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Combined association of triglyceride–glucose index and systemic inflammation index on all-cause and cardiovascular mortality

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The triglyceride–glucose and systemic inflammation index have been linked to mortality outcomes. However, their combined impact on all-cause and cardiovascular mortality remains unclear. This study aimed to evaluate the individual and combined associations of the TyG index and SII with mortality using data from NHANES. Associations between TyG, SII, and mortality were assessed using multivariable Cox proportional hazards models and restricted cubic spline (RCS) regression models. Subgroup and sensitivity analyses were also conducted. Compared to individuals with low TyG and low SII, those with high TyG and high SII had a hazard ratio (HR) of 1.29 (95% CI, 1.16–1.44) for all-cause mortality, 1.54 (95% CI, 1.23–1.94) for cardiovascular mortality, 1.56 (95% CI, 1.20–2.04) for cardiac mortality, and 1.60 (95% CI, 0.83–3.08) for cerebrovascular mortality after full adjustment. The ROC curve analysis indicated that the combination of TyG and SII had an AUC of 0.599 for predicting all-cause mortality and 0.613 for cardiovascular mortality. Subgroup and sensitivity analyses yielded consistent findings. In conclusion, these results underscore the significant combined association of the TyG index and SII on all-cause and cardiovascular mortality, highlighting the importance of jointly assessing these indices to better predict mortality outcomes.

Keywords Triglyceride–glucose index, Insulin resistance, Systemic inflammation index, Inflammation, Mortality

Abbreviations

CVD	Cardiovascular diseases
IR	Insulin resistance
TyG	Triglyceride–glucose
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
CRP	C-reactive protein
SII	Systemic immune-inflammation index
NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
ICD-10	Tenth revision
BMI	Body mass index
HR	Hazard ratio
CI	Confidence intervals
ROC	Operating characteristic curves
AUC	Area under the curve

Cardiovascular disease (CVD) has become the leading cause of death and a major contributor to disability worldwide, encompassing conditions such as ischemic heart disease, stroke, and aortic diseases[1]. According to estimates from the World Health Organization, approximately 30% of global deaths are attributable to CVD,

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with around 17.9 million deaths annually[2]. In 2022, the American Heart Association introduced the "Life's Essential 8"[3], which studies have shown to be associated with reduced mortality risk when higher cardiovascular health levels are achieved[4,5].

Insulin resistance (IR) is one of the most critical risk factors for CVD[6]. The triglyceride–glucose (TyG) index, first proposed in 2008, has emerged as a reliable surrogate marker for IR[7–9] and has demonstrated predictive value for atherosclerotic changes, microvascular complications, coronary artery calcification, and the progression of cardiovascular and cerebrovascular diseases[10,11]. Previous research has established a link between the TyG index and both all-cause and CVD mortality, making it a potential tool for predicting CVD onset and progression[12–14].

In recent years, the prediction of cardiovascular events has increasingly focused on indicators derived from routine blood tests, which are widely available and easily accessible in clinical settings[15]. Among these, composite inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) have been validated for their value in predicting slow coronary flow[16]. However, these biomarkers typically reflect only one or two types of immune-inflammatory cells and may not comprehensively represent the body's inflammatory status[17]. The systemic immune-inflammation index (SII), a novel composite inflammation index incorporating three cellular components, provides a more integrated reflection of inflammation and immune balance in the body[18]. It is easily measurable, stable, and has been widely used in the auxiliary diagnosis and prognosis of malignancies[19], coronary artery disease[20], myocardial infarction[21], and more. Previous studies have confirmed that SII is a prognostic indicator of all-cause mortality and major cardiovascular adverse events in elderly patients aged 65 to 85 years with acute myocardial infarction[22].

However, the combined impact of the TyG index and SII on all-cause and cardiovascular mortality has not been adequately studied. Therefore, this study utilized data from the National Health and Nutrition Examination Survey (NHANES) spanning 1999 to 2018 to assess both the individual and combined associations of the TyG index and SII with all-cause and cardiovascular mortality.

Methods

Study design and population

The data utilized in this study were obtained from the 1999–2018 NHANES, which employs a complex, multistage probability sampling method to select a representative sample of the U.S. population. NHANES is designed to assess the health and nutritional status of American adults and children. The research protocol for NHANES was approved by the Ethics Review Board of the National Center for Health Statistics (NCHS), with all participants providing written informed consent. More detailed information can be found at www.cdc.gov/nchs/nhanes/irba98.htm.

This study analyzed data from ten NHANES cycles conducted between 1999 and 2018, sourced from the National Center for Health Statistics at the Centers for Disease Control and Prevention. The inclusion criteria for the analysis were participants aged 20 years or older who had available TyG and SII data, along with relevant mortality follow-up information. Exclusion criteria included missing baseline TyG or SII data, lack of follow-up data, and absence of essential baseline clinical measurements. After applying these criteria, a total of 20,384 participants were included in the final analysis (Fig. 1).

Definitions of TyG, SII, and mortality

The TyG index was calculated using the formula ln(fasting triglycerides [mg/dL] × fasting glucose [mg/dL]/2), as established in previous research[23]. The systemic inflammation index (SII) was defined by dividing the product of peripheral platelet count and neutrophil count by the lymphocyte count[24].

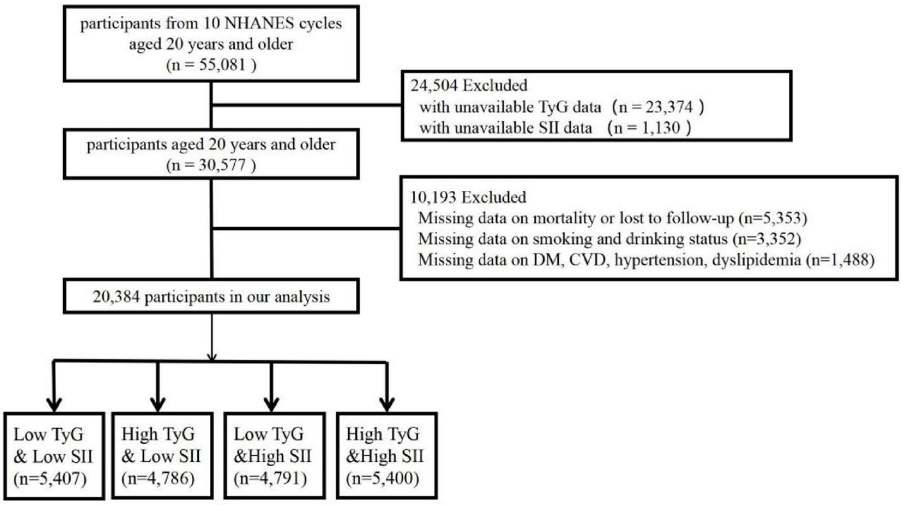


Fig. 1. Flowchart of the selection strategy. TyG triglyceride–glucose index, SII Systemic Inflammation Index, DM diabetes, CVD cardiovascular disease.

