, stroke, bronchitis and cancer were found to be significantly higher in the highest group than those in the lowest group. Additionally, the highest lnPIV quartile was characterized by elevated BMI and PIV, but lower concentrations of HbA1c, lipids (TC, LDL-C, and triglycerides), serum albumin, and eGFR compared with the lowest quartile.

Association between PIV and risk of mortality

During an average follow-up duration of 94.9 months, a total of 2,549 deaths were recorded among participants. Cardiovascular diseases were responsible for 727 of these deaths. Table II presents the relationship between lnPIV and risk of mortality, indicating that an elevated lnPIV level is associated with a higher risk of mortality. In model 1, lnPIV was positively associated with the risk of all-cause mortality (HR = 1.37; 95% CI: 1.29–1.46; $p < 0.0001$) and the risk of cardiovascular mortality (HR = 1.42; 95% CI: 1.27–1.59; $p < 0.0001$). These significant associations were maintained in model 2 after it was further adjusted for BMI, smoking history, drinking status, hypertension, CHD, stroke, bronchitis, cancer, and diabetes medication. After full adjustment, every unit increment in lnPIV was associated with a 27% increase in the risk of all-cause mortality (HR = 1.27; 95% CI: 1.19–1.35; $p < 0.0001$) and a 31% increase in the risk of cardiovascular mortality (HR = 1.31; 95% CI: 1.17–1.47; $p < 0.0001$). Notably, individuals in the highest lnPIV tertile (Q4) demonstrated a statistically significant 46% elevated risk of all-cause mortality, and a 37% elevated risk of cardiovascular mortality compared to those in the lowest tertile (Q1).

Non-linear relationships and threshold analysis

Non-linear relationships and threshold effects were analyzed using RCS analysis (Figure 2). We identified inflection points at lnPIV = 5.056 and lnPIV = 5.586 for the associations between lnPIV and all-cause mortality and cardiovascular mortality, and quantified the non-linear effects (Table III). Below this threshold, each unit increase in lnPIV was associated with a 30% decrease in the risk of all-cause mortality (HR = 0.76; 95% CI = 0.63–0.91, $p = 0.0032$) and a slight increase in the risk of cardiovascular mortality (HR = 1.03; 95% CI = 0.82–1.29, $p = 0.8016$). However, above the threshold, each unit increase in lnPIV was associated with a 43% increase in the risk of all-cause mortality (HR = 1.43; 95% CI = 1.33–1.53, $p < 0.0001$) and a 56% increase in the risk of cardiovascular mortality (HR = 1.56; 95% CI = 1.30–1.86, $p < 0.0001$). This suggests that PIV exhibited a U-shaped association with all-cause mortality and a J-shaped association with cardiovascular mortality.

Table II. Multivariable Cox regression analysis for mortality among participants with diabetes

Parameter	lnPIV quartiles					Per one-unit increment in lnPIV
	Q1	Q2	Q3	Q4	*p* for trend	
All-cause mortality						
Number of deaths (%)	489 (21.34%)	568 (24.78%)	649 (28.32%)	843 (36.76%)		
Model 1	Reference	1.05 (0.93, 1.19) 0.4322	1.17 (1.04, 1.32) 0.0085	1.64 (1.46, 1.84) < 0.0001	< 0.0001	1.37 (1.29, 1.46) < 0.0001
Model 2	Reference	0.99 (0.88, 1.12) 0.8956	1.13 (1.00, 1.27) 0.0541	1.54 (1.37, 1.73) < 0.0001	< 0.0001	1.33 (1.25, 1.41) < 0.0001
Model 3	Reference	0.98 (0.87, 1.11) 0.7522	1.09 (0.97, 1.23) 0.1472	1.46 (1.30, 1.64) < 0.0001	< 0.0001	1.27 (1.19, 1.35) < 0.0001
Cardiovascular mortality						
Number of deaths (%)	148 (6.46%)	157 (6.85%)	178 (7.77%)	244 (10.64%)		
Model 1	Reference	0.96 (0.76, 1.20) 0.7133	1.05 (0.84, 1.32) 0.6391	1.54 (1.24, 1.90) < 0.0001	< 0.0001	1.42 (1.27, 1.59) < 0.0001
Model 2	Reference	0.89 (0.71, 1.12) 0.3115	1.00 (0.80, 1.26) 0.9795	1.42 (1.15, 1.76) 0.0012	0.0001	1.37 (1.22, 1.53) < 0.0001
Model 3	Reference	0.89 (0.71, 1.11) 0.3047	0.97 (0.78, 1.22) 0.8142	1.37 (1.10, 1.69) 0.0041	0.0007	1.31 (1.17, 1.47) < 0.0001

