Cardiovascular Diabetology

RESEARCH

Open Access

The association between novel metabolic parameters and all-cause/cardiovascular mortality in patients with metabolic syndrome is modified by age

Jiajun Liu[1,2], Yihui Fu[3], Pengpeng Liang[1,2], Zhangxiao Song[1,2], Yue Li[1,2*] and Hongyan Wu[1,2*]

Abstract

Background Triglyceride glucose index (TyG) serves as an effective parameter for assessing metabolic status. However, it remains uncertain whether TyG and other metabolic parameters can predict clinical outcomes in people with metabolic syndrome (MetS). We investigated the association of TyG, triglyceride glucose-waist to height ratio (TyG-WHtR), and metabolic score for insulin resistance (METS-IR) with all-cause and cardiovascular mortality in the MetS cohort and determined whether this association changes with age.

Method Participants enrolled in the National Health and Nutrition Examination Survey (NHANES) between 2001 and 2018 were selected and categorized into two groups: younger individuals (age < 65 years) and older individuals (age ≥ 65 years). Three new metabolic indices of TyG, TyG-WHtR, and METS-IR were constructed. The weighted Cox proportional hazards model and restricted cubic spline (RCS) models were employed to evaluate the relation between three indices and mortality outcomes. The time-dependent receiver operating characteristic (ROC) curve assessed the ability of different indices to predict mortality. Sensitivity analysis was conducted to evaluate the robustness and reliability of the findings.

Results The study comprised a total of 8271 participants, including 5456 younger participants and 2815 older participants, and 1407 deaths were observed over a median follow-up period of 8.3 years. Compared with the first quartile (Q1), the fourth quartile's (Q4) TyG, TyG-WHtR, and METS-IR were linked to an increased risk of all-cause mortality (HR 1.63, 95% CI 1.12–2.39; HR 2.78, 95% CI 1.68–4.61; HR 1.36, 95% CI 1.12–2.02, respectively) and cardiovascular mortality (HR 2.04, 95% CI 1.15–4.90; HR 4.99, 95% CI 1.76–14.11; HR 2.69, 95% CI 1.89–8.15, respectively) in the younger group but not in the older group. The RCS results showed no significant non-linear associations between TyG, TyG-WHtR, METS-IR, and all-cause ($P = 0.082$; $P = 0.712$; $P = 0.062$, respectively) or cardiovascular mortality ($P = 0.176$; $P = 0.793$; $P = 0.482$, respectively) in the older age group. TyG-WHtR demonstrated the highest area under

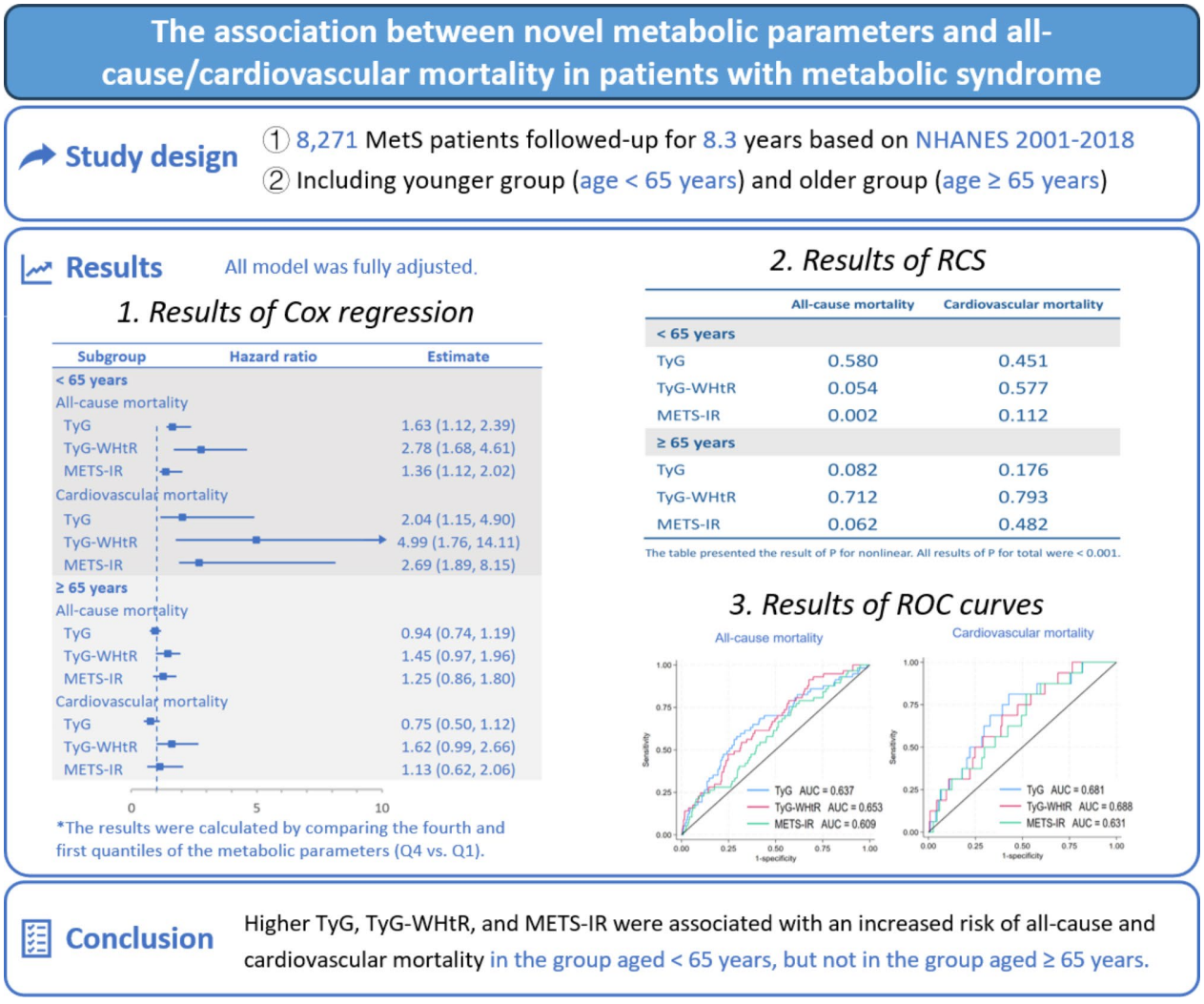
*Correspondence:
Yue Li
yueli0419@163.com
Hongyan Wu
wu.hy@163.com

Full list of author information is available at the end of the article

the curve for predicting 3-year mortality in the younger age group, with values of 0.653 for all-cause mortality and 0.688 for cardiovascular mortality.

Conclusion Our results highlight the predictive value of TyG, TyG-WHtR, and METS-IR in the MetS population, providing new evidence for medical practice and public health.

Graphical abstract A total of 8271 younger (age < 65 years) and older (age ≥ 65 years) participants were enrolled in the study, with a median follow-up of 100 months. Weighted COX regression results (left), restricted cubic spline results (upper right), and time-dependent (cut-off value of 36 months) receiver operating characteristic curve results (lower right). TyG Triglyceride glucose index; WHtR Triglyceride glucose-waist to height ratio; METS-IR Metabolic score for insulin resistance; MetS Metabolic syndrome.



Keywords Novel metabolic parameters, Triglyceride glucose index, Metabolic syndrome, Age, Mortality

Introduction

Metabolic syndrome (MetS) refers to a group of pathological conditions linked to risk factors, often accompanied by abdominal obesity, hypertension, hyperlipidemia, and abnormal blood sugar [1]. One of the major health burdens in Western countries, MetS increases the likelihood of various diseases such as stroke, type 2 diabetes, and coronary heart disease, and is also associated with elevated mortality [2, 3]. Along with shifting lifestyles and dietary habits, the prevalence of MetS is increasing, with more than 30% of Americans suffering from it, especially older adults [4–6]. Due to the high risk of complications and prevalence of MetS, it presents significant global challenges in clinical practice. Therefore, detecting

high-risk populations for MetS early and formulating corresponding strategies are crucial in safeguarding individuals' health.