For the mortality analysis within NHANES, we determined the vital status of participants using publicly available mortality linkage files, updated through December 31, 2019. These files were linked to the National Death Index (NDI) by the NCHS through a probabilistic matching algorithm. Cause-specific mortality was classified according to the International Classification of Diseases, Tenth Revision (ICD-10). The primary outcomes analyzed in this study were all-cause mortality and cardiovascular mortality, with cardiovascular mortality classified under ICD-10 codes I00-I09, I11, I13, I20-I51, and I60-I69. Additionally, subtypes of cardiovascular mortality, including cardiac mortality (I00-I09, I11, I13, I20-I51) and cerebrovascular mortality (I60-I69), were also examined[25].

Ascertainment of covariates

Various demographic and health-related factors were collected through household interviews within the NHANES database, including age, gender, race/ethnicity, education level, household income, marital status, smoking status, alcohol consumption, use of diabetes and hypertension medications, disease status, dyslipidemia, CVD, and hypertension. The diagnoses of hypertension and dyslipidemia were confirmed through physical examinations and laboratory results[26–29]. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Race/ethnicity was categorized into Mexican American, non-Hispanic Black, non-Hispanic White, other Hispanic, or other. Education levels were classified as above high school, high school or equivalent, and below high school. Household income and poverty index were grouped into low (0–1.0), medium (1.0–3.0), or high (> 3.0) categories. Smoking status was recorded as never smokers, former smokers, or current smokers. Alcohol consumption was classified into heavy drinkers, moderate drinkers, light drinkers, non-drinkers, or former drinkers.

Statistical analysis

All statistical analyses were conducted following CDC guidelines, taking into account the complex, multistage stratified probability sampling design of NHANES. Sample weights, clustering, and stratification were incorporated into the analysis. The NHANES survey design was defined using the svydesign function of survey package in R, specifying primary sampling units (PSUs; variable: SDMVPSU) to adjust for clustering effects and account for correlations among individuals within the same PSU, stratum variables (SDMVSTRA) to reflect the stratified sampling design, and sample weights (WTMEC2YR, 2-year examination weights for 1999–2018) to correct for differential sampling probabilities, ensuring nationally representative results. Continuous variables were presented as weighted means with standard errors (SEs) to reflect the variability in the estimates while accounting for the complex survey design, and categorical variables were expressed as counts with weighted proportions[30].Participants' baseline characteristics were described based on the joint assessment of the TyG index and SII. TyG and SII values were dichotomized at the median, resulting in four groups: low TyG & low SII, high TyG & low SII, low TyG & high SII, and high TyG & high SII. Weighted linear regression was used for continuous variable comparisons, and design-adjusted chi-square tests, based on the Rao-Scott methodology to account for the complex survey design[30,31], were applied for categorical variables.

In the separate analyses of TyG and SII for mortality prognosis, we categorized TyG and SII into tertiles. Survival probabilities were estimated using the Kaplan–Meier method, with participants grouped according to baseline categories (TyG Q1, SII Q1, or low TyG & low SII). Differences between survival curves were assessed using the log-rank test. Cox proportional hazards regression models were employed to first explore the individual associations between TyG and SII with mortality, followed by an assessment of their combined impact on mortality. To test for potential multiplicative effects, an interaction term between TyG and SII (TyG_binary * SII_binary, based on their dichotomized values at medians) was included in Model 3 to evaluate whether the effect of TyG on mortality varies by SII level, or vice versa. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Four models were estimated: Model 0 was unadjusted, Model 1 adjusted for age and gender, Model 2 further adjusted for race, household income, marital status, and education level, and Model 3 additionally adjusted for alcohol consumption, smoking, BMI, dyslipidemia, hypertension, and CVD history. The proportional hazards (PH) assumption was tested for all variables in each model using Schoenfeld residuals tests, adjusted for the NHANES complex survey design in R. The PH assumption was assessed by testing the correlation between scaled Schoenfeld residuals and time, with $p > 0.05$ indicating no violation of the assumption. To visualize the linear or non-linear relationship between TyG or SII levels and mortality, restricted cubic spline analysis with four knots was conducted based on multivariable-adjusted Cox regression models. The four knots for TyG and SII were placed at the 5th, 35th, 65th, and 95th percentiles of its distribution.The discriminative ability of TyG, SII, and their combined indices in predicting all-cause and cardiovascular mortality was evaluated using receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) calculated. Combined associations on mortality of subgroup analyses were stratified by age (≤ 60 and > 60), gender, education level, education level, BMI, DM, hypertension, and hyperlipidemia based on Model 3. To strengthen the robustness of the findings, four sensitivity analyses were performed: (1) excluding individuals with a history of CVD, (2) excluding participants under 45 years of age, (3) excluding those who died within the first two years of follow-up to mitigate potential reverse causality, and (4) incorporating additional adjustments for the use of antihypertensive and antidiabetic medications in the primary analysis.

Results

Baseline characteristics of the study population

After screening data from ten NHANES cycles, a total of 20,384 individuals aged over 20 years met the inclusion criteria and were included in the analysis, as outlined in Fig. 1. The study population had a mean age of 47.51 years, with 49.9% of participants being male. Among the participants, 26.5% (5,407 individuals) were classified into the low TyG & low SII group, 23.5% (4,786 individuals) into the high TyG & low SII group, 23.5%

(4,791 individuals) into the low TyG & high SII group, and 26.5% (5,400 individuals) into the high TyG & high SII group. Participants in the high TyG & high SII group were characterized by a higher likelihood of being older, non-Hispanic White, having an education level below high school, belonging to a middle-income household, having a higher BMI, being current smokers, and having higher prevalences of hypertension and CVD (Table 1 and Supplementary Tables S1A-S1B).

TyG and SII and mortality

During a median follow-up period of 9.3 years (interquartile range: 5.3 to 13.9 years), a total of 3,328 participants (16.3%) died, including 1,071 deaths due to CVD, of which 880 were cardiac deaths and 191 were cerebrovascular deaths. Additionally, 2,257 participants died from non-CVD causes. Kaplan–Meier survival curves for the different groups are illustrated in Supplementary Figures S1A and S1C.

In the analysis of the association between the TyG index and mortality, Model 3 revealed that the HR for all-cause mortality in the Q3 was 1.26 (95% CI, 1.13–1.04). For CVD mortality, the HR for Q3 was 1.53 (95% CI, 1.24–1.88). In the case of cardiac mortality, the HR for Q3 was 1.42 (95% CI, 1.11–1.82), while for cerebrovascular mortality, the HR for Q2 was 2.71 (95% CI, 1.56–4.73) (Fig. 2 and Supplementary Table S2A).