Model 1: adjusted for gender, age, race, education, PIR. Model 2: adjusted for gender, age, race, education, PIR, BMI, smoking history, drinking status, hypertension, CHD, stroke, bronchitis, cancer, and diabetes treatment. Model 3: adjusted for gender, age, race, education, PIR, BMI, smoking history, drinking status, hypertension, CHD, stroke, bronchitis, cancer, diabetes treatment, HbA1c, fast blood glucose, HOMA-IR, serum albumin, eGFR, TC, triglyceride, LDL-C, and HDL-C. 95% CI – 95% confidence interval, OR – odds ratio, PIV – pan-immune-inflammation value. P < 0.05 was considered statistically significant.

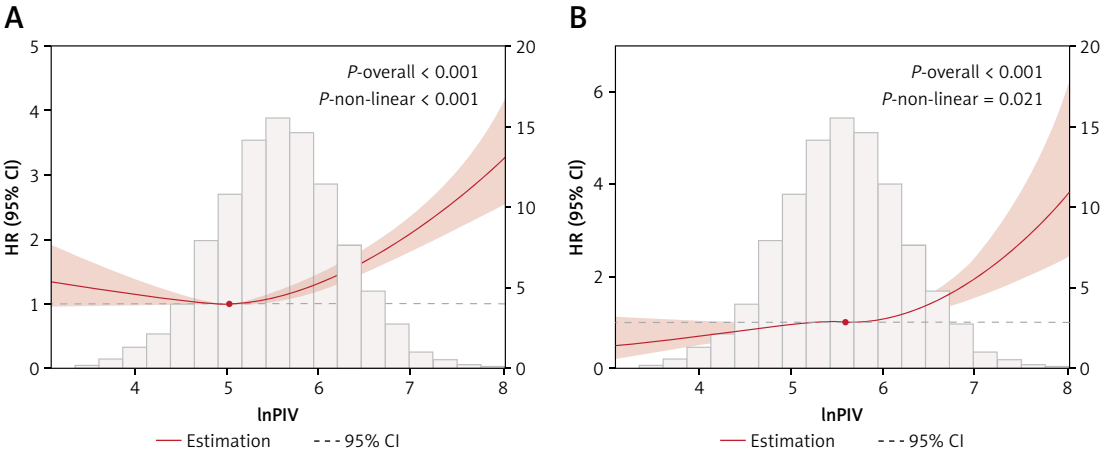


Figure 2. Restricted cubic splines of nonlinear relationships between lnPIV and all-cause (**A**) and cardiovascular mortality (**B**) in participants with diabetes. The analysis was adjusted for gender, age, race, education, PIR, BMI, smoking history, drinking status, hypertension, CHD, stroke, bronchitis, cancer, diabetes treatment, HbA1c, fast blood glucose, HOMA-IR, serum albumin, eGFR, TC, triglyceride, LDL-C, and HDL-C

Table III. Threshold effect for the association between lnPIV and mortality

Parameter	All-cause mortality	Cardiovascular mortality
Infection points (K)	5.056	5.586
K-segment effect 1	0.76 (0.63, 0.91) 0.0032	1.03 (0.82, 1.29) 0.8016
> K-segment effect 2	1.43 (1.33, 1.53) < 0.0001	1.56 (1.30, 1.86) < 0.0001
Effect size difference of 2 versus 1	1.89 (1.51, 2.35) < 0.0001	1.51 (1.08, 2.12) 0.0169

HRs were calculated based on a multivariable Cox proportional hazards regression model adjusted for gender, age, race, education, PIR, BMI, smoking history, drinking status, hypertension, CHD, stroke, bronchitis, cancer, diabetes treatment, HbA1c, fast blood glucose, HOMA-IR, serum albumin, eGFR, TC, triglyceride, LDL-C, and HDL-C.