Insulin resistance (IR) represents a state characterized by a reduction in the sensitivity of insulin-responsive tissues, including fat, bone, and liver, to insulin, leading to hyperinsulinemia [7]. Many metabolic risk factors, such as hypertension and diabetes, are associated with IR, which is considered a central role in the pathogenesis of MetS [8]. The hyperinsulinemic-euglycemic clamp technique, developed by DeFronzo and his team, is widely hailed as the gold standard for the precise assessment of IR [9]. However, this technique is costly and cumbersome, rendering it challenging to implement widely in clinical practice. Many parameters have been devised to measure IR, and the most commonly used is the insulin resistance homeostasis model (HOMA-IR) [10–13]. HOMA-IR, derived from fasting plasma glucose and insulin levels, is hampered by the need for routine measurement of insulin, which may pose a challenge to primary health care settings [14]. Moreover, HOMA-IR presents certain limitations in patients suffering from β-cell failure and those undergoing insulin therapy [15, 16].

Recent studies indicate that novel metabolic parameters, which do not depend on insulin measurements, can predict IR and cardiovascular risk across diverse populations, suggesting their potential as effective alternatives to HOMA-IR [17, 18]. The triglyceride-glucose (TyG) index has the ability to identify people of different races and different regions with severe MetS [19–21]. A meta-analysis of 13 studies involving 49,325 participants demonstrated that TyG is a clinically significant and accurate predictor of MetS [22]. In addition, TyG can assess the risk of disease and mortality across diverse populations, especially in the elderly and critically ill patients [23, 24]. TyG offers a practical solution for predicting diabetes and cardiovascular diseases (CVD) [25]. However, there are limited studies reporting the predictive role of TyG and other novel metabolic parameters in MetS. Besides, recent articles indicate that TyG may have varying predictive power across different age groups [26].

Therefore, our objective was to explore the relationship between TyG, triglyceride glucose-waist height ratio index (TyG-WHtR), and metabolic score for insulin resistance (METS-IR) with all-cause and cardiovascular mortality in individuals with MetS and to determine whether this relationship changes with age.

Methods

Data source

NHANES is a study sponsored by the Centers for Disease Control and Prevention to assess the nutritional health of children and adults in the United States. The study uses a stratified, staged, complex sampling design to ensure that the sample surveyed is nationally representative. Every 2 years, researchers conducted the study, which included general population data, dietary status, examination data, laboratory data, and questionnaires.

Population selection

We selected data from 9 interview cycles of NHANES from 2001 to 2018, with a total of 91,351 participants surveyed. After excluding people under 18 years old and those without a confirmed diagnosis of MetS, a total of 15,798 participants were further studied. Participants missing TyG data ($n = 7,374$), mortality data ($n = 9$), and key covariates ($n = 144$) were further excluded. Ultimately, 8,271 participants were included in our study, including 5,456 in the younger group (age < 65 years) and 2,815 in the older group (age ≥ 65 years). The detailed selection process can refer to Fig. 1.

Measurement of novel metabolic parameters

This study included three novel metabolic parameters: TyG, TyG-WHtR, and METS-IR. TyG was calculated using triglycerides (TG) and fasting blood glucose (FBG) levels from participants' peripheral blood at baseline. Waist-to-height ratio (WHtR) was selected as an obesity indicator for MetS. The calculation formula for the three indicators is as follows:

(1) TyG = ln[TG (mg/dl)*FBG (mg/dl)/2] [27];
(2) TyG-WHtR = TyG*[waist circumference (cm)/height (cm)] [27];
(3) METS-IR = Ln[(2*FBG (mg/dl) + TG (mg/dl)) * BMI]/Ln[HDL (mg/dl)] [28].

Definition of MetS

A diagnosis of MetS is made when 3 or more of the following conditions are met [29]: (1) Waist circumference (WC) was > 102 cm in men or > 88 cm in women; (2) FBG ≥ 100 mg/dl or take medication for diabetes; (3) Fasting HDL-C < 40 mg/dl in men or < 50 mg/dl in women, or take medications that regulate HDL-C; (4) Fasting TG ≥ 150 mg/dl or take medication to lower TG; (5) Blood pressure ≥ 130/85 mmHg or take medication to lower blood pressure.

Assessment of covariates

Standardized questionnaires were employed to gather demographic information about the participants, including age, gender, education attainment, race/ethnicity, body mass index (BMI), smoking status, alcohol consumption, drug use, and disease status. Educational attainment was categorized into three levels: high school and below, college or equivalent, and college or above. Similarly, smoking status was classified into three groups:

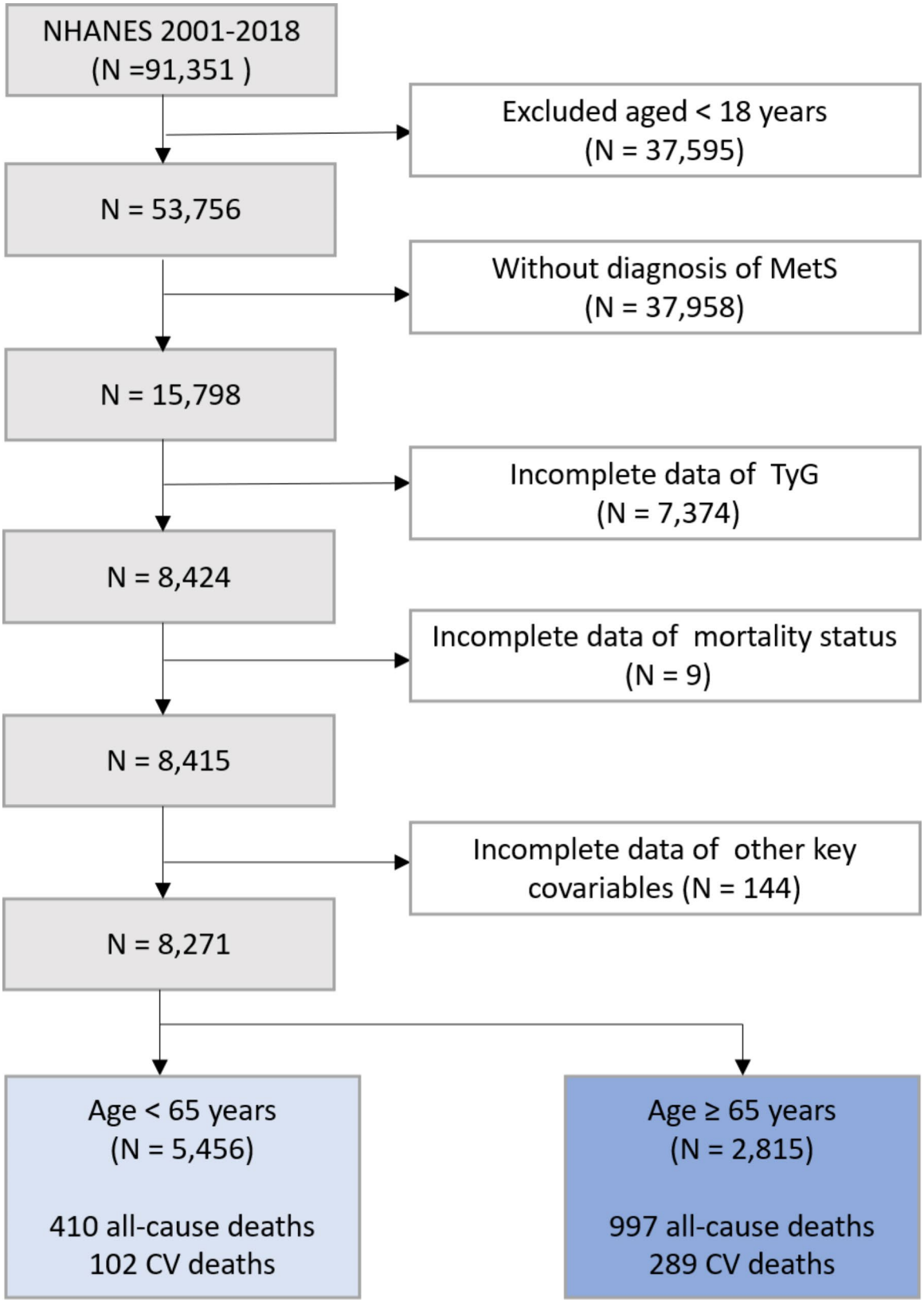


Fig. 1 Flowchart of the sample selection from National Health and Nutrition Examination Survey (NHANES) 2001–2018. TyG Triglyceride glucose index; MetS Metabolic syndrome; CV Cardiovascular.

never smokers, former smokers, and current smokers. Alcohol consumption was divided into never drinking, light drinking, and moderate to heavy drinking. When one or more of the following conditions are met, hypertension is diagnosed: Self-reported history of hypertension; currently taking antihypertensive medication; blood pressure: systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg [30]. A diagnosis of diabetes mellitus is established when any one or more of the following criteria are fulfilled: FBG ≥ 7.0 mmol/L; glycated hemoglobin A1c (HbA1C) ≥ 6.5%; 2-hour plasma glucose level of 11.1 mmol/L or above during an oral glucose tolerance test; individuals with self-reported diabetes or use of hypoglycemic medications [31].