Similarly, in the analysis of SII and mortality, Model 3 demonstrated that the HR for all-cause mortality in Q3 was 1.22 (95% CI, 1.11–1.34). For CVD mortality, the HR was 1.43 (95% CI, 1.20–1.71), and for cardiac mortality, the HR was 1.52 (95% CI, 1.24–1.87). However, the HR for cerebrovascular mortality in Q3 was 1.11 (95% CI, 0.72–1.69) (Fig. 2 and Supplementary Table S2B).

In the combined association of TyG and SII with mortality, compared to the low TyG & low SII group, Model 3 showed the following results: For all-cause mortality, the HRs were 1.29 (95% CI, 1.16–1.44) for the high TyG & high SII group, 1.21 (95% CI, 1.07–1.38) for the low TyG & high SII group, and 1.15 (95% CI, 1.00–1.33) for the high TyG & low SII group. For CVD mortality, the HRs were 1.54 (95% CI, 1.23–1.94), 1.36 (95% CI, 1.08–1.71), and 1.24 (95% CI, 0.95–1.62), respectively. For cardiac mortality, the HRs were 1.56 (95% CI, 1.20–2.04), 1.43 (95% CI, 1.10–1.87), and 1.20 (95% CI, 0.87–1.64). For cerebrovascular mortality, the HRs were 1.60 (95% CI, 0.83–3.08), 0.96 (95% CI, 0.51–1.78), and 1.57 (95% CI, 0.85–2.91), and an increasing trend across different combined groups was observed in Model 3 for mortality outcomes except cerebrovascular mortality (p-trend < 0.001 to < 0.0001) (Fig. 3 and Supplementary Table S2C). To examine potential multiplicative effects between TyG and SII, we included an interaction term (TyG_binary * SII_binary) in the fully adjusted Cox regression model (Model 3). The p-value for the interaction term was 0.4185, indicating no significant multiplicative interaction between TyG and SII in predicting all-cause mortality.

The RCS analysis revealed a nonlinear relationship between the TyG index and all-cause mortality (p for overall trend < 0.001; p for nonlinearity = 0.001), as well as between SII and all-cause mortality (p for overall trend < 0.001; p for nonlinearity = 0.0003). A nonlinear relationship was also observed between the TyG index and CVD mortality (p for overall trend < 0.001; p for nonlinearity = 0.034), while SII showed a linear association with CVD mortality (p for overall trend < 0.001; p for nonlinearity = 0.4645) (Fig. 4).

Finally, the combined predictive value of TyG and SII was evaluated, with ROC curve analysis indicating that the AUC for predicting all-cause mortality was 0.599, and for CVD mortality, it was 0.613. These findings suggest that the combined index has a modest predictive value for CVD mortality (Fig. 5 and Supplementary Figures S2A and S2B).

Subgroup analyses and sensitivity analyses

The results of the Combined association's subgroup analyses for mortality are detailed in Table 2 Supplementary Tables S3A-S3C. The subgroup analysis for all-cause mortality revealed that participants in the high TyG & high SII group had significantly higher mortality risks across various subgroups when compared to the low TyG & low SII group. Specifically, this increased risk was observed in participants aged 20–60 years (HR, 1.81; 95% CI, 1.41–2.33) and those aged 60 years and above (HR, 1.27; 95% CI, 1.12–1.43). Both males (HR, 1.69; 95% CI, 1.42–2.01) and females (HR, 2.26; 95% CI, 1.82–2.82) exhibited higher mortality risks. Higher mortality risks were also noted across BMI categories: BMI ≥ 28 (HR 1.55; 95% CI 1.27–1.89), BMI 24–27.9 (HR 1.80; 95% CI 1.42–2.28), and BMI < 23.9 (HR 2.59; 95% CI 2.02–3.31), as did individuals with varying levels of education, including those with education above high school (HR, 1.95; 95% CI, 1.58–2.40), below high school (HR, 1.67; 95% CI, 1.31–2.13), and those with high school or equivalent education (HR, 2.06; 95% CI, 1.61–2.63). The association was also significant among participants without diabetes (HR, 1.77; 95% CI, 1.53–2.04), with hyperlipidemia (HR, 1.58; 95% CI, 1.35–1.84), without hyperlipidemia (HR, 2.88; 95% CI, 2.15–3.86), with hypertension (HR, 1.45; 95% CI, 1.25–1.68), and without hypertension (HR, 1.76; 95% CI, 1.43–2.15). However, no significant association was found among participants with diabetes (HR, 1.15; 95% CI, 0.87–1.51) (Table 2). The results of the Combined association subgroup analyses for CVD mortality (including heart and cerebrovascular deaths) are thoroughly detailed in Supplementary Tables S3A-S3C.

The Supplementary Tables S4A-S4D, S5A-S5D, S6A-S6D, and S7A-S7B, along with Supplementary Figures S3, S4, and S5, display baseline data, outcomes from various models, and the results of Kaplan–Meier sensitivity tests. After excluding participants with CVD, consistent results were observed. Compared to the low TyG & low SII group, Model 3 showed the following HRs for the high TyG & high SII group: 1.31 (95% CI, 1.15–1.51) for all-cause mortality, 1.47 (95% CI, 1.07–2.01) for CVD mortality, 1.45 (95% CI, 1.02–2.06) for cardiac mortality, and 1.81 (95% CI, 0.78–4.21) for cerebrovascular mortality (Supplementary Tables S4A-S4D). Similarly, after excluding participants who died within two years of follow-up, the high TyG & high SII group showed HRs of 1.31 (95% CI, 1.17–1.46) for all-cause mortality, 1.52 (95% CI, 1.21–1.92) for cardiovascular mortality, 1.58 (95% CI, 1.20–2.09) for cardiac mortality, and 1.39 (95% CI, 0.71–2.73) for cerebrovascular mortality (Supplementary Tables S5A-S5D). Excluding participants under 45 years of age yielded HRs of 1.32 (95% CI, 1.18–1.47) for all-cause mortality, 1.52 (95% CI, 1.22–1.90) for cardiovascular mortality, 1.51 (95% CI, 1.16–