Subgroup analysis and sensitivity analysis

The positive association between lnPIV and mortality risk was found to be robust and generalizable. Subgroup analyses demonstrated that this association was not significantly affected by a wide range of potential confounding factors (Figures 3 and 4). Specifically, the variables gender, race, age, PIR, BMI, smoking status, alcohol status, hypertension, coronary heart disease, stroke, bronchitis, cancer, and diabetes medication use showed no significant interaction effect ($p > 0.05$ for all subgroups).

The consistency of the results was evaluated by sequentially excluding specific subpopulations. Initially, the exclusion of participants with a prior history of CHD, stroke, bronchitis, or cancer at baseline did not materially alter the primary findings. Subsequently, to mitigate the potential influence of early, non-representative events, we excluded individuals who were followed up for less than 2 years, and the results remained consistent. Additionally, the stability of the results was confirmed after excluding participants with missing data for any variable used in the primary analyses and those with extreme lnPIV values. The detailed outcomes of these sensitivity analyses are comprehensively presented in Supplementary Tables SI to SVII.

Mediation analysis of PIV and risk of mortality

Mediation analysis was used to assess the role of eGFR as a mediator in the relationship between lnPIV and both all-cause and cardiovascular mortality, and identified a significant mediating effect. Specifically, lnPIV was inversely associated with eGFR ($\beta \pm SE = -2.059 \pm 0.582$, $p < 0.00001$), while eGFR was positively correlated with survival for both all-cause ($\beta \pm SE = 0.987 \pm 0.002$, $p < 0.00001$) and cardiovascular cause mortality ($\beta \pm SE = 0.984 \pm 0.004$, $p < 0.00001$). Ultimately, eGFR mediated 5.1% (95% CI: 2.8–8.3%) and 6.4% (95% CI: 3.1–11.1%) of the association between lnPIV and risk of all-cause and cardiovascular mortality, respectively (Figure 5).

Discussion

The interplay between diabetes and inflammatory responses is multifaceted, intricately involving interactions between metabolic dysregulation and multiple peripheral organs. Proinflammatory chemokines and cytokines, notably TNF-α, IL-1, and IL-6, play pivotal roles in sustaining chronic low-grade inflammation, which exerts detrimental impacts on organ systems beyond the pancreas [19, 20]. Notably, extensive research has