Determination of death

The primary outcome measures were all-cause and cardiovascular mortality among the MetS population. Use the 10th revised edition of the International Classification of Diseases to determine the specific cause of death

Table 1 Baseline characteristics of patients with MetS by age

Characteristic	Total (*N* = 8271)	< 65 Years (*N* = 5456)	≥ 65 Years (*N* = 2815)	*P* value	
Gender, n (%)				*P* = 0.989	
Male	3442 (41.62%)	2273 (41.67%)	1169 (41.53%)		
Female	4829 (58.38%)	3183 (58.33%)	1646(58.47%)		
BMI (kg/m^2)	28.9 (31.9, 36.3)	29.7 (32.9, 37.6)	27.8 (30.4, 34.0)	*P* < 0.001	
Ethnicity, n (%)				*P* < 0.001	
Mexican American	1447 (17.49%)	1080 (19.79%)	367 (13.04%)		
Other Hispanic	724 (8.75%)	514 (9.42%)	210 (7.46%)		
Non-Hispanic White	3973 (48.04%)	2313 (42,39%)	1660 (58.97%)		
Non-Hispanic Black	1646 (19.90%)	1199 (21.98%)	447 (15.88%)		
Other race	481 (5.82%)	350 (6.41%)	131 (4.65%)		
Education level, n (%)				*P* < 0.001	
≤ High school	4386 (53.03%)	2694 (49.38%)	1692 (59.94%)		
College	2421 (29.27%)	1750 (32.07%)	671 (23.98%)		
> College	1464 (17.70%)	1012 (18.55%)	452 (16.08%)		
Smoking, n (%)				*P* < 0.001	
Current	4,253 (51.42%)	2,866 (52.53%)	1,387 (49.31%)		
Former	1,506 (18.21%)	1,288 (23.62%)	218 (7.93%)		
Never	2,512 (30.37%)	1,302 (23.85%)	1,210 (42.76%)		
Drinking, n (%)				*P* < 0.001	
Never	2,359 (28.52%)	1,249 (22.89%)	1,110 (39.82%)		
Mild	4,754 (57.48%)	3,452 (63.28%)	1,302 (45.84%)		
Moderate or Heavy	1,158 (14.00%)	755 (13.83%)	403 (14.34%)		
Diabetes mellitus, n (%)				*P* < 0.001	
Yes	2,842 (34.36%)	1,550 (28.41%)	1,292 (45.9%)		
No	5,429 (65.64%)	3,906 (71.59%)	1,523 (54.1%)		
Hypertension, n (%)				*P* < 0.001	
Yes	6,005 (72.60%)	3,563 (65.30%)	2,442 (86.75%)		
No	2,266 (27.40%)	1,893 (34.70%)	373 (13.25%)		
Hyperlipidaemia, n (%)				*P* < 0.001	
Yes	4,819 (58.26%)	2,912 (53.37%)	1,907 (67.74%)		
No	3,452 (41.74%)	2,544 (46.63%)	908 (32.26%)		
Laboratory measurements					
FBG (mg/dL)	99.0 (107.0, 122.1)	97.9 (105.0, 118.0)	101.1 (111.6, 130.0)	*P* < 0.001	
INS (uU/mL)	9.3 (14.2, 22.1)	10.1 (15.4, 23.9)	8.2 (12.4, 18.8)	*P* < 0.001	
TG (mg/dL)		167 (196, 226)	172 (199, 230)	160 (187, 219)	*P* < 0.001
TC (mg/dL)	167 (196, 226)	172 (199, 230)	160 (187, 219)	*P* < 0.001	
HDL-C (mg/dL)	39 (46, 57)	38 (45, 54)	42 (50, 61)	*P* < 0.001	
LDL-C (mg/dL)	91 (115, 141)	97 (120, 145)	82 (106, 133)	*P* < 0.001	

Values are number (percentage), or median (25th-75th percentile)

BMI, Body mass index; FBG, Fasting blood-glucose; TG, Triglyceride; INS, Fasting insulin; TC, Total cholesterol; HDL, High-density-lipoprotein; LDL-C, Low-density-lipoprotein cholesterol

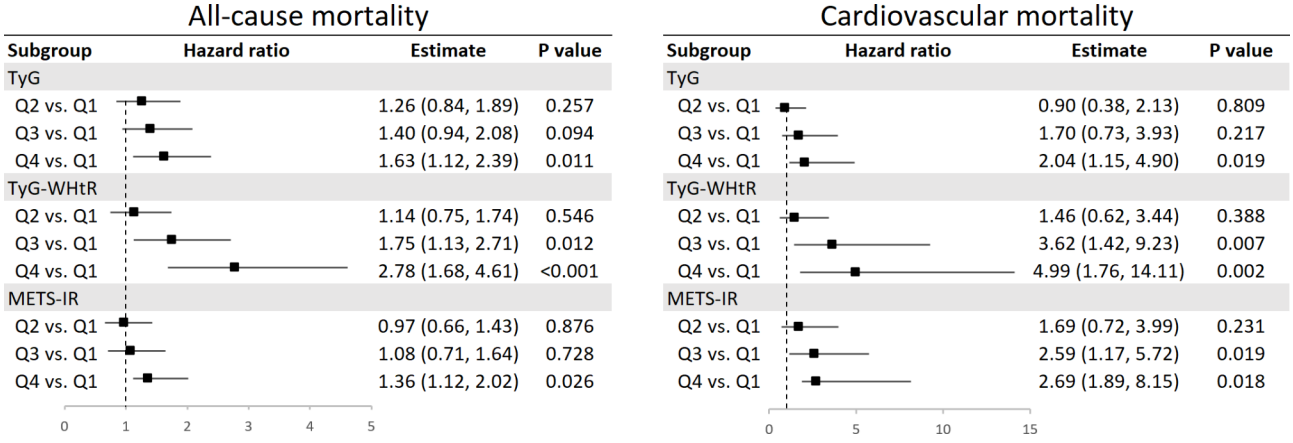


Fig. 2 The association between three novel metabolic parameters with all-cause and cardiovascular mortality in individuals < 65 years of age with MetS. Weighted Cox proportional hazard models were used to estimate hazard ratio (HR) and 95% confidence interval (CI). Model was adjusted for age, gender, ethnicity, educational level, BMI, hypertension, hyperlipidemia, diabetes, smoking status and drinking status. TyG Triglyceride glucose index; WHtR Triglyceride glucose-waist to height ratio; METS-IR Metabolic score for insulin resistance; MetS Metabolic syndrome.