Characteristics	Total (n = 20,384)	High TyG & High SII (n = 5400)	High TyG & Low SII (n = 4786)	Low TyG & High SII (n = 4791)	Low TyG & Low SII (n = 5407)	*p* value
Age, years	47.51(0.23)	51.56(0.30)	50.18(0.31)	45.42(0.37)	43.37(0.40)	< 0.001
TyG	8.63(0.01)	9.17(0.01)	9.18(0.01)	8.17(0.01)	8.10(0.01)	< 0.001
SII	548.27(3.66)	748.15(5.03)	335.87(1.72)	759.23(7.11)	323.70(1.58)	< 0.001
Sex, n(%)						< 0.001
Female	10,092(50.08)	2667(49.06)	1887(38.00)	2795(60.41)	2743(51.03)	
Male	10,292(49.92)	2733(50.94)	2899(62.00)	1996(39.59)	2664(48.97)	
Ethnicity, n (%)						< 0.001
Mexican American	3561(7.94)	1100(8.34)	1053(10.06)	689(6.65)	719(7.07)	
Non-Hispanic Black	4009(10.19)	545(4.81)	814(8.92)	976(10.48)	1674(16.20)	
Non-Hispanic White	9406(70.23)	2945(75.96)	1989(67.85)	2398(72.20)	2074(64.66)	
Other Hispanic	1718(5.45)	472(5.62)	464(5.65)	376(5.33)	406(5.24)	
Other Race: Including Multi-Racial	1690(6.19)	338(5.27)	466(7.52)	352(5.34)	534(6.83)	
Educational level, n (%)						< 0.001
Above high school	10,238(58.69)	2420(53.35)	2172(55.05)	2546(59.66)	3100(65.93)	
High school or equivalent	4709(24.27)	1306(26.64)	1106(25.06)	1153(25.32)	1144(20.32)	
Under high school	5437(17.04)	1674(20.00)	1508(19.89)	1092(15.02)	1163(13.75)	
Family income, n (%)						0.001
High	6400(42.89)	1581(40.99)	1417(41.13)	1538(42.69)	1864(46.33)	
Low	6100(20.72)	1683(21.07)	1526(21.92)	1396(20.89)	1495(19.26)	
Medium	7884(36.39)	2136(37.93)	1843(36.94)	1857(36.41)	2048(34.42)	
Marital status, n (%)						< 0.001
Living with partner	1539(7.73)	347(6.85)	345(7.27)	364(7.52)	483(9.17)	
Married	10,837(56.87)	2977(58.74)	2814(61.43)	2353(53.79)	2693(54.30)	
Never married	3453(17.11)	631(12.36)	585(13.67)	1001(19.84)	1236(21.96)	
other	4555(18.28)	1445(22.05)	1042(17.63)	1073(18.86)	995(14.57)	
BMI[a], kg/m2						< 0.001
< 23.9	4687(24.64)	711(12.98)	624(13.05)	1526(33.87)	1826(36.70)	
≥ 28	10,114(48.19)	3331(62.96)	2873(60.13)	1947(38.48)	1963(33.25)	
24 ~ 27.9	5583(27.17)	1358(24.06)	1289(26.83)	1318(27.65)	1618(30.05)	
Smoking status, n (%)						< 0.001
Former	5269(25.85)	1623(29.77)	1382(28.46)	1075(22.14)	1189(23.40)	
Never	10,812(52.65)	2486(45.53)	2444(50.42)	2617(53.78)	3265(60.36)	
Now	4303(21.50)	1291(24.70)	960(21.12)	1099(24.09)	953(16.24)	
Alcohol user, n (%)						< 0.001
Former	3649(14.70)	1188(18.61)	961(16.47)	769(13.97)	731(10.11)	
Heavy	4015(20.77)	1013(19.63)	998(21.27)	1008(22.78)	996(19.61)	
Mild	6888(36.67)	1772(36.20)	1575(37.38)	1600(34.66)	1941(38.43)	
Moderate	2963(16.70)	660(14.29)	564(13.58)	785(18.20)	954(20.15)	
Never	2869(11.17)	767(11.27)	688(11.30)	629(10.39)	785(11.69)	
Hyperlipidemia, n (%)						< 0.001
No	5407(27.79)	467(8.69)	422(7.95)	2007(42.48)	2511(48.63)	
Yes	14,977(72.21)	4933(91.31)	4364(92.05)	2784(57.52)	2896(51.37)	
Hypertension, n(%)						< 0.001
No	11,541(62.15)	2447(50.07)	2376(53.29)	3026(68.58)	3692(75.06)	
Yes	8843(37.85)	2953(49.93)	2410(46.71)	1765(31.42)	1715(24.94)	
CVD, n (%)						< 0.001
No	18,044(90.95)	4536(87.05)	4148(88.59)	4344(93.07)	5016(94.69)	
Yes	2340(9.05)	864(12.95)	638(11.41)	447(6.93)	391(5.31)	

Table 1. Characteristics of 20,384 participants according to TyG and SII levels. Data are presented as weighted means with standard errors (SEs) for continuous variables and as counts with weighted proportions for categorical variables. Median TyG index: 8.618; Median SII: 466.667. BMI body mass index, TyG triglyceride-glucose index, SII Systemic Inflammation Index, CVD cardiovascular diseases. [a]Calculated as weight in kilograms divided by height in meters squared.