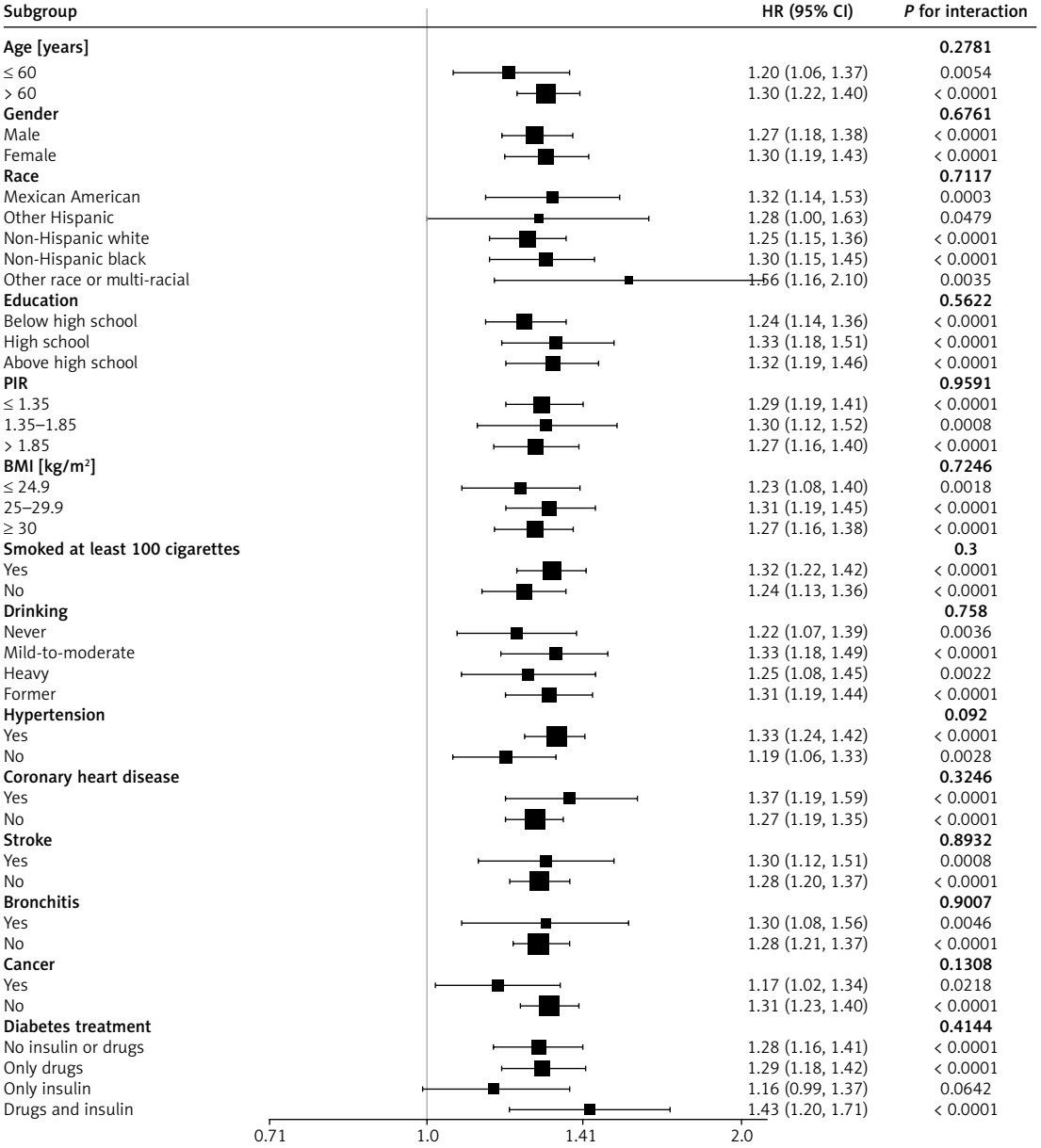
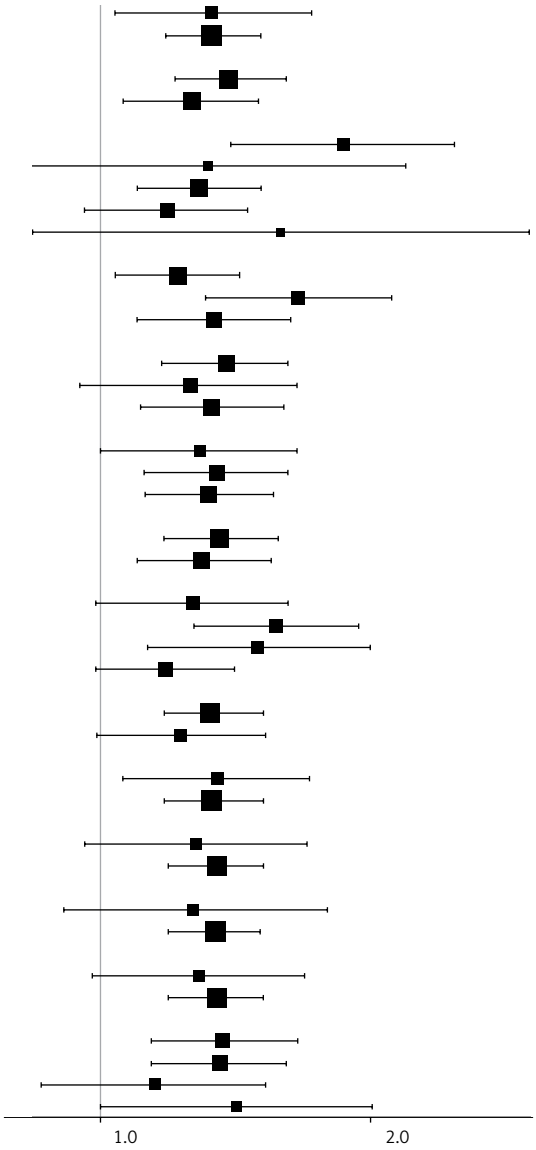


Figure 3. Forest plot for subgroup analysis of the association between lnPIV and all-cause mortality

PIR – poverty income ratio, BMI – body mass index.

confirmed the crucial involvement of these cytokines in the complex mechanisms underlying the pathogenesis of diabetes. Additionally, inflammatory responders including neutrophils, monocytes, lymphocytes, and platelets are also activated and recruited during the development of diabetes. Also, novel inflammatory scores, including the systemic immune-inflammation index and the neutrophil-to-lymphocyte ratio, among others, have been investigated and shown promising potential in predicting diabetes and subsequent all-cause mortality [21, 22]. Thus, as an indicator integrating the four major immune cells, PIV has received great attention ever since it was first proposed.