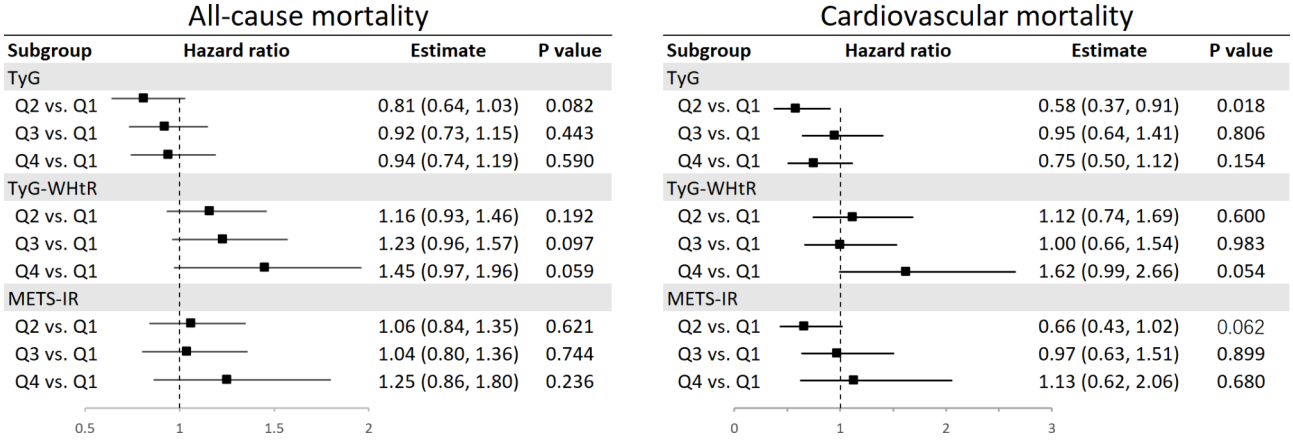


Fig. 3 The association between three novel metabolic parameters with all-cause and cardiovascular mortality in individuals ≥ 65 years of age with MetS. Weighted Cox proportional hazard models were used to estimate hazard ratio (HR) and 95% confidence interval (CI). Model was adjusted for age, gender, ethnicity, educational level, BMI, hypertension, hyperlipidemia, diabetes, smoking status and drinking status. TyG Triglyceride glucose index; WHtR Triglyceride glucose-waist to height ratio; METS-IR Metabolic score for insulin resistance; MetS Metabolic syndrome.

for participants. All-cause death refers to mortality from any cause, while the primary causes of cardiovascular death include ischemic heart disease and heart failure, etc. To determine whether participants died during follow-up and the specific cause of death, we used the newly published mortality data from NHANES, which were connected to the national mortality registry records [32].

Statistical analysis

Participants were divided into two age groups: younger (< 65 years) and older (≥ 65 years). Categorical variables are expressed as numbers and percentages (%), while continuous variables are expressed as medians and 25th to 75th percentiles. The chi-square test and Wilcoxon rank test were used to compare the differences among age groups. We divided TyG, TyG-WHtR, and METS-IR into quartiles (Q1-Q4). Kaplan-Meier survival analysis was used to explore the predictive value of three metabolic parameters. The Schoenfeld Residuals method and log-log survival plots were used to assess whether the Cox model met the proportional risk assumption. Weighted Cox proportional hazard models were employed to evaluate the relationship between novel metabolic markers and mortality, with hazard ratios (HR) and 95% confidence intervals (CI) being computed to quantify these associations. Directed acyclic graph (DAG) clarified confounding factors in the model. Model 1 was unadjusted; Model 2 adjusted for age, gender, ethnicity, education level, and BMI; Model 3 further adjusted for smoking status, drinking status, diabetes, hypertension, and hyperlipidemia, in addition to the factors in Model 2. In addition, we used E-value to assess the potential impact of unmeasured confounders. We employed a restrictive cubic spline (RCS) analysis to assess the potential non-linear

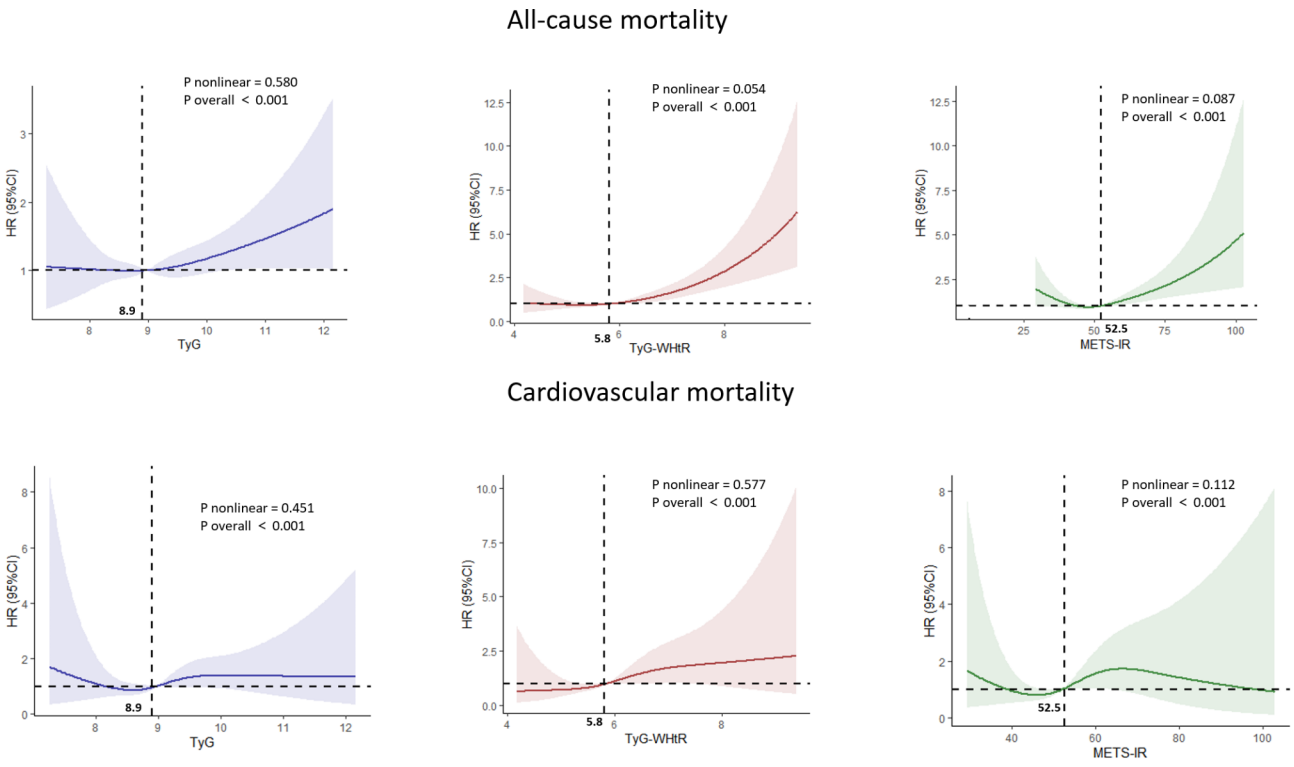


Fig. 4 The restricted cubic spline (RCS) analysis between three novel metabolic parameters with all-cause and cardiovascular mortality in individuals < 65 years of age with MetS. We chose four percentiles (0.05, 0.35, 0.65, 0.95) as the knots of RCS to form a smooth curve. The shaded areas represent the 95% CI. Model was adjusted for age, gender, ethnicity, educational level, BMI, hypertension, hyperlipidemia, diabetes, smoking status and drinking status. TyG Triglyceride glucose index; WHtR Triglyceride glucose-waist to height ratio; METS-IR Metabolic score for insulin resistance; MetS Metabolic syndrome.

relationship between three novel measures and mortality in MetS populations. In order to balance the smoothness of the fitted curves and to avoid the reduction in accuracy due to overfitting, we constructed a four-knot RCS [33]. The time-dependent receiver operating characteristic (ROC) curves were used to assess the ability of three parameters to predict mortality, with time cut-offs of 36, 60, and 120 months. We then performed subgroup analyses by age, gender, BMI, ethnicity, education level, smoking status, diabetes, etc. To ensure the reliability and consistency of the observed association between different measures and mortality, we performed a sensitivity analysis. All data analysis was done using Stata (version 18.1) and R (version 4.4.2) software, and $P < 0.05$ means a significant difference.

Results

Demographic characteristics of study participants

The study involved 8,271 participants with MetS, including 5,456 (65.97%) in the younger group (age < 65 years) and 2,815 (34.03%) in the older group (age ≥ 65 years). In comparison to the younger group, the older group exhibited a higher prevalence of diabetes, hypertension, and hyperlipidemia, along with higher levels of FBG and lower levels of TG, fasting insulin, total cholesterol, and low-density lipoprotein. Across both age groups, women demonstrated higher rates of MetS detection than men, with the majority of participants being non-Hispanic whites (Table 1).