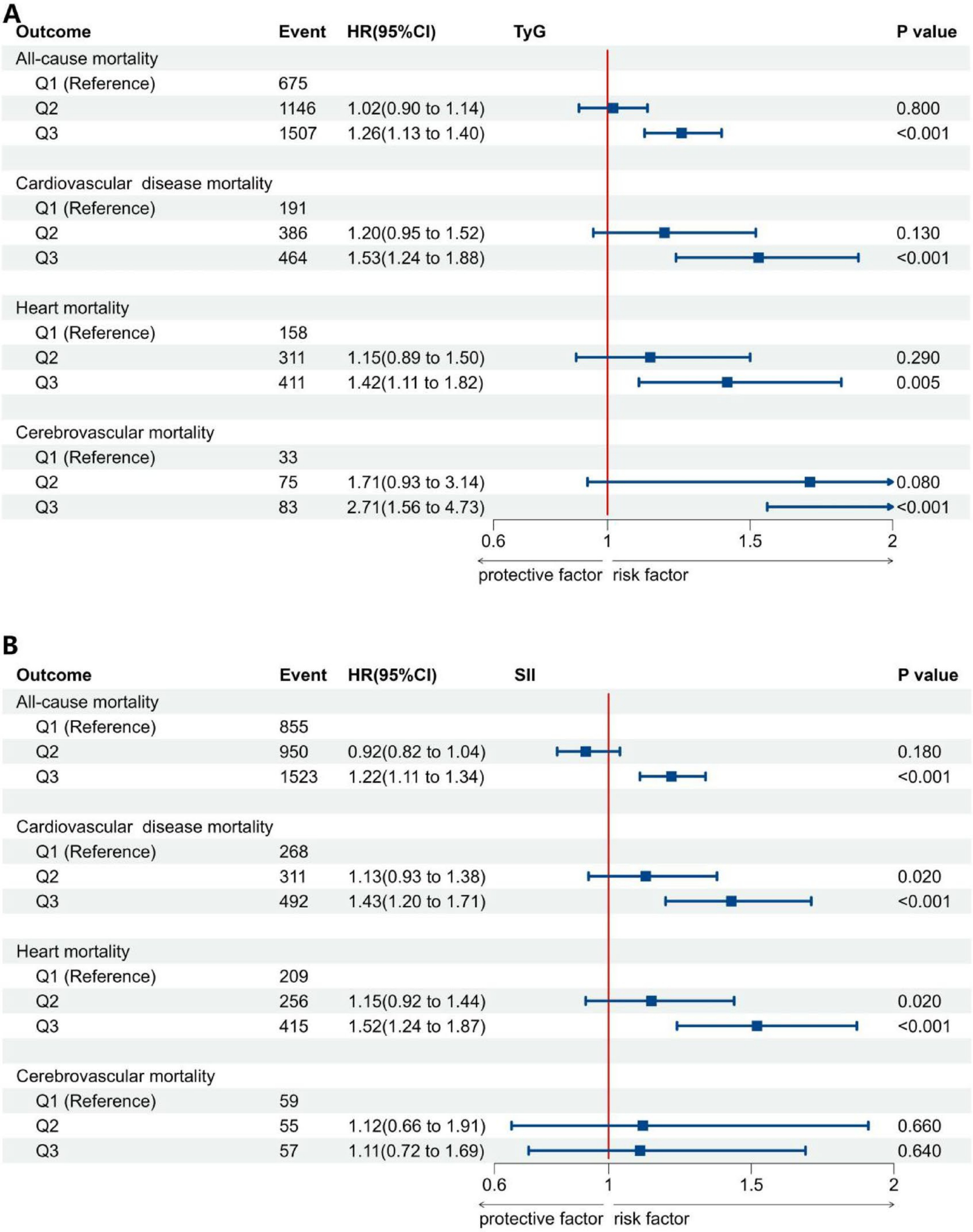
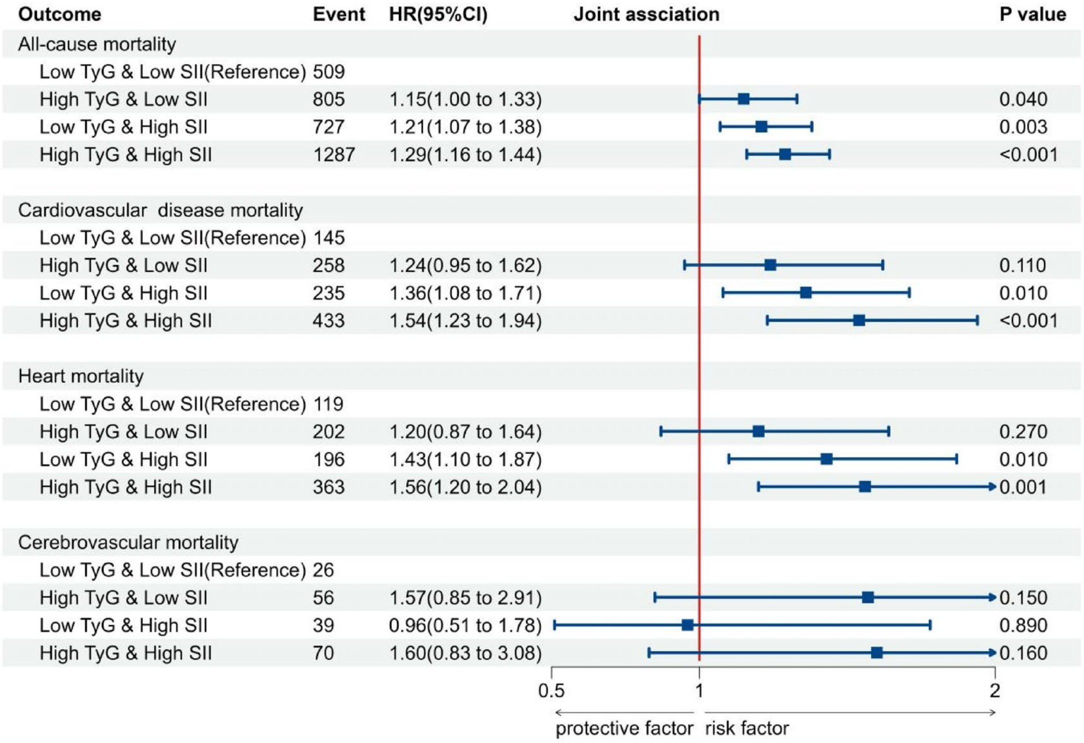


Fig. 2. Forest plot showing the association of TyG and SII with mortality. This forest plot presents the HRs with 95% CIs for mortality according to TyG and SII levels, using Q1 as the reference group. HR hazard ratio, CI confdence interval, TyG triglyceride–glucose index, SII Systemic Inflammation Index. (**A**) Association of TyG with the risk of mortality; (**B**) association of SII with the risk of mortality. The event column represents the number of individuals with positive outcomes.

1.96) for cardiac mortality, and 1.83 (95% CI, 1.04–3.22) for cerebrovascular mortality in the high TyG & high SII group (Supplementary Tables S6A-S6D). Additionally, adjusting for medication use resulted in HRs of 1.25 (95% CI, 1.12–1.39) for all-cause mortality, 1.46 (95% CI, 1.16–1.84) for cardiovascular mortality, 1.49 (95% CI, 1.14–1.94) for cardiac mortality, and 1.53 (95% CI, 0.78–3.03) for cerebrovascular mortality in the high TyG & high SII group (Supplementary Tables S7A-S7B). Statistical differences in survival probabilities among different groups were observed across several sensitivity analyses for mortality (Supplementary Figures S3, S4, and S5).



Outcome	Event	HR(95%CI)	P value
All-cause mortality			
Low TyG & Low SII(Reference)	509		
High TyG & Low SII	805	1.15(1.00 to 1.33)	0.040
Low TyG & High SII	727	1.21(1.07 to 1.38)	0.003
High TyG & High SII	1287	1.29(1.16 to 1.44)	<0.001
Cardiovascular disease mortality			
Low TyG & Low SII(Reference)	145		
High TyG & Low SII	258	1.24(0.95 to 1.62)	0.110
Low TyG & High SII	235	1.36(1.08 to 1.71)	0.010
High TyG & High SII	433	1.54(1.23 to 1.94)	<0.001
Heart mortality			
Low TyG & Low SII(Reference)	119		
High TyG & Low SII	202	1.20(0.87 to 1.64)	0.270
Low TyG & High SII	196	1.43(1.10 to 1.87)	0.010
High TyG & High SII	363	1.56(1.20 to 2.04)	0.001
Cerebrovascular mortality			
Low TyG & Low SII(Reference)	26		
High TyG & Low SII	56	1.57(0.85 to 2.91)	0.150
Low TyG & High SII	39	0.96(0.51 to 1.78)	0.890
High TyG & High SII	70	1.60(0.83 to 3.08)	0.160

Fig. 3. Forest plot showing the association of joint effect with mortality. This forest plot presents the HRs with 95% CIs for mortality,according to the Combined associations of TyG and SII, using the low TyG & low SII group as a reference. HR hazard ratio, CI confdence interval, TyG triglyceride–glucose index, SII Systemic Inflammation Index. The event column represents the number of individuals with positive outcomes.

