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Impact of the Triglyceride–Glucose index on all-cause and cardiovascular mortalities across different metabolic health and obesity statuses in US adults

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Abstract

Background Data for the study cohort were sourced from the National Health and Nutrition Examination Survey (1999–2018). Study participants were classified as obese (BMI ≥ 30 kg/m^2) or nonobese (BMI < 30 kg/m^2) then further categorized as metabolically healthy or unhealthy on the basis of metabolic syndrome criteria, resulting in four groups: metabolically healthy obese (MHO), metabolically unhealthy obese (MUO), metabolically healthy nonobese (MHNO), and metabolically unhealthy nonobese (MUNO). Complex sampling statistical methods were employed for descriptive analysis. The associations between the TyG index and mortality, including all-cause and cardiovascular mortalities, were examined by using multivariable Cox regression and restricted cubic splines (RCS). The reliability of the results was confirmed through multiple sensitivity analyses.

Methods Data for the study cohort were sourced from the National Health and Nutrition Examination Survey (1999–2018). Study participants were classified as obese (BMI ≥ 30 kg/m^2) or nonobese (BMI < 30 kg/m^2) then further categorized as metabolically healthy or unhealthy on the basis of metabolic syndrome criteria, resulting in four groups: metabolically healthy obese (MHO), metabolically unhealthy obese (MUO), metabolically healthy nonobese (MHNO), and metabolically unhealthy nonobese (MUNO). Complex sampling statistical methods were employed for descriptive analysis. The associations between the TyG index and mortality, including all-cause and cardiovascular mortalities, were examined by using multivariable Cox regression and restricted cubic splines (RCS). The reliability of the results was confirmed through multiple sensitivity analyses.

Results A total of 16 179 participants were included, with a median follow-up of 129 months. Over this follow-up period, 1875 participants (11.59%) died from all causes, including 568 (3.51%) who died due to cardiovascular diseases. After adjustment for confounding variables, the TyG index significantly predicted mortality in the overall and metabolically unhealthy populations: for each one standard deviation increase in the TyG index, all-cause mortality increased by 1.42 times (95% confidence interval [CI]: 1.27, 1.58) in the overall population, by 1.62 times (95% CI:

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1.36, 1.93) in the MUNO group, and by 1.47 times (95% CI: 1.26, 1.71) in the MUO group. Cardiovascular mortality in the overall population increased by 1.52 times (95% CI: 1.27, 1.82), that in the MUNO group increased by 2.01 times (95% CI: 1.49, 2.72), and that in the MUO group increased by 1.47 times (95% CI: 1.14, 1.88). No significant association was found in the metabolically healthy populations regardless of obesity status. RCS and sensitivity analyses further confirmed and visualized these conclusions.

Conclusions The TyG index is positively correlated with mortality risk in the overall and metabolically unhealthy populations but not in the metabolically healthy populations. This finding indicates that the predictive value of the TyG index for mortality differs across populations, highlighting the necessity of accounting for metabolic status when the TyG index is used for prognostic evaluation.

Keywords TyG index, Metabolic health, Obesity, Mortality, NHANES

Introduction

Over time, obesity has been recognized as a chronic disease and has become a global epidemic, affecting nearly 1 billion adults, with more than 40% of Americans impacted, and its prevalence continues to rise [1, 2]. Obesity-related metabolic complications, such as type 2 diabetes, hypertension, and atherosclerotic cardiovascular diseases, are major causes of mortality, severely affecting quality of life and considerably increasing healthcare costs [3].

In obesity research, the concept of metabolically healthy obese (MHO) refers to individuals who are obese but metabolically normal [4]. However, no unified standard for defining metabolic health exists. Most studies classify individuals on the basis of the presence of metabolic syndrome (MetS), whereas others assess insulin resistance, with some suggesting that all components of MetS should be excluded [5–7]. This diversity has led to varying reports of MHO prevalence rates that range from 6–75% [8, 9]. MHO individuals tend to have better prognoses than metabolically unhealthy obese (MUO) individuals. However, they are generally considered to have worse prognoses than metabolically healthy nonobese (MHNO) individuals, highlighting the limitations of the "healthy obese" perspective [10].

Insulin resistance is a connecting factor between obesity and metabolic abnormalities [11]. The triglyceride–glucose (TyG) index has emerged as a widely recognized indicator of insulin resistance due to its simplicity and accessibility. Substantial epidemiological evidence supports the predictive value of the TyG index for the occurrence of metabolic cardiovascular diseases [12–14]. In recent years, an increasing number of studies have demonstrated the relationship between the TyG index and all-cause mortality, with some reporting a unidirectional relationship [15, 16] and others a U-shaped relationship [17, 18].

However, whether these patterns apply to different populations with varying obesity and metabolic statuses remains unclear. We utilized large-scale prospective cohort data from the US to explore the associations between the TyG index and all-cause and cardiovascular mortalities among four distinct obesity and metabolic groups, namely, MHO, MUO, MHNO, and metabolically unhealthy nonobese (MUNO), to address the above knowledge gap.

Materials and methods

Data source and ethics considerations

The datasets used in our work were derived from the National Health and Nutrition Examination Survey (NHANES) database. The NHANES is a cross-sectional, multistage, stratified, clustered probability survey conducted by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention. The NCHS Research Ethics Review Board approved the NHANES study protocol, and all participants provided written informed consent.

Study population

Our study utilized data from 10 NHANES cycles, which included a total of 101 316 participants, conducted between 1999 and 2018. We applied specific exclusion criteria to investigate the relationship between the TyG index and mortality in the general population: (1) absence of data on body mass index (BMI), waist circumference (WC), triglycerides (TGs), fasting blood glucose (FBG), systolic blood pressure (SBP), or diastolic blood pressure (DBP); (2) age under 18 years or over 85 years; (3) pregnancy at the time of the survey; (4) cancer diagnosis at the time of the survey; and (5) lack of survival data. After these criteria were applied, the final cohort consisted of 16 179 individuals. Patient selection is illustrated in Fig. 1.