The current study is the first investigation designed to explore the association between PIV and the risk of all-cause and cardiovascular mortality in individuals with diabetes. It involved a comprehensive analysis of epidemiological data derived from the U.S. adult population. As a novel biomarker in oncology, PIV has received considerable attention for its potential in evaluating the prognosis of various malignant tumors. Specifically, it has been extensively studied in the context of colorectal cancer and breast cancer, demonstrating its ability to reflect the systemic inflammation and immune status of the body. Şahin *et al*. reported that PIV was a pivotal predictor of an enhanced response to chemotherapy among Turkish women diagnosed with breast cancer [23]. Similarly, Sahin *et al*. found a correlation between a decreased PIV level and improved survival out-



Subgroup	HR (95% CI)	*P* for interaction
Age [years]		**0.9987**
≤ 60	1.33 (1.04, 1.72)	0.0251
> 60	1.33 (1.18, 1.51)	< 0.0001
Gender		**0.3756**
Male	1.39 (1.21, 1.61)	< 0.0001
Female	1.26 (1.06, 1.50)	0.0083
Race		**0.1492**
Mexican American	1.86 (1.40, 2.48)	< 0.0001
Other Hispanic	1.32 (0.79, 2.19)	0.2850
Non-Hispanic white	1.29 (1.10, 1.51)	0.0019
Non-Hispanic black	1.19 (0.96, 1.46)	0.1062
Other race or multi-racial	1.59 (0.84, 3.01)	0.1506
Education		**0.1019**
Below high school	1.22 (1.04, 1.43)	0.0166
High school	1.66 (1.31, 2.11)	< 0.0001
Above high school	1.34 (1.10, 1.63)	0.0036
PIR		**0.8497**
≤ 1.35	1.38 (1.17, 1.62)	0.0001
1.35–1.85	1.26 (0.95, 1.66)	0.1080
> 1.85	1.33 (1.11, 1.60)	0.0019
BMI [kg/m^2]		**0.9661**
≤ 24.9	1.29 (1.00, 1.66)	0.0468
25–29.9	1.35 (1.12, 1.62)	0.0016
≥ 30	1.32 (1.12, 1.56)	0.0009
Smoked at least 100 cigarettes		**0.6867**
Yes	1.36 (1.18, 1.58)	< 0.0001
No	1.30 (1.10, 1.55)	0.0025
Drinking		**0.1637**
Never	1.27 (0.99, 1.62)	0.0578
Mild-to-moderate	1.57 (1.27, 1.94)	< 0.0001
Heavy	1.50 (1.13, 2.00)	0.0054
Former	1.18 (0.99, 1.41)	0.0688
Hypertension		**0.3775**
Yes	1.33 (1.18, 1.52)	< 0.0001
No	1.23 (0.99, 1.53)	0.0600
Coronary heart disease		**0.9467**
Yes	1.35 (1.06, 1.71)	0.0141
No	1.33 (1.18, 1.52)	< 0.0001
Stroke		**0.746**
Yes	1.28 (0.96, 1.70)	0.0906
No	1.35 (1.19, 1.52)	< 0.0001
Bronchitis		**0.7607**
Yes	1.27 (0.91, 1.79)	0.1633
No	1.34 (1.19, 1.51)	< 0.0001
Cancer		**0.7587**
Yes	1.29 (0.98, 1.69)	0.0704
No	1.35 (1.19, 1.52)	< 0.0001
Diabetes medication		**0.7283**
No insulin or drugs	1.37 (1.14, 1.66)	0.0009
Only drugs	1.36 (1.14, 1.61)	0.0005
Only insulin	1.15 (0.86, 1.53)	0.3564
Drugs and insulin	1.42 (1.00, 2.01)	0.0472

Figure 4. Forest plot for stratified analysis of the association between lnPIV and cardiovascular mortality

PIR – poverty income ratio, BMI – body mass index.

comes in HER2-positive patients treated with adjuvant trastuzumab [24], whereas no significant association was observed with regard to the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio indicators [25]. In addition, recent investigations have also yielded substantial insights into the relationship between PIV and cardiovascular diseases. Some studies have found that individuals affected by the coronary slow flow phenomenon exhibit markedly elevated PIV levels compared to those with normal coronary flow [26]. Furthermore, a high PIV level serves as an independent risk predictor for ischemic complications following primary percutaneous coronary intervention in patients diagnosed with ST-segment elevation myocardial infarction [27]. Among hypertensive patients, elevated PIV is associated with an increased risk of both all-cause and cardiovascular mortality [28]. Our research suggests that PIV may be considered an independent factor for the risk of all-cause and cardiovascular mortality. The findings would be strengthened if more confounders were taken into account.