Results of survival analysis

After a median follow-up of 100 months, a total of 1,407 deaths were recorded, with 389 attributed to cardiovascular causes. The Schoenfeld Residuals method and log-log survival plots indicated that the Cox modeling was consistent with a proportional-hazards model (Table S1, Fig. S1). Compared with the first quartile (Q1), the fourth quartile (Q4) of TyG, TyG-WHtR, and METS-IR were linked to an elevated risk of all-cause mortality (HR 1.63, 95% CI 1.12–2.39; HR 2.78, 95% CI 1.68–4.61; HR 1.36, 95% CI 1.12–2.02, respectively) and cardiovascular mortality (HR 2.04, 95% CI 1.15–4.90; HR 4.99, 95% CI 1.76–14.11; HR 2.69, 95% CI 1.89–8.15, respectively) in the younger group (Fig. 2). This association was not affected by confounding factors (Table S2). In the older group, TyG-WHtR was associated with an increased risk of all-cause and cardiovascular mortality, but the association became insignificant after adjustment for confounding factors (Fig. 3, Table S3). Fig. S2 presented the Kaplan–Meier survival curve for mortality in participants with

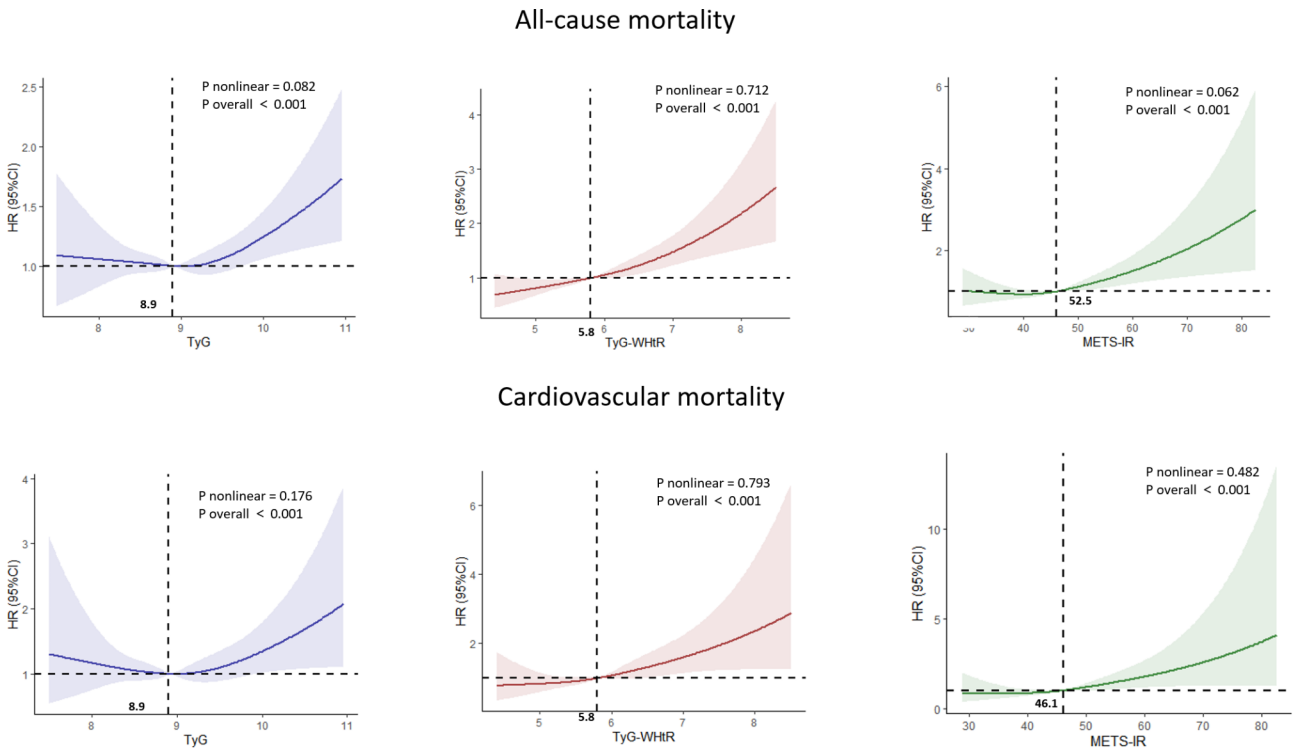


Fig. 5 The restricted cubic spline (RCS) analysis between three novel metabolic parameters with all-cause and cardiovascular mortality in individuals ≥ 65 years of age with MetS. We chose four percentiles (0.05, 0.35, 0.65, 0.95) as the knots of RCS to form a smooth curve. The shaded areas represent the 95% CI. Model was adjusted for age, gender, ethnicity, educational level, BMI, hypertension, hyperlipidemia, diabetes, smoking status and drinking status. TyG Triglyceride glucose index; WHtR Triglyceride glucose-waist to height ratio; METS-IR Metabolic score for insulin resistance; MetS Metabolic syndrome.

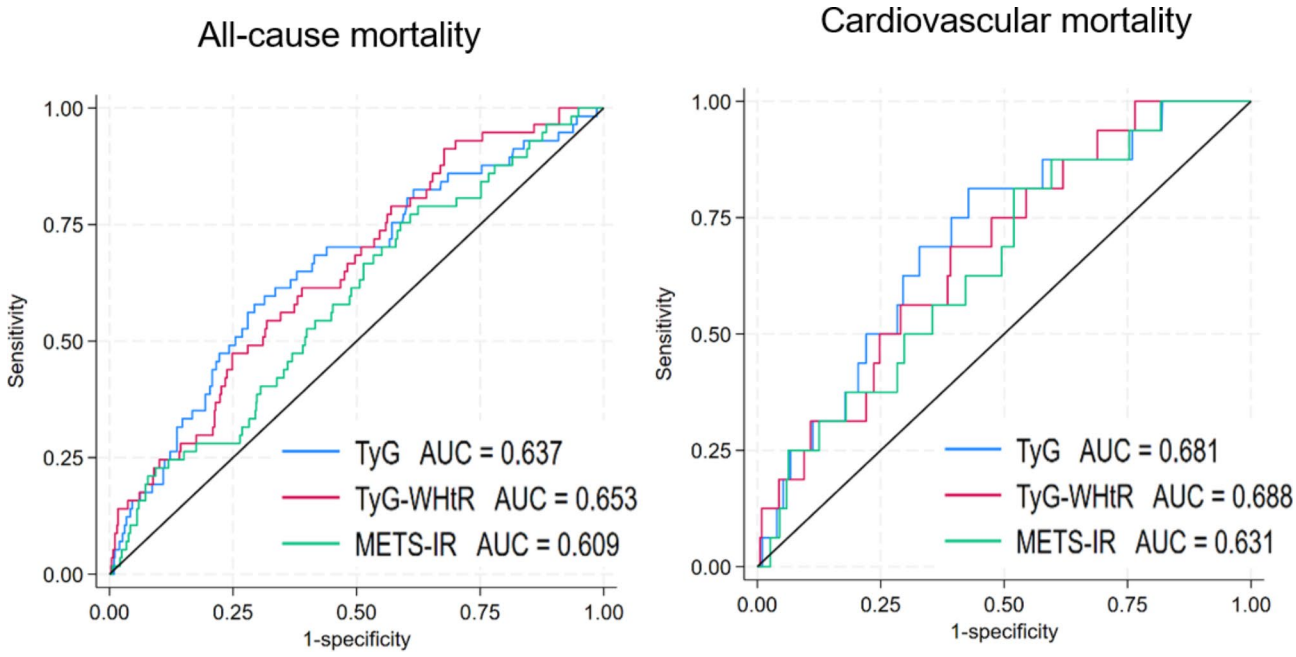


Fig. 6 ROC curve for evaluating the diagnostic power of three novel metabolic parameters. Time-dependent ROC curve was used to construct the model, with a time cutoff value of 36 months. ROC Receiver operating characteristic; TyG Triglyceride glucose index; WHtR Triglyceride glucose-waist to height ratio; METS-IR Metabolic score for insulin resistance.

MetS. We observed that in younger individuals, the metabolic parameters of the Q4 group had a higher mortality rate compared to the Q1 group, which is consistent with the results of Cox regression.