Classification criteria

Study participants were categorized on the basis of their BMI into obese (BMI ≥ 30 kg/m²) and nonobese (BMI < 30 kg/m²) groups. Additionally, they were further classified into metabolically healthy and metabolically unhealthy groups on the basis of the presence of MetS criteria. The definition of MetS followed the standards

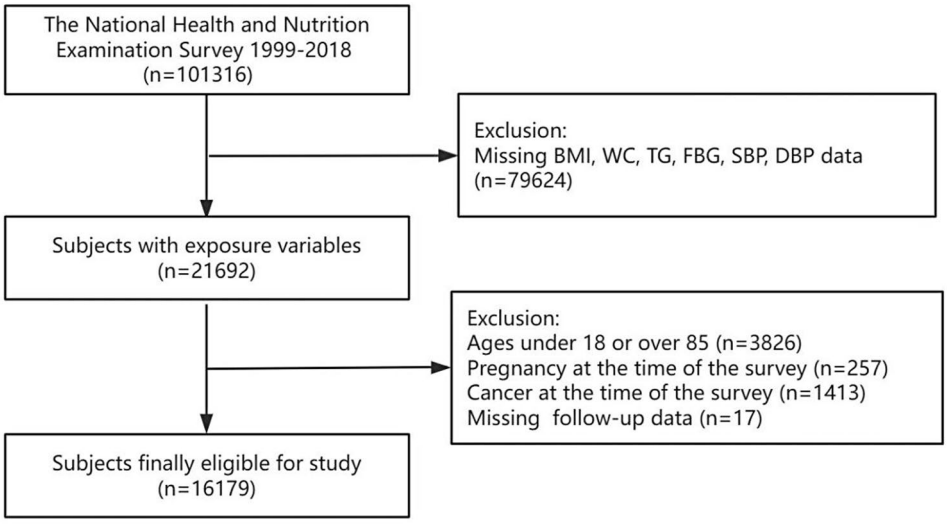

Fig. 1 Study Flow

set by the American Heart Association/National Heart, Lung, and Blood Institute [19]. Participants were considered to have MetS if they exhibited at least three of the following five cardiovascular risk factors:

1. Fasting blood glucose ≥ 100 mg/dL or currently receiving treatment for diabetes;
2. Low high-density lipoprotein (HDL) cholesterol (< 40 mg/dL in men or < 50 mg/dL in women) or currently receiving treatment for abnormal HDL cholesterol levels;
3. Triglycerides ≥ 150 mg/dL or currently receiving treatment for hypertriglyceridemia;
4. Waist circumference ≥ 102 cm in men or ≥ 88 cm in women;
5. Blood pressure ≥ 130/85 mm Hg or currently receiving treatment for hypertension.

On the basis of these criteria, the study population was divided into four groups: MHO, MUO, MHNO, and MUNO [6, 7].

Exposure and outcome variables

The TyG index was calculated by using the following formula:

$$\text{TyG Index} = \ln\left(\begin{matrix}\text{Fasting Triglycerides (mg/dL)} \\ \times\text{Fasting Glucose (mg/dL)}\end{matrix}\right)/2$$

The outcome variables in this study included all-cause and cardiovascular mortalities. Death records were obtained from publicly accessible linked mortality files, which encompass mortality-related variables specific to adults. The National Death Index provides information on the survival status and causes of death for the surveyed individuals, with data recorded up to December 31, 2019. Causes of death were determined in accordance with the NCHS "113 Causes of Death" recode adapted from the International Classification of Diseases, Tenth Revision (ICD-10). All-cause mortality was defined as death from any cause. Cardiovascular mortality was determined by the recode categories "Diseases of Heart" (codes 054–068; corresponding to ICD-10 I00–I09, I11, I13, and I20–I51) and "Cerebrovascular Diseases" (code 070; corresponding to ICD-10 I60–I69).

Covariate definitions

Data were obtained from questionnaires, laboratory examinations, and physical assessments conducted by the NHANES. Demographic and lifestyle information, including age, sex, race, poverty-to-income ratio (PIR), educational level, and smoking and drinking habits, were collected through interviews. Race was categorized into five groups: Mexican American, non-Hispanic black, non-Hispanic white, other Hispanic, and other race. The PIR was calculated as the ratio of household income to the poverty threshold. Educational levels were classified as below high school, high school, and above high school. Smoking status was determined by whether participants had smoked at least 100 cigarettes in their lifetime, and drinking status was based on the consumption of more than 12 glasses of alcohol per year.

Laboratory examinations provided data on serum biochemical indicators, including TG, FBG, serum uric acid (SUA), hemoglobin A1c (HbA1c), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Baseline assessments also included comorbidities, such as hypertension, coronary heart disease (CHD), stroke, hyperlipidemia, diabetes, and chronic kidney disease (CKD), as well as

medication usage, including antidiabetic, antihypertensive, and lipid-lowering drugs. BMI and WC were measured by following standardized procedures.

Hypertension was identified as SBP ≥ 140 mmHg or/and DBP ≥ 90 mmHg, the use of antihypertensive medications, or a history of hypertension diagnosed by physicians [21]. A history of CHD included self-reported angina pectoris, CHD, heart attack, and stroke. Hyperlipidemia was defined as TC ≥ 200 mg/dL, TG ≥ 150 mg/dL, LDL-C ≥ 130 mg/dL, or HDL-C ≤ 50 mg/dL in women and ≤ 40 mg/dL in men or the use of lipid-lowering drugs. Diabetes mellitus was defined as FBG level ≥ 126 mg/dL, HbA1C level ≥ 6.5%, or 2-h blood glucose ≥ 200 mg/dL from an oral glucose tolerance test, in addition to self-reported diagnosis or use of insulin or oral hypoglycemic medication. Estimated glomerular filtration rate (eGFR) was calculated via the CKD epidemiology collaboration equation [20]. CKD was defined as eGFR < 60 mL/min/1.73 m^2.