Discussion

This study, utilizing data from NHANES, investigated the individual and combined associations of the TyG index and the SII with all-cause and cardiovascular mortality. The findings revealed that the combined assessment of TyG and SII significantly enhanced the predictive ability for both all-cause and cardiovascular mortality. This underscores the critical role of insulin resistance and systemic inflammation in determining patient outcomes and highlights the synergistic effect of these two biomarkers.

Specifically, participants in the high TyG & high SII group exhibited a markedly increased risk of mortality, particularly from cardiovascular causes, compared to those in the low TyG & low SII group. Subgroup and sensitivity analyses further confirmed the consistency of these effects across various populations, reinforcing the robustness and reliability of the study's results.

The findings of this study align with previous research that has demonstrated an association between the TyG index and both all-cause and CVD mortality. Liu et al.[32] and Chen et al.[33] found a nonlinear relationship between the TyG index and all-cause and CVD mortality. Liang et al.[34] observed that higher TyG levels were associated with an increased likelihood of CVD events in older adults in the United States. Sun et al.[35] reported that elevated TyG levels were linked to an increased risk of all-cause mortality among middle-aged men in the U.S. However, Chen et al.[33] noted that, with increasing TyG levels, both all-cause and CVD mortality risks rise in women, whereas men only show an increased risk for all-cause mortality. In Iranian men, higher TyG levels were associated with increased risks for both all-cause and CVD mortality[36]. There is no consensus on the relationship between TyG index and mortality risk across different genders, which may be influenced by factors such as environmental conditions, biological aging, and heterogeneity within populations. In our study, subgroup analyses revealed that although the combination of high TyG and high SII increases mortality risk for both genders, the effect is more pronounced in women. Postmenopausal women experience a reduction in estrogen, which diminishes cardiovascular protection, leading to increased IR and heightened sensitivity to changes in metabolic and inflammatory states, thereby elevating CVD risk[37].

Regarding the SII, Yang et al.[20] investigated the predictive value of the SII for major cardiovascular events in patients undergoing coronary heart disease interventions. They found that when the optimal SII cutoff was set at 694.3 × 10^9/L, higher SII levels (≥ 694.3) were independently associated with an increased risk of cardiac death (HR = 2.02; 95% CI: 1.43–2.86) and were also linked to major adverse cardiovascular events and overall major events. SII significantly improved risk stratification for cardiac death in coronary heart disease patients and outperformed traditional risk factors in predicting major cardiovascular events following coronary intervention. Taha Sert et al.[38] studied 237 out-of-hospital cardiac arrest (OHCA) patients, with an in-hospital mortality rate of 82.7%. They observed that survivors had significantly lower SII, NLR, and PLR values compared to the non-survivor group. SII was identified as an independent predictor of survival to hospital discharge in OHCA

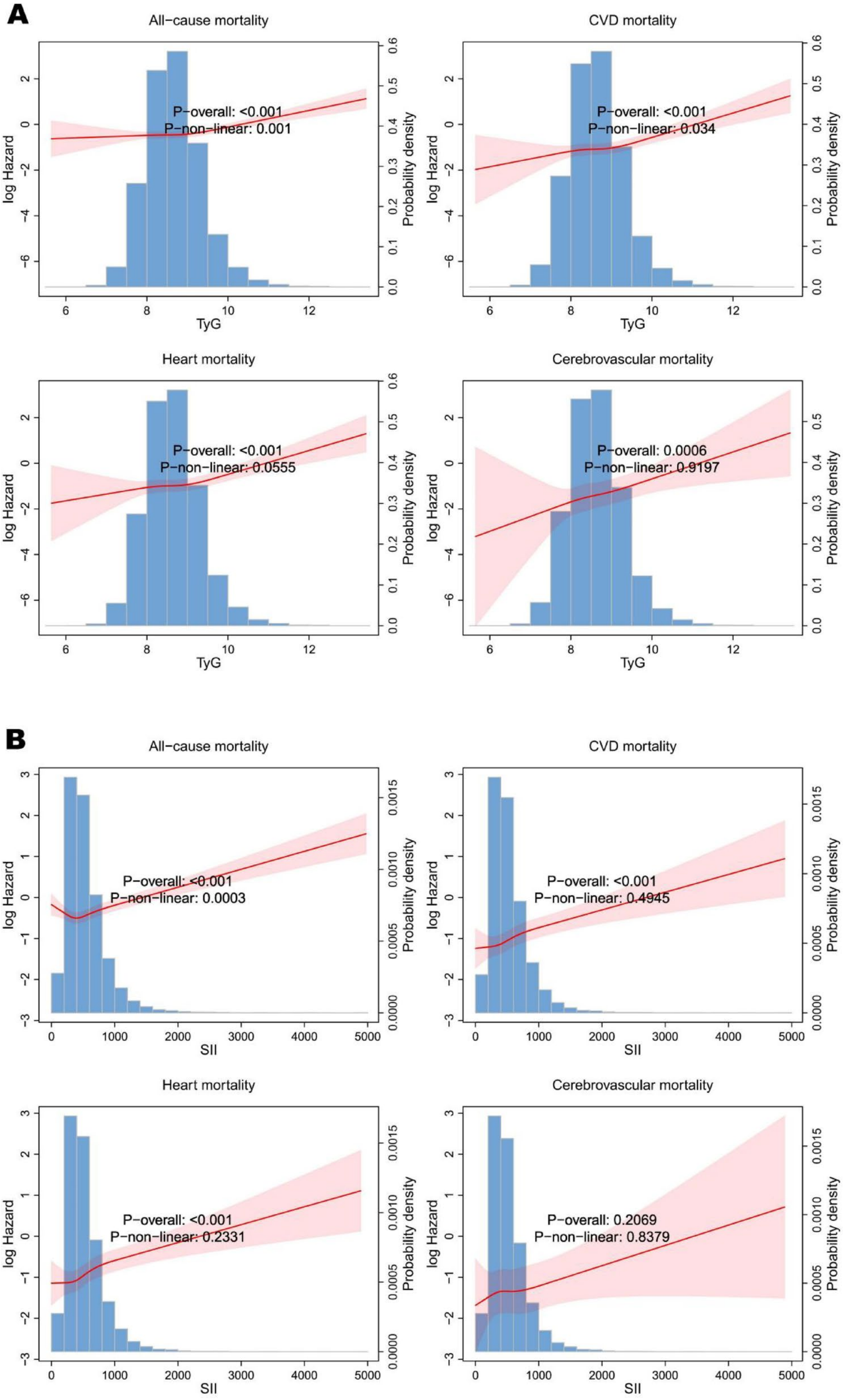


Fig. 4. Association of TyG and SII with All-Cause and CVD Mortality using RCS. Restricted cubic spline analysis has four knots. In the RCS analysis, adjustments were made for age, sex, ethnicity, marital status, education level, family income, BMI, smoking status, current alcohol consumption, dyslipidemia, hypertension, and CVD. TyG triglyceride–glucose index, SII Systemic Inflammation Index, BMI body mass index, CVD cardiovascular disease. (A) Association of TyG with the risk of mortality; (**B**) association of SII with the risk of mortality.