Results of RCS analysis

We selected four percentiles (0.05, 0.35, 0.65, and 0.95) as the RCS knots to create a smooth curve. There were no significant nonlinear associations between the three new metabolic measures and all-cause or cardiovascular mortality in either the older or younger groups (all nonlinear *P* values were > 0.05) (Figs. 4 and 5). Combined with the Cox and linear regression (Table S4) results, no linear or nonlinear associations of TyG, TyG-WHtR and METS-IR with all-cause and cardiovascular mortality were observed in the older group.

Results of ROC analysis

In the preceding analysis, the three parameters were not significantly associated with all-cause or cardiovascular mortality in the older group. Therefore, we performed ROC curve analysis only in the younger group, with the size of the area under the curve (AUC) indicating the strength of the predictive ability. TyG-WHtR demonstrated the highest AUC for predicting 3-year mortality, with values of 0.653 for all-cause mortality and 0.688 for cardiovascular mortality (Fig. 6). We also performed ROC curve analyses to predict 5-year and 10-year mortality (Table S5). It is noteworthy that the predictive power of the three parameters for mortality may gradually decrease with longer follow-up time.

Subgroup analysis and sensitivity analysis

We conducted subgroup analyses by stratifying the data according to various factors, including age, gender, educational attainment, BMI, smoking habits, and alcohol consumption, among others. For detailed information, please refer to Tables S6-S11. The sensitivity analysis revealed that the associations of TyG, TyG-WHtR, and METS-IR with all-cause and cardiovascular mortality remained robust after excluding participants with diabetes at baseline and those who died within two years of interview (Tables S12-S13).

Discussion

To the best of our knowledge, this is the first study to report the association between three novel metabolic parameters—TyG, TyG-WHtR, and METS-IR—and both all-cause and cardiovascular mortality in individuals with MetS. Our research, which enrolled a total of 8,271 participants with MetS from 2001 to 2018, revealed that higher levels of these parameters were associated with an increased likelihood of all-cause and cardiovascular mortality only in the group aged < 65 years, but not in the group aged ≥ 65 years.

Previous studies have indicated that elevated levels of TyG are linked to a higher risk of cardiac adverse events, including myocardial ischemia and cardiac arrest, suggesting that TyG can effectively predict heart disease [34, 35]. However, TyG has yielded inconsistent results in predicting mortality. Several studies have documented a U-shaped [36] or positive association [37] of TyG with all-cause or cardiovascular mortality. The interaction effect of age on TyG and mortality may account for this [25], and these studies did not analyze different age subgroups separately. A recent meta-analysis reported no significant association between TyG and mortality [38]. However, the large heterogeneity among the included studies (with I^2 values of 87% for all-cause mortality and 76% for cardiovascular mortality) may weaken the reliability of the results. Consistent with our results, a large prospective cohort study involving participants aged 25 to 70 years spanning 22 countries showed that elevated TyG was associated with an increased individual risk of CVD [15].

Research indicates that pancreatic adipose tissue content is inversely related to β-cell function and directly related to IR. Individuals with varying body weights exhibit different levels of pancreatic fat deposition, influencing their susceptibility to diabetes [39]. Given the close relationship between obesity and IR, the TyG in combination with obesity indicators such as BMI, WC, and WHtR has increasingly been utilized to predict CVD [40]. WHtR, as a valid indicator of visceral obesity and a sensitive indicator of early health risk, is superior to BMI and WC in predicting CVD risk [41]. Two cohort studies have shown that TyG and TyG-WHtR are associated with CVD, and TyG-WHtR is superior to TyG alone in the diagnosis of CVD [42, 43]. Our results also showed that compared with TyG, TyG-WHtR had a larger AUC for predicting all-cause and cardiovascular mortality in patients younger than 65 years of age.

In 2018, Bello-Chavolla and colleagues developed METS-IR as an alternative to HOMA-IR to assess IR. The results indicate that METS-IR has excellent diagnostic efficacy and can identify pathophysiological changes in individuals at high risk of IR while saving the cost of insulin measurement [28]. Researchers have also reported that METS-IR, being more representative of peripheral metabolic dysfunction, is a better predictor of nonalcoholic fatty liver disease than HOMA-IR [44]. A study involving 802 patients found that METS-IR can predict the occurrence and severity of coronary artery disease [45]. This is in contrast to another cross-sectional study that found no significant association between METS-IR and coronary artery disease [46]. However, the cross-sectional design may have influenced the final conclusions of

these two studies to some extent. After a median follow-up period of 8.3 years, we found that METS-IR serves as an effective predictor of mortality in the MetS population. We assessed how different parameters related to each other and found that METS-IR and TyG-WHtR had a weak relationship in the MetS population aged 65 and younger (correlation coefficient = 0.063, $P < 0.001$) (Table S14). This may be due to the fact that METS-IR also contains HDL data and therefore reflects different information from TyG-WHtR.

Surprisingly, TyG, TyG-WHtR, and METS-IR were not significantly associated with either all-cause or cardiovascular mortality in the MetS population older than 65 years. This result could be explained by the following factors: First, compared with younger patients, older patients had higher baseline HDL levels and lower TG, fasting insulin, total cholesterol, and LDL levels, indicating that older patients were more concerned about their health status and were more likely to receive intensive treatment for daily activities. Medical interventions during follow-up may optimize lipid and glucose levels, thereby affecting the predictive power of these metabolic parameters. Secondly, the measurement of TyG in the elderly is susceptible to various confounding factors, such as nutritional status, lipid levels and various comorbidities. Therefore, TyG and other parameters may not truly reflect the level of IR in the elderly [47]. Third, studies have shown that younger people are more susceptible to IR [48, 49]. It is conceivable that younger patients with longer disease duration may lead to increased IR and thus more severe complications.

Our results showed that TyG-related indicators have excellent performance in predicting the risk of mortality, but their exact mechanism of action remains unclear. This may be because TyG, TyG-WHtR and METS-IR can reflect the IR status of the body. IR triggers glycosylation products and free radical formation, which results in decreased bioavailability of nitric oxide [50]. In addition, IR activates the mitochondrial electron transport chain, leading to excessive oxidative stress [51]. The reduced utilization of nitric oxide and excessive oxidative stress can damage the vascular endothelium and promote the occurrence of various diseases [52]. Significantly, IR emerges as a pivotal indicator of obesity, hypertension, lipid abnormalities, and an array of metabolic disorders, all of which are intricately associated with CVD and fatal outcomes.

Strengths and limitations

This is the first study to focus on assessing the association of different novel metabolic markers with all-cause and cardiovascular mortality among the MetS participants and to explore whether this association changes with age. Population-based, large-scale prospective design will provide new and powerful evidence for clinical practice and public health.

Our study has the following limitations: First, we identified novel metabolic parameters based on laboratory tests at baseline and therefore cannot evaluate how changes in these indicators over time affect mortality among the MetS population. However, like baseline TyG data, cumulative TyG is also a valid predictor of IR [53, 54]. Second, about half of the participants had no FBG, TG, and HDL measurements at baseline, so we excluded these participants from further analysis. Compared with the population with TyG data, the population without TyG data exhibited a greater BMI level and higher prevalence of diabetes, which may affect the reliability of our results. Third, the selection of age boundaries was empirical, and whether the relation of these three parameters with mortality continues at different age boundaries may require further exploration. Fourth, we used a directed acyclic graph (Fig. S3) approach to determine potential confounders, but unknown or unmeasured confounders may affect the validity of the research results. However, we evaluated the sensitivity of our findings to unmeasured confounding factors by calculating the E-value [55], and the results showed that they were reliable (Table S15). Fifth, the AUC was low, and this finding must be interpreted with caution. Finally, we included residents of the United States, which may limit the broad global applicability of our findings. In the future, large samples and carefully designed prospective studies can be used.

Conclusion

The study revealed that the associations between TyG, TyG-WHtR, and METS-IR with all-cause and cardiovascular mortality differed according to age among participants with MetS. In the younger cohort, higher levels of TyG, TyG-WHtR, and METS-IR were linked to an increased risk of both all-cause and cardiovascular mortality, whereas such associations were not evident in the older cohort. Our results highlighted the predictive value of TyG, TyG-WHtR, and METS-IR in the MetS population, offering new insights for clinical practice and public health.