Statistical analysis

Owing to the complex sampling design of the NHANES, continuous variables were presented as weighted medians (25th percentile, 75th percentile) after the Kolmogorov–Smirnov test for normality, whereas categorical variables were presented as unweighted frequencies (weighted percentages). Continuous variables were compared between groups through the Wilcoxon rank-sum test, and categorical variables were compared by using the chi-square test with Rao and Scott's second-order correction. Four Cox regression models were utilized for analysis, as follows: The crude model was an unadjusted baseline with no covariates. Model 1 was adjusted for age and gender. Model 2 was adjusted for age, gender, ethnicity, educational level, smoking status, alcohol use, and PIR. Model 3 included all factors from Model 2 and added total serum cholesterol, eGFR, total cholesterol, LDL cholesterol, HDL cholesterol, the presence of hypertension, and high cholesterol. Additionally, it accounted for the use of antihypercholesterolemia and antihypertension medications and included cardiovascular conditions, such as CHD, myocardial infarction, heart failure, and stroke. This stepwise approach allowed for a comprehensive analysis of how various covariates could influence the primary relationship, providing insights into potential confounding or mediating factors. We aimed to identify potentially valuable predictors for all-cause and cardiovascular mortalities on the basis of the shape of restricted cubic spline (RCS) curves to examine whether a nonlinear relationship existed between the TyG index and mortality. Four knots were selected at the 5th, 35th, 65th, and 95th percentiles to fit the RCS curve. Finally, multiple sensitivity analyses were conducted to evaluate the reliability of the findings. Missing covariates were imputed via the random forest method [21]. All the statistical analyses were performed with R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was considered at a threshold of $p < 0.05$.

Results

Baseline characteristics

Our study provided a baseline description of 16 179 participants (Table 1), with an average age of 44 years, of whom 51% were male. The proportion of MHO individuals in the total study population was 11.6% (weighted), whereas that in the obese population was approximately 35.1% (weighted). Compared with metabolically healthy individuals, those who were metabolically unhealthy had higher TyG index values; ages; smoking rates; WCs; and FBG, HbA1c, TC, TG, and SUA levels but lower HDL-C levels and eGFR values. The PIR in the MHNO group was highest, followed by that in the MUHO group, with that in the MHO group being lowest, suggesting that wealthy individuals tend to be obese but healthy. The prevalence rates of cardiovascular disease were 14% and 12% in the MUNO and MUO groups, respectively, and were significantly higher than those (3.1% and 2.8%) reported in the MHNO and MHO groups.

Mortality rates

The median follow-up time for this study was 129 months (interquartile range 84–187 months), with a total of 1875 participants (11.59%) dying from various causes, of which 568 (3.51%) were related to cardiovascular diseases. The all-cause mortality rates for MUNO and MUO individuals were 23.38% and 14.85%, respectively, whereas those for MHNO and MHO individuals were 7.63% and 5.47%, respectively. The cardiovascular mortality rates for MUNO and MUO individuals were 6.97% and 5.04%, respectively, and those for MHNO and MHO individuals were 2.08% and 1.79%, respectively (Tables 2 and 3).

Hazard ratios of the TyG index for mortality

When the TyG index was treated as a continuous variable, the predictions for mortality in the overall and metabolically unhealthy populations were statistically significant after adjustment for confounding variables. Specifically, for each one standard deviation increase, the all-cause mortality rate increased by 1.42 times (95% confidence interval [CI]: 1.27, 1.58) in the overall population; by 1.62 times (95% CI: 1.36, 1.93) in the MUNO group; and by 1.47 times (95% CI: 1.26, 1.71) in the MUHO group (Table 2). Cardiovascular mortality in the overall population increased by 1.52 times (95% CI: 1.27, 1.82), that in the MUNO group increased by 2.01 times (95% CI: 1.49, 2.72), and that in the MUHO group increased by 1.47 times (95% CI: 1.14, 1.88) (Table 3). However, in the

Table 1 Baseline characteristics of the study population stratified by metabolic health and obesity status