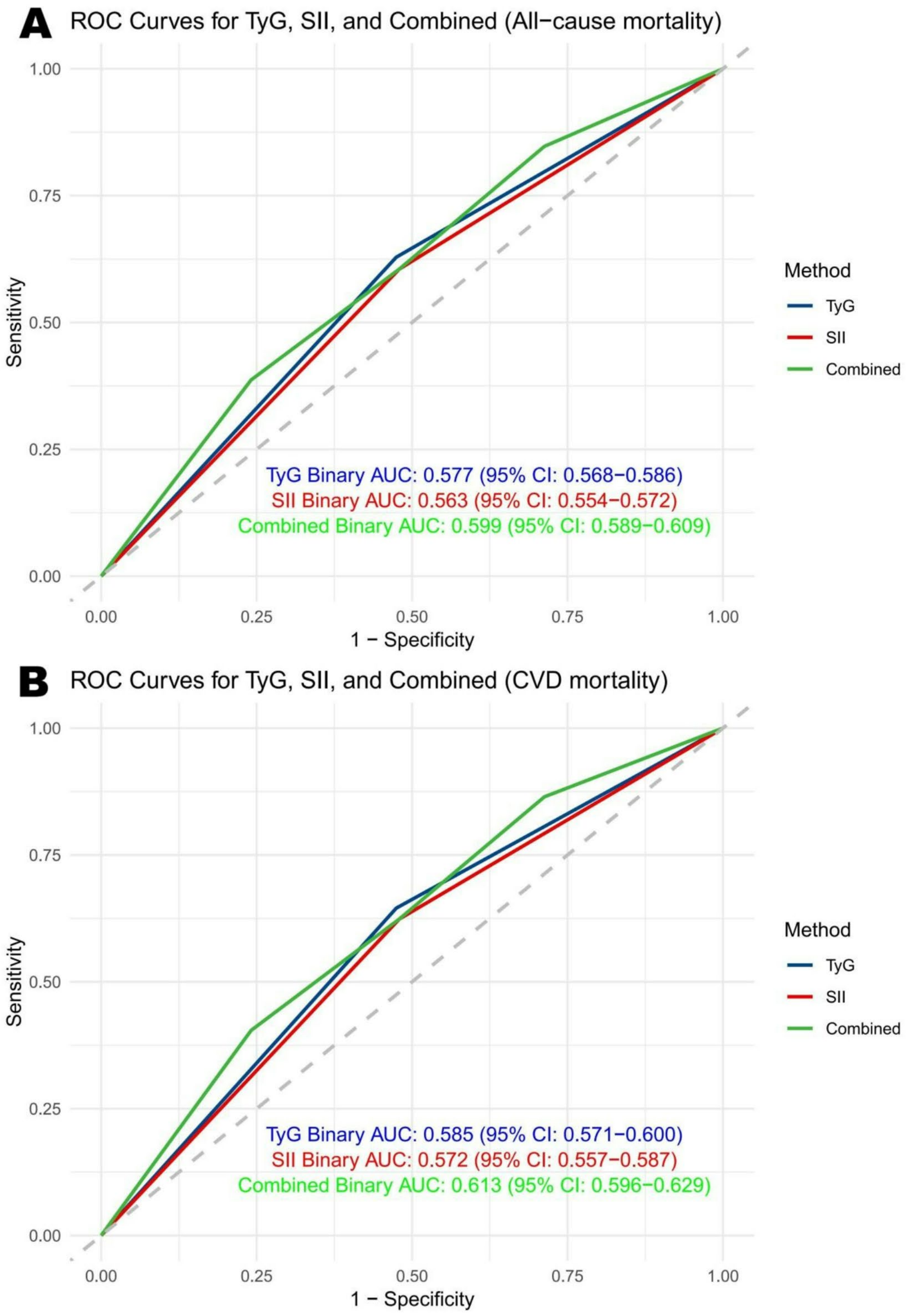


Fig. 5. Predictive performance of the combined TyG and SII for mortality. The receiver operating characteristic (ROC) curve evaluating the discriminative capabilities by calculating the AUC. AUC area under curve, TyG triglyceride–glucose index, SII Systemic Inflammation Index, CVD cardiovascular disease. (**A**) Combined association with the All-Cause mortality; (**B**) Combined association with the CVD mortality.

patients. ROC curve analysis further demonstrated that the AUC for SII was higher than that for NLR or PLR, indicating that SII has a superior predictive ability for post-discharge survival in OHCA patients.

The exact mechanisms linking the TyG index to mortality are still being explored. However, several hypotheses have been proposed. Firstly, the TyG index is closely associated with a range of adverse health conditions such