Abbreviations

AUC	Area under the curve
BMI	Body mass index
CVD	Cardiovascular diseases
DAG	Directed acyclic graph
FBG	Fasting blood glucose
HBA1c	Glycated hemoglobin A1c
HDL	High-density lipoprotein
HOMA-IR	Insulin resistance homeostasis model
IR	Insulin resistance
LDL	Low-density lipoprotein
MetS	Metabolic syndrome
METS-IR	Metabolic score for insulin resistance
NHANES	National health and nutrition examination survey
RCS	Restricted cubic spline

ROC	Receiver operating curve
TG	Triglycerides
TyG	Triglyceride glucose index
TyG-WHtR	Triglyceride glucose-waist to height ratio
WC	Waist circumference
WHtR	Waist-to-height ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02587-x .

Supplementary Material 1

Author contributions

Jiajun Liu was responsible for the conceptualization and design of the research. Yihui Fu carried out the data extraction and performed the necessary statistical analyses for the study. Pengpeng Liang assessed the feasibility of the study. Zhangxiao Song contributed to the drafting of the paper. Yue Li and Hongyan Wu provided a thorough review of the manuscript, offered essential scientific insights, and supervised the overall research process to ensure its integrity.

Funding

This study was supported by grants from the Sanming Project of Medicine in Shenzhen (SZZYSM202201007), the Shenzhen Medical Research Fund (C2401025 and A2303019), and the China Postdoctoral Science Foundation (2024M752087).

Data availability

The National Center for Health Statistics' Ethics Review Committee has given its approval to the NHANES study protocol, ensuring that all participants have provided their written informed consent before engaging in the study.

Declarations

Conflict of interests

The authors declare no competing interests.

Ethical approval and consent to participate

The National Center for Health Statistics' Ethics Review Committee has given its approval to the NHANES study protocol, ensuring that all participants have provided their written informed consent before engaging in the study.

Consent for publication

Not applicable.

Author details

[1]Shanghai University of Traditional Chinese Medicine, Shenzhen Hospital, Shenzhen, China
[2]Luohu District Hospital of Traditional Chinese Medicine, Shenzhen, China
[3]The First Clinical Medical School, Guangzhou University of Chinese Medicine, Guangzhou, China

Received: 31 October 2024 / Accepted: 7 January 2025
Published online: 28 February 2025

References

1. DeVallance E, Branyan KW, Lemaster KC, Anderson R, Marshall KL, Olfert IM, Smith DM, Kelley EE, Bryner RW, Frisbee JC, et al. Exercise training prevents the perivascular adipose tissue-induced aortic dysfunction with metabolic syndrome. Redox Biol. 2019;26:101285.
2. Hirode G, Wong RJ. Trends in the prevalence of metabolic syndrome in the United States, 2011–2016. JAMA. 2020;323(24):2526–8.
3. Xu L, Balzarolo M, Robinson EL, Lorenz V, Della Verde G, Joray L, Mochizuki M, Kaufmann BA, Valstar G, de Jager SCA, et al. NOX1 mediates metabolic heart disease in mice and is upregulated in monocytes of humans with diastolic dysfunction. Cardiovasc Res. 2022;118(14):2973–84.
4. Beltrán-Sánchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and trends of metabolic syndrome in the adult U.S. population, 1999–2010. J Am Coll Cardiol. 2013;62(8):697–703.
5. Liu Q, Zhang Y, Chen S, Xiang H, Ouyang J, Liu H, Zhang J, Chai Y, Zhan Z, Gao P, et al. Association of the triglyceride-glucose index with all-cause and cardiovascular mortality in patients with cardiometabolic syndrome: a national cohort study. Cardiovasc Diabetol. 2024;23(1):80.
6. Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018;20(2):12.
7. Gastaldelli A. Measuring and estimating insulin resistance in clinical and research settings. Obes (Silver Spring). 2022;30(8):1549–63.
8. Zhao X, An X, Yang C, Sun W, Ji H, Lian F. The crucial role and mechanism of insulin resistance in metabolic disease. Front Endocrinol (Lausanne). 2023;14:1149239.
9. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol. 1979;237(3):E214–23.
10. Baneu P, Văcărescu C, Drăgan S-R, Cirin L, Lazăr-Höcher A-I, Cozgarea A, Faur-Grigori A-A, Crișan S, Gaiță D, Luca C-T et al. The Triglyceride/HDL ratio as a surrogate biomarker for insulin resistance. Biomedicines 2024, 12(7):1493.
11. Chao Y-P, Kao T-W, Chang Y-W, Peng T-C, Chen W-L, Wu L-W. Utilization of anthropometric parameters as a novel tool for detection of insulin resistance. Clin Nutr. 2020;39(8):2571–9.
12. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care. 1998;21(12):2191–2.
13. Yetim A, Şahin M, Kandemir İ, Bulakçı B, Aksakal MT, Karapınar E, Sever H, Baş F. Evaluation of the ability of insulin resistance and lipid-related indices to predict the presence of NAFLD in obese adolescents. Lipids Health Dis. 2024;23(1):208.
14. Liu L, Luo Y, Liu M, Tang C, Liu H, Feng G, Wang M, Wu J, Zhang W. Triglyceride glucose-related indexes and lipid accumulation products-reliable markers of insulin resistance in the Chinese population. Front Nutr. 2024;11:1373039.
15. Lopez-Jaramillo P, Gomez-Arbelaez D, Martinez-Bello D, Abat MEM, Alhabib KF, Avezum Á, Barbarash O, Chifamba J, Diaz ML, Gulec S, et al. Association of the triglyceride glucose index as a measure of insulin resistance with mortality and cardiovascular disease in populations from five continents (PURE study): a prospective cohort study. Lancet Healthy Longev. 2023;4(1):e23–33.
16. Tao L-C, Xu J-N, Wang T-T, Hua F, Li J-J. Triglyceride-glucose index as a marker in cardiovascular diseases: landscape and limitations. Cardiovasc Diabetol. 2022;21(1):68.
17. Liu C, Liang D, Xiao K, Xie L. Association between the triglyceride-glucose index and all-cause and CVD mortality in the young population with diabetes. Cardiovasc Diabetol. 2024;23(1):171.
18. Wu X, Qiu W, Yang H, Chen Y-J, Liu J, Zhao G. Associations of the triglyceride-glucose index and atherogenic index of plasma with the severity of new-onset coronary artery disease in different glucose metabolic states. Cardiovasc Diabetol. 2024;23(1):76.
19. Li Y, Gui J, Liu H, Guo L-L, Li J, Lei Y, Li X, Sun L, Yang L, Yuan T, et al. Predicting metabolic syndrome by obesity- and lipid-related indices in mid-aged and elderly Chinese: a population-based cross-sectional study. Front Endocrinol (Lausanne). 2023;14:1201132.
20. Primo D, Izaola O, de Luis DA. Triglyceride-glucose index cutoff point is an accurate marker for Predicting the prevalence of metabolic syndrome in obese caucasian subjects. Ann Nutr Metab. 2023;79(2):238–45.
21. Son D-H, Lee HS, Lee Y-J, Lee J-H, Han J-H. Comparison of triglyceride-glucose index and HOMA-IR for predicting prevalence and incidence of metabolic syndrome. Nutr Metab Cardiovasc Dis. 2022;32(3):596–604.
22. Nabipoorashrafi SA, Seyedi SA, Rabizadeh S, Ebrahimi M, Ranjbar SA, Reyhan SK, Meysamie A, Nakhjavani M, Esteghamati A. The accuracy of triglyceride-glucose (TyG) index for the screening of metabolic syndrome in adults: a systematic review and meta-analysis. Nutr Metab Cardiovasc Dis. 2022;32(12):2677–88.
23. Zhou Z, Liu Q, Zheng M, Zuo Z, Zhang G, Shi R, Wu T. Comparative study on the predictive value of TG/HDL-C, TyG and TyG-BMI indices for 5-year mortality in critically ill patients with chronic heart failure: a retrospective study. Cardiovasc Diabetol. 2024;23(1):213.
24. Huang Y, Li Z, Yin X. Triglyceride-glucose index: a novel evaluation tool for all-cause mortality in critically ill hemorrhagic stroke patients-a retrospective analysis of the MIMIC-IV database. Cardiovasc Diabetol. 2024;23(1):100.