Characteristics	Overall	Metabolically healthy nonobese (MHNO)	Metabolically healthy obese (MHO)	Metabolically unhealthy nonobese (MUNO)	Metabolically unhealthy obese (MUO)
Unweighted Number of subjects (n)	16,179	8037	1901	2712	3529
Percentage (Unweighted) (%)		49.6	11.7	16.8	21.8
Weighted Number of subjects (n)	65,485,725	33,901,014	7,580,361	10,025,263	13,979,088
Percentage (Weighted) (%)		51.8	11.6	15.3	21.3
TyG index	8.56 (8.15, 9.00)	8.31 (7.97, 8.65)	8.42 (8.10, 8.70)	9.05 (8.61, 9.42)	9.05 (8.69, 9.43)
Age (years)	44 (31, 56)	38 (27, 50)	37 (28, 48)	57 (45, 68)	51 (40, 61)
Male, n(%)	8,196 (51%)	4,311 (52%)	782 (44%)	1,416 (51%)	1,687 (50%)
Ethnicity, n(%)					
Mexican American	3,223 (8.9%)	1,530 (8.5%)	421 (12%)	540 (7.4%)	732 (9.2%)
Non-Hispanic Black	3,282 (11%)	1,527 (9.6%)	567 (18%)	379 (6.8%)	809 (12%)
Non-Hispanic White	6,834 (68%)	3,420 (68%)	643 (59%)	1,244 (72%)	1,527 (70%)
Other Hispanic	1,470 (5.8%)	679 (5.7%)	181 (7.4%)	287 (6.4%)	323 (4.8%)
Other Race	1,370 (6.6%)	881 (7.9%)	89 (3.9%)	262 (7.3%)	138 (4.3%)
Education, n(%)					
Above High School	8,098 (59%)	4,443 (64%)	990 (60%)	1,115 (51%)	1,550 (53%)
Below High School	4,474 (18%)	1,971 (16%)	463 (18%)	929 (22%)	1,111 (21%)
High School	3,607 (23%)	1,623 (20%)	448 (23%)	668 (27%)	868 (27%)
Poverty-income Ratio, n(%)	2.93 (1.51, 4.80)	3.11 (1.59, 5.00)	2.58 (1.44, 4.19)	2.79 (1.48, 4.76)	2.80 (1.45, 4.67)
Smoking, n(%)	7,050 (46%)	3,264 (44%)	693 (39%)	1,429 (53%)	1,664 (49%)
Drinking, n(%)	11,563 (77%)	5,971 (80%)	1,327 (74%)	1,882 (74%)	2,383 (72%)
BMI, kg/m2	27 (24, 32)	24 (22, 27)	33 (31, 37)	27 (25, 29)	34 (32, 39)
Waist Circumference, cm	96 (86, 107)	87 (80, 94)	108 (101, 116)	98 (92, 104)	114 (107, 123)
Fasting Glucose, mg/dL	98 (91, 106)	94 (88, 99)	95 (90, 99)	106 (100, 115)	107 (100, 120)
Glycohemoglobin, n(%)	5.40 (5.10, 5.70)	5.20 (5.00, 5.50)	5.30 (5.10, 5.60)	5.60 (5.30, 5.90)	5.60 (5.40, 6.10)
Total Cholesterol, mmol/L	4.94 (4.27, 5.66)	4.86 (4.22, 5.53)	4.89 (4.27, 5.56)	5.15 (4.42, 6.00)	5.04 (4.40, 5.82)
Triglycerides, mmol/L	1.19 (0.81, 1.75)	0.97 (0.70, 1.34)	1.07 (0.78, 1.40)	1.78 (1.15, 2.51)	1.75 (1.22, 2.41)
LDL-C, mmol/L	2.92 (2.35, 3.54)	2.85 (2.28, 3.44)	3.05 (2.48, 3.57)	3.00 (2.46, 3.65)	3.02 (2.46, 3.60)
HDL-C, mmol/L	1.32 (1.09, 1.60)	1.45 (1.22, 1.73)	1.34 (1.16, 1.55)	1.16 (0.96, 1.45)	1.11 (0.96, 1.32)
Uric Acid, mmol/L	321 (268, 375)	297 (250, 351)	327 (280, 387)	333 (280, 393)	357 (303, 416)
eGFR, mL/min/1.73 m^2	102 (88, 114)	106 (92, 117)	105 (92, 117)	93 (78, 104)	98 (83, 109)
Diabetes, n(%)	2,356 (11%)	308 (2.6%)	84 (3.4%)	780 (22%)	1,184 (28%)
Hypertension, n(%)	5,817 (33%)	1,356 (15%)	398 (18%)	1,739 (60%)	2,324 (63%)
Hyperlipidemia, n(%)	11,728 (73%)	4,653 (59%)	1,167 (61%)	2,600 (96%)	3,308 (94%)
Gout, n(%)	378 (2.0%)	57 (0.6%)	20 (0.9%)	113 (3.2%)	188 (4.9%)
Antihypertension Medication, n(%)	4,011 (22%)	689 (7.4%)	195 (8.8%)	1,306 (45%)	1,821 (50%)
Antidiabetic Medications, n(%)	668 (3.0%)	80 (0.7%)	17 (0.5%)	201 (5.2%)	370 (8.0%)
Cholesterol-lowering Medications, n(%)	2,949 (18%)	483 (6.6%)	52 (3.2%)	1,146 (41%)	1,268 (35%)
Cardiovascular Disease, n(%)	1,338 (6.8%)	288 (3.1%)	67 (2.8%)	457 (14%)	526 (12%)
Coronary Heart Disease, n(%)	918 (4.8%)	192 (2.2%)	31 (1.3%)	322 (10%)	373 (9.1%)
Myocardial Infarction, n(%)	529 (2.7%)	113 (1.2%)	23 (1.0%)	173 (5.6%)	220 (5.2%)
Angina, n(%)	342 (1.9%)	72 (0.9%)	11 (0.4%)	109 (3.8%)	150 (3.9%)
Heart Failure, n(%)	377 (1.7%)	61 (0.6%)	19 (0.9%)	133 (4.0%)	164 (3.3%)
Stroke, n(%)	429 (2.1%)	97 (1.0%)	32 (1.4%)	145 (4.3%)	155 (3.7%)

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate

metabolically healthy population, no statistical significance was observed regardless of obesity status.

When grouped by quartiles of the TyG index, all-cause and cardiovascular mortality rates tended to increase across all populations. Consistent with previous findings, statistically significant differences were detected in the overall and metabolically unhealthy populations when the mortality rates of the fourth quartile (Q4) were compared with those of the first quartile (Q1), whereas no significant differences were detected in the metabolically healthy populations.

Table 2 HRs of TyG index for All-Cause mortality in the overall population and stratified by metabolic health and obesity status