The precise mechanisms underlying novel immune markers in the development and progression of diabetes mellitus remain incompletely understood. However, some related research in this field has garnered recognition. Leukocytes contribute to both the pathogenesis and progression of an inflammatory cascade that can exacerbate metabolic derangements and immune cell activation, further compromising vascular structure and

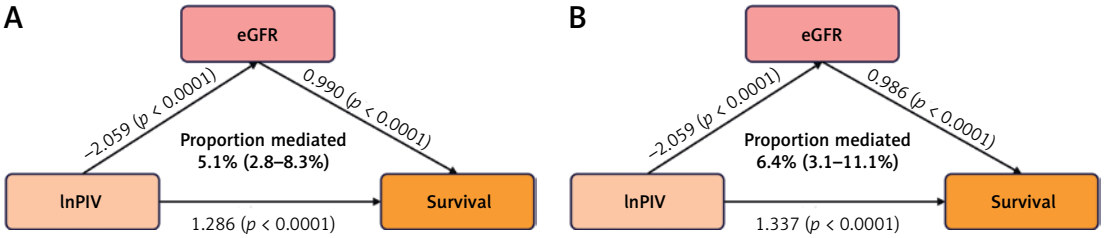


Figure 5. The mediating effect of eGFR on the association between lnPIV and all-cause (**A**) and cardiovascular mortality (**B**). The analysis was adjusted for gender, age, race, education, PIR, BMI, smoking history, drinking status, hypertension, CHD, stroke, bronchitis, cancer, diabetes treatment, HbA1c, fast blood glucose, HOMA-IR, serum albumin, eGFR, TC, triglyceride, LDL-C, and HDL-C

leading to a vicious cycle of decline [29]. The inflammatory response in diabetes is triggered by a myriad of factors, including insulin resistance, β-cell dysfunction, and the development of diabetic complications. These stimuli activate the production of reactive oxygen species and advanced glycation end products, which are patent inducers of oxidative stress and inflammation [30]. Neutrophils, the primary responders in acute inflammation, undergo hyperactivation and prolonged survival in diabetes, leading to excessive release of reactive oxygen species and proteolytic enzymes, which can cause tissue damage and exacerbate chronic inflammation [31, 32]. This neutrophil dysfunction is particularly evident in the development of macrovascular complications, such as atherosclerosis, where neutrophils infiltrate vessel walls and promote plaque formation and instability. As the inflammatory response progresses, monocytes differentiate into functionally distinct subsets, M1 and M2, in response to the diabetic milieu. M1 macrophages are highly inflammatory, secreting pro-inflammatory cytokines and chemokines that amplify the immune response and contribute to insulin resistance. Conversely, M2 macrophages, which are induced by the persistent inflammatory state in diabetes, promote tissue repair and fibrosis but also exacerbate the progression of diabetic nephropathy, retinopathy, and neuropathy [33, 34]. Lymphocytes, particularly T and B cells, play a pivotal role in the autoimmune destruction of pancreatic β cells in type 1 diabetes. However, in type 2 diabetes, T-cell infiltration into adipose tissue and vascular walls promotes insulin resistance and endothelial dysfunction [35], while B cells contribute to inflammation through the production of autoantibodies and cytokines. Platelets, traditionally recognized for their hemostatic function, have emerged as dynamic players in the inflammatory pathways that characterize diabetes mellitus [30]. Hyperglycemia-induced oxidative stress impairs platelet apoptosis, leading to their prolonged survival and sustained inflammatory activity [36, 37]. Additionally, this hyper-reactive platelet phenotype contributes to the progression of diabetic vascular complications by promoting endothelial dysfunction, microvascular damage, and thrombosis. Hyperglycemia also alters the composition and function of the endothelial glycocalyx, a protective layer lining the vessel wall, further perpetuating vascular inflammation and accelerating the development of diabetic complications [38]. We hypothesize that the relationship between inflammatory markers and mortality risk merits further investigation, with potential broader implications for diabetes management. While atherosclerotic cardiovascular disease is the leading cause of death in diabetes, it represents one manifestation of a spectrum of complications arising from chronic inflammation and metabolic disturbance [39]. Our finding that PIV is associated with both all-cause and cardiovascular mortality underscores its utility as a biomarker of this systemic pathological state. The inflammatory pathways reflected by PIV, including endothelial dysfunction, oxidative stress, and immune cell activation, are central to the pathogenesis of other critical diabetic complications, such as diabetic kidney disease and heart failure with preserved ejection fraction [40]. Thus, an elevated PIV may identify patients with a high global burden of inflammatory-driven end-organ damage, accounting for its strong association with all-cause and cardiovascular mortality.