25. Chen J, Wu K, Lin Y, Huang M, Xie S. Association of triglyceride glucose index with all-cause and cardiovascular mortality in the general population. Cardiovasc Diabetol. 2023;22(1):320.
26. Yao Y, Wang B, Geng T, Chen J, Chen W, Li L. The association between TyG and all-cause/non-cardiovascular mortality in general patients with type 2 diabetes mellitus is modified by age: results from the cohort study of NHANES 1999–2018. Cardiovasc Diabetol. 2024;23(1):43.
27. Dang K, Wang X, Hu J, Zhang Y, Cheng L, Qi X, Liu L, Ming Z, Tao X, Li Y. The association between triglyceride-glucose index and its combination with obesity indicators and cardiovascular disease: NHANES 2003–2018. Cardiovasc Diabetol. 2024;23(1):8.
28. Bello-Chavolla OY, Almeda-Valdes P, Gomez-Velasco D, Viveros-Ruiz T, Cruz-Bautista I, Romo-Romo A, Sánchez-Lázaro D, Meza-Oviedo D, Vargas-Vázquez A, Campos OA, et al. METS-IR, a novel score to evaluate insulin sensitivity, is predictive of visceral adiposity and incident type 2 diabetes. Eur J Endocrinol. 2018;178(5):533–44.
29. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP). Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486–97.
30. Wang C, Su J, Li J, Wei W, Yuan Z, Chen R, Wei W, Huang Y, Ye L, Liang H et al. Blood lead mediates the relationship between Biological Aging and Hypertension: based on the NHANES database. Nutrients 2024, 16(13):2144.
31. Song J, Li Y, Zhu J, Liang J, Xue S, Zhu Z. Non-linear associations of cardiometabolic index with insulin resistance, impaired fasting glucose, and type 2 diabetes among US adults: a cross-sectional study. Front Endocrinol (Lausanne). 2024;15:1341828.
32. Zhou Y, Wang C, Che H, Cheng L, Zhu D, Rao C, Zhong Q, Li Z, Wang X, Wu Z, et al. Association between the triglyceride-glucose index and the risk of mortality among patients with chronic heart failure: results from a retrospective cohort study in China. Cardiovasc Diabetol. 2023;22(1):171.
33. Frank E, Harrell J. Regression modeling strategies with applications to Linear models, logistic and ordinal regression, and Survival Analysis. Springer; 2015.
34. Wang W, Yang J, Wang K, Niu J, Liu Y, Ge H. Association between the triglyceride-glucose index and in-hospital major adverse cardiovascular events in patients with acute coronary syndrome: results from the improving care for Cardiovascular Disease in China (CCC)-Acute Coronary Syndrome project. Cardiovasc Diabetol. 2024;23(1):170.
35. Zhang W, Liu L, Yin G, Mohammed A-Q, Xiang L, Lv X, Shi T, Galip J, Wang C, Mohammed AA, et al. Triglyceride-glucose index is associated with myocardial ischemia and poor prognosis in patients with ischemia and no obstructive coronary artery disease. Cardiovasc Diabetol. 2024;23(1):187.
36. Yu Y, Wang J, Ding L, Huang H, Cheng S, Deng Y, Gu M, Cai C, Ning X, Chen X, et al. Sex differences in the nonlinear association of triglyceride glucose index with all-cause and cardiovascular mortality in the general population. Diabetol Metab Syndr. 2023;15(1):136.
37. Kim J, Shin S-J, Kang H-T. The association between triglyceride-glucose index, cardio-cerebrovascular diseases, and death in Korean adults: a retrospective study based on the NHIS-HEALS cohort. PLoS ONE. 2021;16(11):e0259212.
38. Liu X, Tan Z, Huang Y, Zhao H, Liu M, Yu P, Ma J, Zhao Y, Zhu W, Wang J. Relationship between the triglyceride-glucose index and risk of cardiovascular diseases and mortality in the general population: a systematic review and meta-analysis. Cardiovasc Diabetol. 2022;21(1):124.
39. Roh E, Kim KM, Park KS, Kim YJ, Chun EJ, Choi SH, Park KS, Jang HC, Lim S. Comparison of pancreatic volume and fat amount linked with glucose homeostasis between healthy caucasians and koreans. Diabetes Obes Metab. 2018;20(11):2642–52.
40. Mirjalili SR, Soltani S, Meybodi ZH, Marques-Vidal P, Firouzabadi DD, Eshraghi R, Restrepo D, Ghoshouni H, Sarebanhassanabadi M. Which surrogate insulin resistance indices best predict coronary artery disease? A machine learning approach. Cardiovasc Diabetol. 2024;23(1):214.
41. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. Obes Rev. 2012;13(3):275–86.
42. Xia X, Chen S, Tian X, Xu Q, Zhang Y, Zhang X, Li J, Wu S, Wang A. Association of triglyceride-glucose index and its related parameters with atherosclerotic cardiovascular disease: evidence from a 15-year follow-up of Kailuan cohort. Cardiovasc Diabetol. 2024;23(1):208.
43. Ren Q, Huang Y, Liu Q, Chu T, Li G, Wu Z. Association between triglyceride glucose-waist height ratio index and cardiovascular disease in middle-aged and older Chinese individuals: a nationwide cohort study. Cardiovasc Diabetol. 2024;23(1):247.
44. Lee J-H, Park K, Lee HS, Park H-K, Han JH, Ahn SB. The usefulness of metabolic score for insulin resistance for the prediction of incident non-alcoholic fatty liver disease in Korean adults. Clin Mol Hepatol. 2022;28(4):814–26.
45. Wu Z, Cui H, Li W, Zhang Y, Liu L, Liu Z, Zhang W, Zheng T, Yang J. Comparison of three non-insulin-based insulin resistance indexes in predicting the presence and severity of coronary artery disease. Front Cardiovasc Med. 2022;9:918359.
46. Mahdavi-Roshan M, Mozafarihashjin M, Shoaibinobarian N, Ghorbani Z, Salari A, Savarrakhsh A, Hekmatdoost A. Evaluating the use of novel atherogenicity indices and insulin resistance surrogate markers in predicting the risk of coronary artery disease: a case–control investigation with comparison to traditional biomarkers. Lipids Health Dis. 2022;21(1):126.
47. Schuetz P, Seres D, Lobo DN, Gomes F, Kaegi-Braun N, Stanga Z. Management of disease-related malnutrition for patients being treated in hospital. Lancet. 2021;398(10314):1927–38.
48. Sharif S, Groenwold RHH, van der Graaf Y, Berkelmans GFN, Cramer MJ, Visseren FLJ, Westerink J. Mediation analysis of the relationship between type 2 diabetes and cardiovascular events and all-cause mortality: findings from the SMART cohort. Diabetes Obes Metab. 2019;21(8):1935–43.
49. Liu R, Li L, Wang L, Zhang S. Triglyceride-glucose index predicts death in patients with stroke younger than 65. Front Neurol. 2023;14:1198487.
50. Bateman RM, Sharpe MD, Jagger JE, Ellis CG, Solé-Violán J, López-Rodríguez M, Herrera-Ramos E, Ruíz-Hernández J, Borderías L, Horcajada J et al. March: 36th International Symposium on Intensive Care and Emergency Medicine: Brussels, Belgium. 15–18 2016. *Crit Care* 2016, 20(Suppl 2):94.
51. Yang Q, Vijayakumar A, Kahn BB. Metabolites as regulators of insulin sensitivity and metabolism. Nat Rev Mol Cell Biol. 2018;19(10):654–72.
52. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Invest. 2016;126(1):12–22.
53. Tai S, Fu L, Zhang N, Yang R, Zhou Y, Xing Z, Wang Y, Zhou S. Association of the cumulative triglyceride-glucose index with major adverse cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol. 2022;21(1):161.
54. Zheng H, Chen G, Wu K, Wu W, Huang Z, Wang X, Chen Z, Cai Z, Cai Z, Lan Y, et al. Relationship between cumulative exposure to triglyceride-glucose index and heart failure: a prospective cohort study. Cardiovasc Diabetol. 2023;22(1):239.
55. VanderWeele TJ, Ding P. Sensitivity analysis in Observational Research: introducing the E-Value. Ann Intern Med. 2017;167(4):268–74.

Publisher's note