Population and variables	Event, *n*(%)	Crude Model		Model I		Model II		Model III	
		HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Overall									
Per SD increase	1875 (11.59%)	1.48(1.39,1.57)	<0.001	1.21(1.13,1.3)	<0.001	1.18(1.11,1.26)	<0.001	1.42(1.27,1.58)	<0.001
Quartiles of TyG									
Q1 [5.65 - 8.15]	216 (5.3%)	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*
Q2 [8.15 - 8.57]	390 (9.6%)	1.54(1.21,1.97)	0.001	0.84(0.65,1.08)	0.171	0.83(0.65,1.07)	0.148	0.89(0.69,1.14)	0.348
Q3 [8.57 - 9.02]	540 (13.3%)	2.22(1.79,2.75)	<0.001	0.95(0.77,1.18)	0.670	0.92(0.73,1.15)	0.457	1(0.79,1.25)	0.988
Q4 [9.02 - 13.4]	729 (18%)	3.18(2.54,3.98)	<0.001	1.19(0.95,1.49)	0.122	1.12(0.89,1.41)	0.317	1.25(0.96,1.63)	0.100
p for trend			<0.001		<0.001		0.007		0.006
MHNO									
Per SD increase	613 (7.63%)	1.35(1.23,1.47)	<0.001	1.12(0.99,1.28)	0.071	1.12(0.99,1.27)	0.084	1.15(0.89,1.49)	0.287
Quartiles of TyG									
Q1 [5.65 - 8.15]	83 (4.1%)	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*
Q2 [8.15 - 8.57]	129 (6.4%)	1.33(0.95,1.88)	0.100	0.96(0.67,1.38)	0.843	1(0.7,1.43)	0.979	0.98(0.69,1.4)	0.932
Q3 [8.57 - 9.02]	189 (9.4%)	1.91(1.36,2.68)	<0.001	1.04(0.74,1.48)	0.809	1.02(0.72,1.44)	0.912	1.01(0.71,1.46)	0.942
Q4 [9.02 - 13.4]	212 (10.6%)	2.14(1.51,3.05)	<0.001	1.08(0.75,1.55)	0.675	1.06(0.75,1.5)	0.749	0.93(0.59,1.45)	0.744
p for trend			<0.001		0.498		0.683		0.760
MHO									
Per SD increase	104 (5.47%)	1.02(0.8,1.31)	0.853	0.86(0.65,1.12)	0.263	0.81(0.6,1.1)	0.170	0.72(0.51,1.03)	0.071
Quartiles of TyG									
Q1 [5.65 - 8.15]	18 (3.8%)	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*
Q2 [8.15 - 8.57]	23 (4.8%)	0.84(0.38,1.89)	0.681	0.59(0.27,1.28)	0.183	0.48(0.2,1.17)	0.106	0.43(0.17,1.08)	0.073
Q3 [8.57 - 9.02]	34 (7.2%)	1.19(0.58,2.47)	0.638	0.78(0.38,1.59)	0.495	0.68(0.31,1.47)	0.323	0.77(0.36,1.66)	0.507
Q4 [9.02 - 13.4]	29 (6.1%)	1.24(0.59,2.58)	0.572	0.74(0.35,1.57)	0.428	0.61(0.27,1.36)	0.226	0.75(0.29,1.9)	0.538
p for trend			0.424		0.696		0.517		0.858
MUNO									
Per SD increase	634 (23.38%)	1.02(0.9,1.14)	0.797	1.22(1.1,1.35)	<0.001	1.21(1.09,1.34)	<0.001	1.62(1.36,1.93)	<0.001
Quartiles of TyG									
Q1 [5.65 - 8.15]	129 (19%)	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*
Q2 [8.15 - 8.57]	158 (23.3%)	0.94(0.69,1.27)	0.681	1.06(0.79,1.42)	0.695	1.11(0.82,1.5)	0.483	1.29(0.93,1.8)	0.129
Q3 [8.57 - 9.02]	173 (25.5%)	1.11(0.82,1.52)	0.498	1.34(0.99,1.81)	0.056	1.41(1.04,1.91)	0.028	1.86(1.31,2.65)	0.001
Q4 [9.02 - 13.4]	174 (25.7%)	1.1(0.79,1.51)	0.577	1.81(1.38,2.37)	<0.001	1.83(1.4,2.4)	<0.001	2.81(1.9,4.16)	<0.001
p for trend			0.404		<0.001		<0.001		<0.001
MUO									
Per SD increase	524 (14.85%)	1.21(1.09,1.35)	0.001	1.26(1.12,1.42)	<0.001	1.24(1.09,1.4)	0.001	1.47(1.26,1.71)	<0.001
Quartiles of TyG									
Q1 [5.65 - 8.15]	108 (12.2%)	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*
Q2 [8.15 - 8.57]	132 (15%)	1.16(0.84,1.61)	0.373	1.24(0.9,1.71)	0.197	1.25(0.9,1.73)	0.187	1.28(0.9,1.82)	0.177
Q3 [8.57 - 9.02]	123 (13.9%)	0.93(0.68,1.27)	0.649	0.97(0.71,1.32)	0.835	0.92(0.66,1.28)	0.612	0.99(0.7,1.4)	0.958
Q4 [9.02 - 13.4]	161 (18.3%)	1.49(1.11,2.01)	0.009	1.56(1.15,2.11)	0.004	1.55(1.13,2.13)	0.007	1.79(1.2,2.69)	0.005
p for trend			0.019		0.012		0.021		0.016

Abbreviations: MHNO, metabolically healthy non-obese; MHO, metabolically healthy obesity; MUNO, metabolically unhealthy non-obese; MUO, metabolically unhealthy obesity; Ref, Reference; HR, hazard ratio; CI, confidence interval.

Model I: Adjusted for gender, age.

Model II: Adjusted for gender, age, race or ethnicity, education level, smoking status, alcohol use, and family income to poverty ratio.

Model III: Additionally adjusted for estimated glomerular filtration rate, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, hypertension status, high cholesterol status, use of antihypercholesterolemia medications, use of antihypertensive medications, history of coronary heart disease, myocardial infarction, heart failure, and stroke

RCS analysis of the relationship between the TyG index and mortality

When the four population groups were analyzed, all-cause and cardiovascular mortalities displayed similar trends: the curves for the overall and metabolically unhealthy populations showed a consistent upward trend, whereas those for the metabolically healthy populations were flat or even downward. The hazard ratio for all-cause mortality was approximately half that for cardiovascular mortality. The curves for the overall

Table 3 HRs of TyG index for cardiovascular mortality in the overall population and stratified by metabolic health and obesity status