The mediating role of eGFR in the association between PIV and mortality among individuals with diabetes underscores an interconnected cascade driven by metabolic dysregulation, chronic inflammation, and progressive organ damage. Accumulating evidence has established renal function as a central modulator of systemic immune homeostasis, with eGFR decline exacerbating inflammatory pathways that elevate mortality risk in this population [41, 42]. The underlying mechanisms involve a self-perpetuating cycle in which reduced renal filtration capacity and immune dysregulation mutually reinforce each other. As eGFR declines, renal clearance of uremic toxins such as indoxyl sulfate and p-cresyl sulfate diminishes, promoting their accumulation [43]. These solutes act as pro-inflammatory mediators, activating innate immune signaling and sustaining

a low-grade inflammatory state that promotes vascular injury and diabetic complications [44, 45]. Elevated circulating levels of IL-6, TNF-α, and other cytokines further amplify this process, fostering endothelial dysfunction through reduced nitric oxide bioavailability and increased expression of adhesion molecules [46, 47]. Concurrently, oxidative stress, intensified by both uremic toxin accumulation and chronic inflammation, accelerates macrovascular and microvascular damage, thereby driving cardiovascular mortality in diabetes [48, 49]. Taken together, these findings suggest that in diabetic patients with elevated PIV, a therapeutic strategy combining glucose-lowering agents and cardiorenal-protective drugs may yield synergistic survival benefits by simultaneously addressing hyperglycemia, inflammation, and renal vulnerability.

Our study has some strengths and limitations. Firstly, the study was based on multi-ethnic and nationally representative U.S. adults, spanning an extended time period and including a diverse population. This allowed us to conduct subgroup analyses and sensitivity analyses to minimize residual confounding. Furthermore, our study revealed a dose-response relationship through performing non-linear and threshold effect analyses. Nevertheless, the study has some limitations. First, information on participants' diagnostic testing is limited, as diabetes diagnosis were primarily based on self-reported medical questionnaires completed during personal interviews, or just a single serum measurement. Second, the study did not differentiate between type 1 and type 2 diabetes, meaning our results may differ depending on the type of diabetes. Furthermore, due to the constraints of the database, we were unable to incorporate other potential covariates that might influence the association between PIV and risk of mortality. Third, the nature of the retrospective cohort study inherently restricts the conclusion to an association rather than causality. Consequently, future longitudinal studies are crucial to reveal the underlying causal relationship and to evaluate the effectiveness of anti-inflammatory treatment in diabetes.

In conclusion, PIV is independently associated with increased risks of all-cause and cardiovascular mortality in individuals with diabetes, characterized by a nonlinear association and a distinct threshold effect. Notably, eGFR emerged as a mediating factor in the relationship between PIV and mortality. These findings suggest that PIV could serve as a practical biomarker for risk stratification, potentially identifying patients who may benefit from more intensive management of both inflammation and renal function. Future research should focus on elucidating the precise pathophysiological mechanisms through which PIV contributes to adverse outcomes, particularly its interaction with diabetic complications and cardiorenal pathways.

Data availability

The data used in this study are publicly available on the NHANES website. (https://www.cdc.gov/nchs/nhanes/index.htm).

Acknowledgments

The authors wish to thank the participants for their valuable time and effort during the data collection phase of the NHANES project.

Funding

No external funding.

Ethical approval

The protocols for NHANES received approval from the ethics review board of the National Center for Health Statistics, and all participants provided written informed consent.

Conflict of interest

The authors declare no conflict of interest.

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