Subgroup	**N (events)**	**Low TyG & LowSII**	**High TyG & Low SII HR (95%CI)**	**Low TyG & High SII HR (95%CI)**	**High TyG & High SII HR (95%CI)**	***p* value**	***p* for interaction**
Overall	1287	ref	1.15(1.00,1.33)	1.21(1.07,1.38)	1.29(1.16,1.44)	< 0.001	–
Age							< 0.001
≤ 60	245	ref	1.63(1.23,2.18)	1.11(0.86,1.44)	1.81(1.41,2.33)	< 0.001	
> 60	1042	ref	1.03(0.90,1.18)	1.35(1.16,1.57)	1.27(1.12,1.43)	< 0.001	
sex							< 0.001
Male	606	ref	1.43(1.19,1.72)	1.64(1.36,1.99)	1.69(1.42,2.01)	< 0.001	
Female	681	ref	1.80(1.39,2.34)	1.22(0.96,1.54)	2.26(1.82,2.82)	< 0.001	
BMI							0.030
24 ~ 27.9	360	ref	1.31(1.05,1.64)	1.12(0.87,1.45)	1.55(1.27,1.89)	< 0.001	
< 23.9	246	ref	1.52(1.17,1.99)	1.26(1.01,1.58)	1.80(1.42,2.28)	< 0.001	
≥ 28	681	ref	1.74(1.30,2.33)	1.75(1.40,2.18)	2.59(2.02,3.31)	< 0.001	
Edu							0.020
Above high school	464	ref	1.36(1.02,1.80)	1.25(1.01,1.54)	1.95(1.58,2.40)	< 0.001	
Under high school	335	ref	1.51(1.16,1.96)	1.50(1.14,1.98)	1.67(1.31,2.13)	< 0.001	
High school or equivalent	488	ref	1.87(1.43,2.43)	1.46(1.12,1.90)	2.06(1.61,2.63)	< 0.001	
DM							< 0.001
No	728	ref	1.35(1.11,1.65)	1.34(1.15,1.56)	1.77(1.53,2.04)	< 0.001	
Yes	559	ref	1.02(0.77,1.36)	1.51(1.09,2.09)	1.15(0.87,1.51)	0.330	
Hyperlipidemia							< 0.001
Yes	1181	ref	1.30(1.09,1.55)	1.22(1.01,1.47)	1.58(1.35,1.84)	< 0.001	
No	106	ref	2.26(1.56,3.29)	1.76(1.39,2.23)	2.88(2.15,3.86)	< 0.001	
Hypertension							< 0.001
Yes	949	ref	1.21(1.00,1.45)	1.41(1.17,1.69)	1.45(1.25,1.68)	< 0.001	
No	338	ref	1.54(1.19,2.01)	1.10(0.87,1.38)	1.76(1.43,2.15)	< 0.001	

Table 2. Subgroup analysis of the joint association of TyG and SII levels with all-cause mortality in NHANES 1999–2018. HR hazard ratio, CI confidence interval, BMI body mass index, TyG triglyceride–glucose index, SII Systemic Inflammation Index, CVD cardiovascular disease. Median TyG index: 8.618; Median SII: 466.667. HR, 95% CI and *p*-values are based on Cox proportional hazards regression Model 3. The *p*-value refers to the statistical significance of the HR for the High TyG & High SII category compared to the reference group (Low TyG & Low SII). The event represents the number of individuals with positive outcomes in High TyG and High SII group.

as obesity, diabetes, CVD, elevated blood pressure, reduced eGFR, and low HDL-C levels[39–41]. A higher TyG index may thus indicate negative effects on cardiometabolic health. Secondly, endothelial dysfunction might contribute to the relationship between the TyG index and mortality. Unlike other indicators of IR, the TyG index specifically measures IR in muscle tissue and is considered a more accurate marker for peripheral IR. As such, it may be linked to endothelial dysfunction, oxidative stress, and inflammatory responses[42–44]. IR is recognized for initiating the production of glycosylation products and free radicals, which in turn decrease the availability of nitric oxide (NO). This reduction in NO bioavailability adversely affects endothelium-dependent vasodilation[45]. Chronic inflammation can damage the vascular endothelium, leading to leakage of blood components into surrounding tissues and further vascular damage[44]. Furthermore, IR activates the mitochondrial electron transport chain, leading to increased oxidative stress and subsequent endothelial damage[33]. Lastly, insulin might contribute to lipohyalinosis by increasing sympathetic activity, which can result in diffuse hypoperfusion or obstruct small arterioles[44,46]. Additionally, IR may facilitate the development of atherosclerosis and progression of arterial plaques[46].

The exact mechanisms by which the SII increases mortality risk are also not fully understood, but several explanations may be considered. First, elevated SII is associated with increased levels of cytokines, including interleukin-6, interleukin-8, and interleukin-10, which are linked to chronic systemic inflammation[47]. Increased mortality in individuals with higher SII levels may be due to chronic inflammation, which produces reactive nitrogen and oxygen species, leading to genomic instability and cellular senescence, thereby raising the risk of cardiovascular diseases and mortality[48]. Additionally, high SII levels could be attributed to elevated neutrophil counts, high platelet counts, and/or low lymphocyte counts[49]. Different inflammatory components may play varying roles in mortality risk[50]. Activated neutrophils release extracellular traps, and neutrophil elastase, a major component of these traps, has been linked to increased all-cause and cardiovascular mortality risk in chronic hemodialysis patients[51]. Thus, we hypothesize that high SII may exacerbate cardiovascular adverse events through enhanced inflammation and oxidative stress, which can burden the heart and damage tissues. However, the exact role of TyG index and SII in mortality still requires further investigation.

Moreover, ROC curve analysis demonstrated that the combined assessment of TyG and SII provided better discriminative ability for predicting all-cause and cardiovascular mortality compared to individual indicators. Although the AUC values indicated only moderate predictive capability, the combined assessment of TyG and SII, when integrated with other risk factors, may still offer significant clinical value. This suggests that incorporating both metabolic and inflammatory markers in risk assessment and early intervention could provide a more comprehensive evaluation of mortality risk.

This study uses the TyG index to estimate insulin resistance, though its correlation with HOMA-IR is weak ($r \approx 0.322$), indicating it may not directly reflect insulin resistance. However, the research focuses on how TyG combined with SII predicts mortality risk, not their direct relationship. TyG remains useful for its simplicity and broad use in large-scale studies[52,53]. While NHANES data allow calculating HOMA or QUICKI, TyG was chosen to match the study's goals. Future studies could test combining HOMA, QUICKI, SII, or C-reactive protein to expand these findings.

Despite these important findings, several limitations of this study should be acknowledged. Firstly, although we used a large, nationally representative sample, the observational nature of NHANES data precludes causal inferences. Secondly, despite adjusting for multiple confounders in our models, unmeasured confounding factors may still influence the results. Finally, the findings are primarily applicable to the U.S. population and may not be directly generalizable to other regions or ethnic groups.

Conclusion

Overall, the findings of this study underscore the importance of the combined assessment of the TyG index and SII in clinical practice. This approach not only enhances the accuracy of predicting all-cause and cardiovascular mortality but also provides a basis for developing personalized prevention and intervention strategies. Future research should focus on optimizing the predictive capability of these indices across different populations and exploring the underlying mechanisms to better understand the roles of metabolism and inflammation in mortality risk.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Conceptualization: QZ, GL,ZA, and SL. Data curation: QZ, RZ and QZ. Formal analysis: QZ . Writing-original draft: QZ . Writing-review & editing: ZA and SL. Supervision: ZA and SL. All authors actively participated in the research process made substantial contributions to manuscript revisions, and carefully reviewed and approved the final version.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study was performed according to the guidelines of the Helsinki Declaration. Consent to participate was obtained and the National Center for Health Statistics ethics committee approved the protocol of the NHANES study. The data is publicly available, therefore, the ethical approval statement and the requirement for informed consent were waived for this study.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-06770-8.

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