Population and variables	Event, *n*(%)	Crude Model		Model I		Model II		Model III	
		HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Overall									
Per SD increase	568 (3.51%)	1.51(1.38,1.66)	<0.001	1.2(1.06,1.36)	0.004	1.2(1.05,1.36)	0.005	1.52(1.27,1.82)	<0.001
Quartiles of TyG									
Q1 [5.65 - 8.15]	54 (1.3%)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2 [8.15 - 8.57]	121 (3%)	2.17(1.42,3.32)	<0.001	1.02(0.66,1.58)	0.920	1.05(0.69,1.62)	0.811	1.14(0.74,1.75)	0.545
Q3 [8.57 - 9.02]	169 (4.2%)	3.09(2.07,4.61)	<0.001	1.11(0.73,1.67)	0.631	1.13(0.75,1.72)	0.555	1.3(0.82,2.06)	0.272
Q4 [9.02 - 13.4]	224 (5.5%)	4.21(2.87,6.19)	<0.001	1.28(0.85,1.94)	0.240	1.31(0.86,2.01)	0.214	1.6(0.98,2.61)	0.061
p for trend			<0.001		0.104		0.113		0.033
MHNO									
Per SD increase	167 (2.08%)	1.35(1.19,1.52)	<0.001	1.05(0.86,1.29)	0.639	1.02(0.84,1.24)	0.847	1.23(0.88,1.73)	0.230
Quartiles of TyG									
Q1 [5.65 - 8.15]	20 (1%)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2 [8.15 - 8.57]	26 (1.3%)	1.16(0.56,2.38)	0.690	0.77(0.38,1.59)	0.487	0.78(0.38,1.59)	0.493	0.84(0.4,1.77)	0.647
Q3 [8.57 - 9.02]	62 (3.1%)	2.88(1.5,5.5)	0.001	1.29(0.66,2.53)	0.455	1.17(0.6,2.28)	0.636	1.49(0.72,3.09)	0.288
Q4 [9.02 - 13.4]	59 (2.9%)	2.75(1.39,5.41)	0.004	1.12(0.56,2.25)	0.747	1.03(0.53,2.02)	0.925	1.45(0.57,3.69)	0.437
p for trend			<0.001		0.440		0.631		0.241
MHO									
Per SD increase	34 (1.79%)	1.12(0.72,1.73)	0.620	0.9(0.53,1.53)	0.694	0.87(0.5,1.5)	0.615	0.65(0.36,1.18)	0.160
Quartiles of TyG									
Q1 [5.65 - 8.15]	5 (1.1%)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2 [8.15 - 8.57]	9 (1.9%)	0.87(0.23,3.22)	0.830	0.39(0.09,1.67)	0.206	0.4(0.07,2.29)	0.302	0.48(0.18,1.32)	0.154
Q3 [8.57 - 9.02]	7 (1.5%)	0.53(0.15,1.95)	0.343	0.27(0.08,0.93)	0.038	0.26(0.07,1.05)	0.058	0.36(0.13,0.97)	0.044
Q4 [9.02 - 13.4]	13 (2.7%)	1.63(0.46,5.71)	0.448	0.67(0.2,2.31)	0.528	0.69(0.17,2.84)	0.609	0.99(0.42,2.32)	0.982
p for trend			0.520		0.857		0.847		0.969
MUNO									
Per SD increase	189 (6.97%)	1.08(0.91,1.28)	0.370	1.36(1.16,1.6)	<0.001	1.4(1.18,1.65)	<0.001	2.01(1.49,2.72)	<0.001
Quartiles of TyG									
Q1 [5.65 - 8.15]	39 (5.8%)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2 [8.15 - 8.57]	46 (6.8%)	0.81(0.46,1.41)	0.452	0.96(0.58,1.57)	0.857	1.01(0.6,1.7)	0.966	1.18(0.69,2.01)	0.547
Q3 [8.57 - 9.02]	49 (7.2%)	0.97(0.61,1.55)	0.902	1.23(0.78,1.96)	0.372	1.33(0.83,2.15)	0.241	1.77(1.04,3.03)	0.036
Q4 [9.02 - 13.4]	55 (8.1%)	1.16(0.71,1.88)	0.555	2.22(1.38,3.56)	0.001	2.38(1.48,3.83)	<0.001	3.67(2.08,6.46)	<0.001
p for trend			0.392		0.001		<0.001		<0.001
MUO									
Per SD increase	178 (5.04%)	1.17(0.98,1.39)	0.080	1.22(1.01,1.47)	0.044	1.22(1,1.48)	0.045	1.47(1.14,1.88)	0.003
Quartiles of TyG									
Q1 [5.65 - 8.15]	42 (4.8%)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2 [8.15 - 8.57]	40 (4.5%)	1.06(0.6,1.88)	0.832	1.17(0.65,2.1)	0.600	1.22(0.69,2.18)	0.492	1.42(0.77,2.62)	0.266
Q3 [8.57 - 9.02]	43 (4.9%)	0.82(0.5,1.36)	0.451	0.87(0.51,1.48)	0.605	0.86(0.49,1.52)	0.612	1.16(0.64,2.11)	0.623
Q4 [9.02 - 13.4]	53 (6%)	1.34(0.79,2.27)	0.271	1.42(0.84,2.42)	0.192	1.51(0.86,2.63)	0.148	2.25(1.08,4.69)	0.031
p for trend			0.325		0.265		0.219		0.049

Abbreviations: MHNO, metabolically healthy non-obese; MHO, metabolically healthy obesity; MUNO, metabolically unhealthy non-obese; MUO, metabolically unhealthy obesity; Ref, Reference; HR, hazard ratio; CI, confidence interval

Model I: Adjusted for gender, age

Model II: Adjusted for gender, age, race or ethnicity, education level, smoking status, alcohol use, and family income to poverty ratio

Model III: Additionally adjusted for estimated glomerular filtration rate, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, hypertension status, high cholesterol status, use of antihypercholesterolemia medications, use of antihypertensive medications, history of coronary heart disease, myocardial infarction, heart failure, and stroke

population and MUNO group were nonlinear, whereas those for the other groups were linear (Figs. 2 and 3).

Sensitivity analysis

First, we excluded patients who died within three years to minimize the effect of severe acute illnesses on the outcomes. Second, in consideration of the effects of lipid-lowering and antidiabetic medications on TyG index levels, individuals taking these medications at baseline were not included in the analysis. Third, given previous findings that the TyG index in the elderly population from the NHANES data showed poor predictive performance for mortality [16], we excluded study subjects aged over 75 years to account for the sample size in

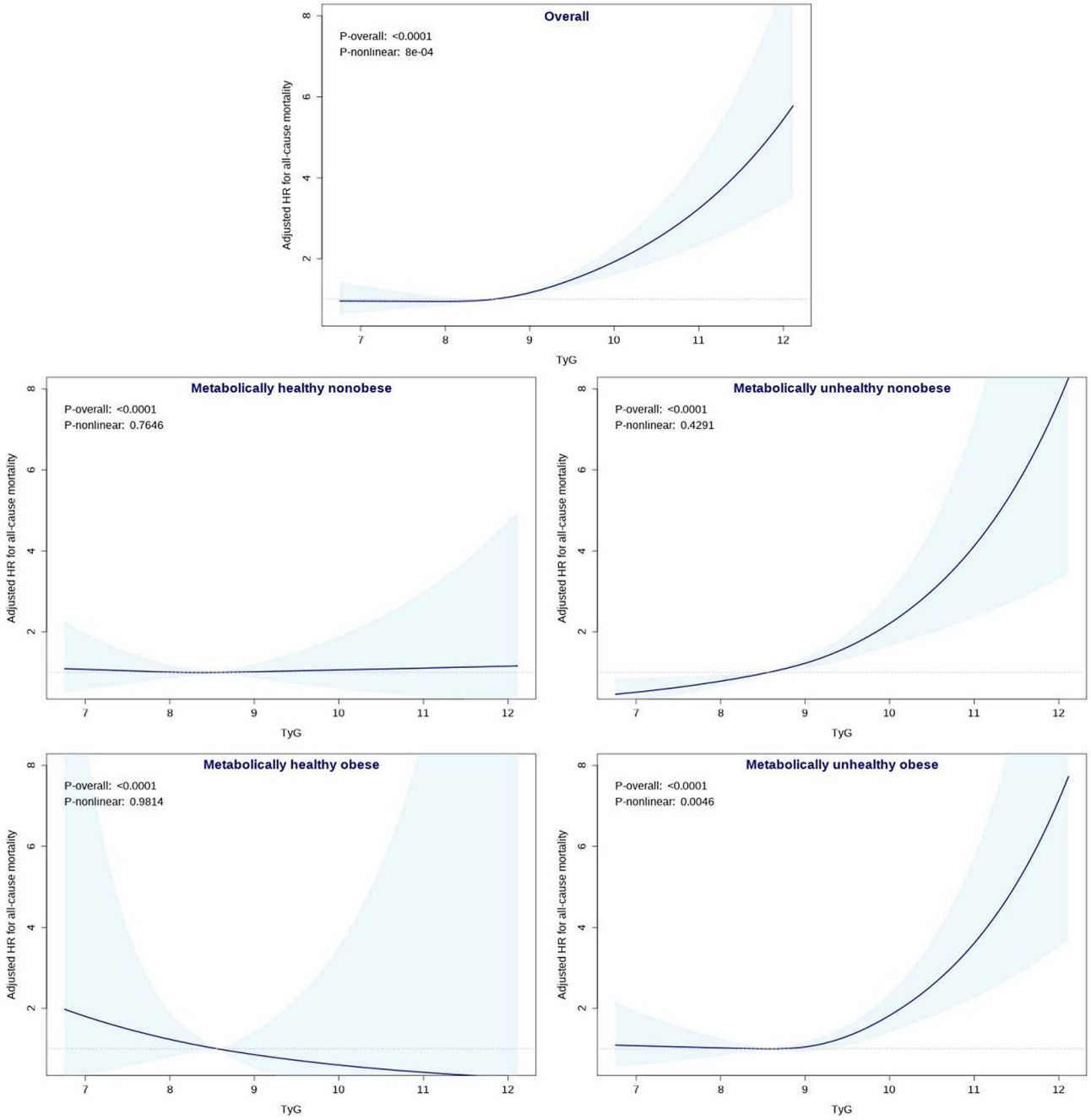

Fig. 2 RCS Analysis of the Relationship Between the TyG Index and All-Cause Mortality. Hazard ratios were adjusted for gender, age, race or ethnicity, educational level, smoking status, alcohol use, family income-to-poverty ratio, estimated glomerular filtration rate, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, hypertension status, high cholesterol status, use of antihypercholesterolemia medications, use of antihypertensive medications, history of coronary heart disease, myocardial infarction, heart failure, and stroke

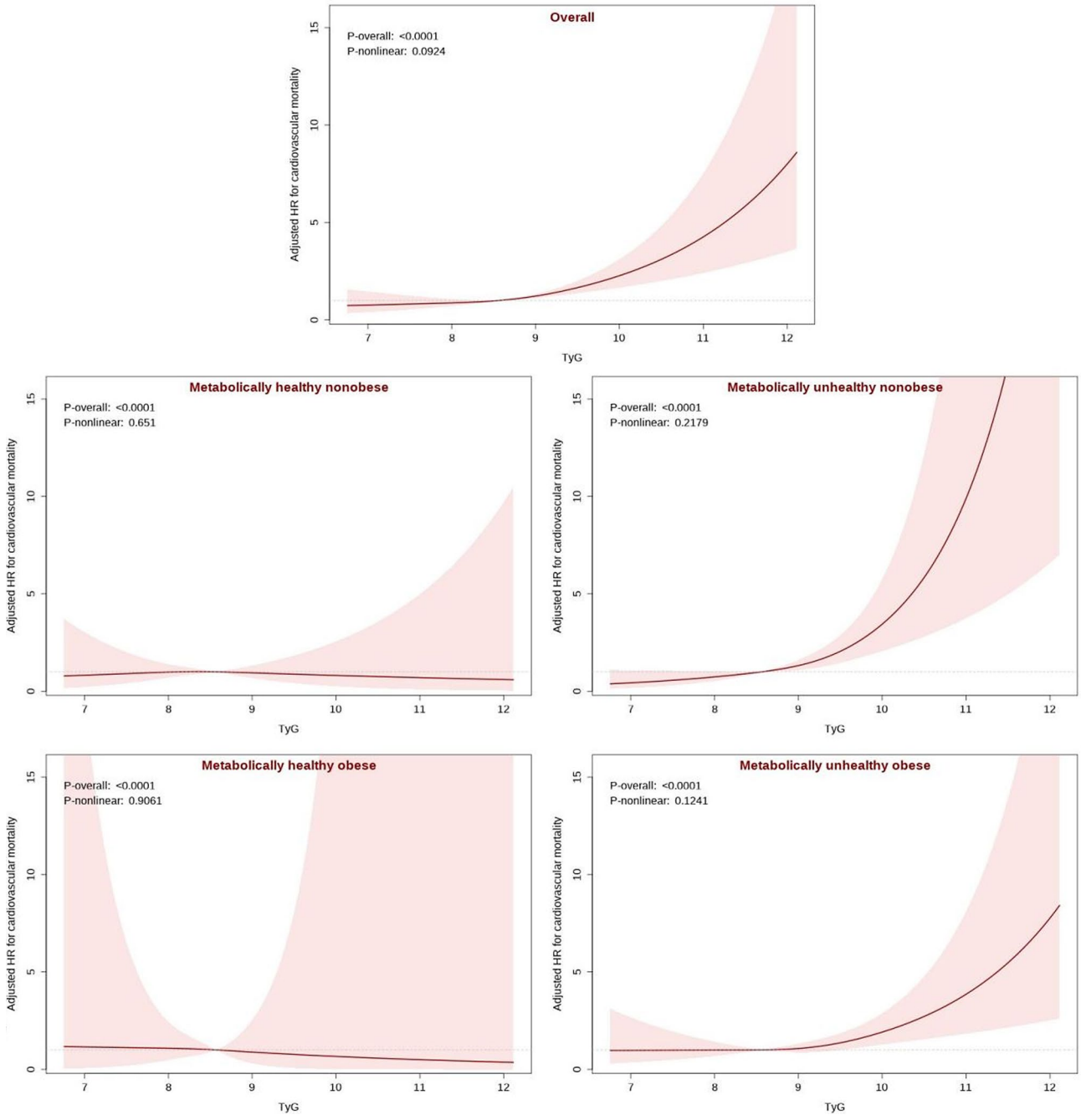

Fig. 3 RCS Analysis of the Relationship Between the TyG Index and Cardiovascular Mortality. Hazard ratios were adjusted for gender, age, race or ethnicity, educational level, smoking status, alcohol use, family income-to-poverty ratio, estimated glomerular filtration rate, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, hypertension status, high cholesterol status, use of antihypercholesterolemia medications, use of antihypertensive medications, history of coronary heart disease, myocardial infarction, heart failure, and stroke

the groups. Fourth, considering that the TyG index and MetS grouping originally relied on the TG indicator, we redefined MetS by excluding TG-related criteria to evaluate potential merger bias, even though this adjustment reduced the number of subjects classified as metabolically unhealthy. All sensitivity analyses consistently supported our findings, with the predictive trend of the TyG index for mortality maintained across these various analyses. These results further confirm the credibility and reliability of our research conclusions (Supplementary Figures S1–8).

Discussion

Our study revealed that the TyG index had a significant positive correlation with all-cause and cardiovascular mortalities in the overall population. However, stratifying the population by obesity and metabolic statuses led to different conclusions: (1) In the metabolically unhealthy population, regardless of obesity status, the TyG index had good predictive value for all-cause and cardiovascular mortalities. (2) In the metabolically healthy population, the predictive value of the TyG index for all-cause and cardiovascular mortalities was limited. These findings suggest that the value of the TyG index for the prediction of mortality varies across different populations, highlighting the necessity of accounting for metabolic status when using the TyG index for prognostic evaluation.

In the overall population, despite some negative results [22, 23], numerous studies in recent years have demonstrated the predictive value of the TyG index for all-cause and cardiovascular mortalities, reporting various relationships, such as linear, J-shaped, inverse L-shaped, and U-shaped relationships [15, 17, 24, 25]. A high TyG index typically indicates strong insulin resistance and is associated with metabolic abnormalities and atherosclerotic cardiovascular diseases [26]. This association can explain the aforementioned phenomenon. Our study also identified a similar association. In our study population, over 60% of the participants were metabolically healthy individuals. Even after adjusting for confounding factors, the same conclusion was reached, suggesting that the predictive capability of the TyG index in metabolically unhealthy populations is robust. This situation further emphasizes the need for the careful selection of populations when the TyG index is used as a mortality predictor.

Consistent with our viewpoint, the predictive value of the TyG index varies across different populations. A large-scale study stratified by economic factors revealed that the TyG index has predictive value for mortality in low- and middle-income countries but not in high-income countries likely due to increased susceptibility to insulin resistance from factors, such as malnutrition, low birth weight, modern lifestyles, and obesogenic environments [27]. Another NHANES-based study revealed that antidiabetic and hypolipidemic agents modify this association, with a U-shaped relationship in users and a linear positive trend in nonusers [28].

In the metabolically unhealthy population, our findings were consistent with a study assessing the predictive value of the TyG index in patients with MetS, which reported unidirectional curves [29]. To our knowledge, only one study with a similar population grouping to ours exists. This study was based on a health screening cohort established by the Korean National Health Insurance Service. It ultimately included 292 206 subjects and followed them for six years, with cardiovascular mortality as the endpoint [30]. Its results indicated that after adjusting for covariates, the risk ratio of TyG Q4 to Q1 was statistically significant only in the MUHO population but not in the MHO and MHNO populations. Unlike our study, this research did not find a predictive ability for TyG in the MUNO population, whereas our work obtained a positive result. This discrepancy may be related to differences in the definitions of the grouping standards. The previous study employed a strict definition of metabolic health, requiring the absence of all MetS criteria. This requirement resulted in its MUNO group including additional individuals with mild metabolic abnormalities. This situation may have reduced the predictive value of the TyG index in this subset of the population.

In the metabolically healthy population, regardless of MHNO or MHO status, the TyG index did not show significant predictive value for mortality, a conclusion consistent with those of studies from Korea [30]. The possible reasons might be as follows: (1) Compared with metabolically unhealthy individuals, metabolically healthy individuals typically have fewer underlying diseases (consistent with the results in Table 1), resulting in a lower risk of mortality and a longer time to the occurrence of death. Although we employed a lenient definition of metabolic health, even including those with mild metabolic abnormalities, we still found consistent negative results, further confirming the validity of the aforementioned conclusion. (2) During the long follow-up period, deceased and nondeceased individuals may experience phenotypic transitions in terms of obesity and metabolic status, increasing confounding factors. (3) For this population, other cardiovascular risk factors (such as age, blood pressure, and cholesterol levels) may have a significant effect on cardiovascular mortality, whereas the role of the TyG index is relatively minor. Therefore, additional data are needed to validate these findings.

Strengths and limitations

The strengths of our study lie in its use of national data, which have a large sample size and a long follow-up period and have been validated through numerous studies related to TyG, for analysis. However, we must also acknowledge the limitations of our work: (1) The data were retrospective, making it difficult to completely eliminate confounding factors, such as grouping on the basis solely of BMI without excluding secondary obesity. (2) Metabolic phenotypes may differ from each other, and longitudinal data on TyG are lacking. (3) This study focused exclusively on the American population, which may limit the generalizability of the results.

Conclusion

The TyG index is positively correlated with mortality risk in the overall and metabolically unhealthy populations but not in the metabolically healthy population. This finding indicates that the predictive value of the TyG index for mortality differs across populations, highlighting the necessity of accounting for metabolic status when using the TyG index for prognostic evaluation.

Abbreviations

BMI	Body Mass Index
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CI	Confidence Interval
DBP	Diastolic Blood Pressure
FBG	Fasting Blood Glucose
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
MHO	Metabolically Healthy Obese
MUO	Metabolically Unhealthy Obese
MHNO	Metabolically Healthy Nonobese
MUNO	Metabolically Unhealthy Nonobese
MetS	Metabolic Syndrome
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
PIR	Poverty-to-Income Ratio
RCS	Restricted Cubic Splines
SBP	Systolic Blood Pressure
SUA	Serum Uric Acid
TC	Total Cholesterol
TyG	Triglyceride-Glucose
TG	Triglycerides

Supplementary Information

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Supplementary Material 1

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Author contributions

TY: Writing– original draft. ZL: Writing– review & editing. FH: Writing– review & editing. JHC: Writing– review & editing. LLC: Writing– review & editing.

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Data availability

Data availability statement The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://www.cdc.gov/nchs/nhanes/?CDC_AAref_Val.https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate

The studies involving humans were approved by the US Centers for Disease Control and Prevention. The studies were conducted in accordance with local legislation and institutional requirements. The participants provided written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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