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Associations of triglyceride-glucose-obesity composite indices with all-cause and cardiovascular mortality in individuals with cardiovascular-kidney-metabolic syndrome stages 0–3 and their potential incremental value beyond a PREVENT-variable-based model

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Abstract

Background The PREVENT equations represent a paradigm shift in cardiovascular risk assessment by incorporating cardiovascular-kidney-metabolic (CKM) health metrics. However, in individuals with CKM stages 0–3, the associations of TyG and TyG-obesity composite indices with all-cause mortality (ACM) and cardiovascular mortality (CVM), and whether they provide incremental predictive value beyond a PREVENT-variable-based model, remain unclear.

Methods We analyzed data from 12,947 adults with CKM stages 0–3 in the National Health and Nutrition Examination Survey (NHANES), with a median follow-up of 10.25 years. Seven indices were calculated: TyG alone and six TyG-obesity composite indices. Weighted Cox proportional hazards models assessed associations with ACM and CVM. Kaplan-Meier curves were used for ACM, and Aalen-Johansen cumulative incidence functions with cause-specific Cox and Fine-Gray models were used for CVM. Restricted cubic splines (RCS) examined nonlinearity, and Cox-based quantile g-computation (qgcomp) assessed the joint effect of all seven indices. Incremental predictive value beyond the PREVENT-variable-based model was evaluated using changes in C-statistic (ΔC), time-dependent AUC at 10 years, survival-based continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI), bootstrap resampling, calibration, and decision curve analysis. Subgroup, stage-specific and sensitivity analyses were also performed.

Results During follow-up, 1,284 ACM and 342 CVM occurred. Kaplan-Meier and Aalen-Johansen curves showed that cumulative incidence increased across TyG quartiles for both ACM and CVM. After full adjustment, all seven indices were independently associated with ACM; TyG-BMI showed the strongest association (HR = 1.99, 95% CI: 1.21–3.28), followed by TyG-BRI (HR = 1.89, 95% CI: 1.38–2.59). For CVM, none of the indices remained significant in Model 3, and competing-risk analyses using cause-specific Cox and Fine-Gray models also showed no significant associations. In quartile analyses, TyG-WWI was associated with increased CVM risk in Q3 (HR = 4.53, 95% CI: 1.41–14.58), but not in Q4. Stage-specific analyses showed that associations with

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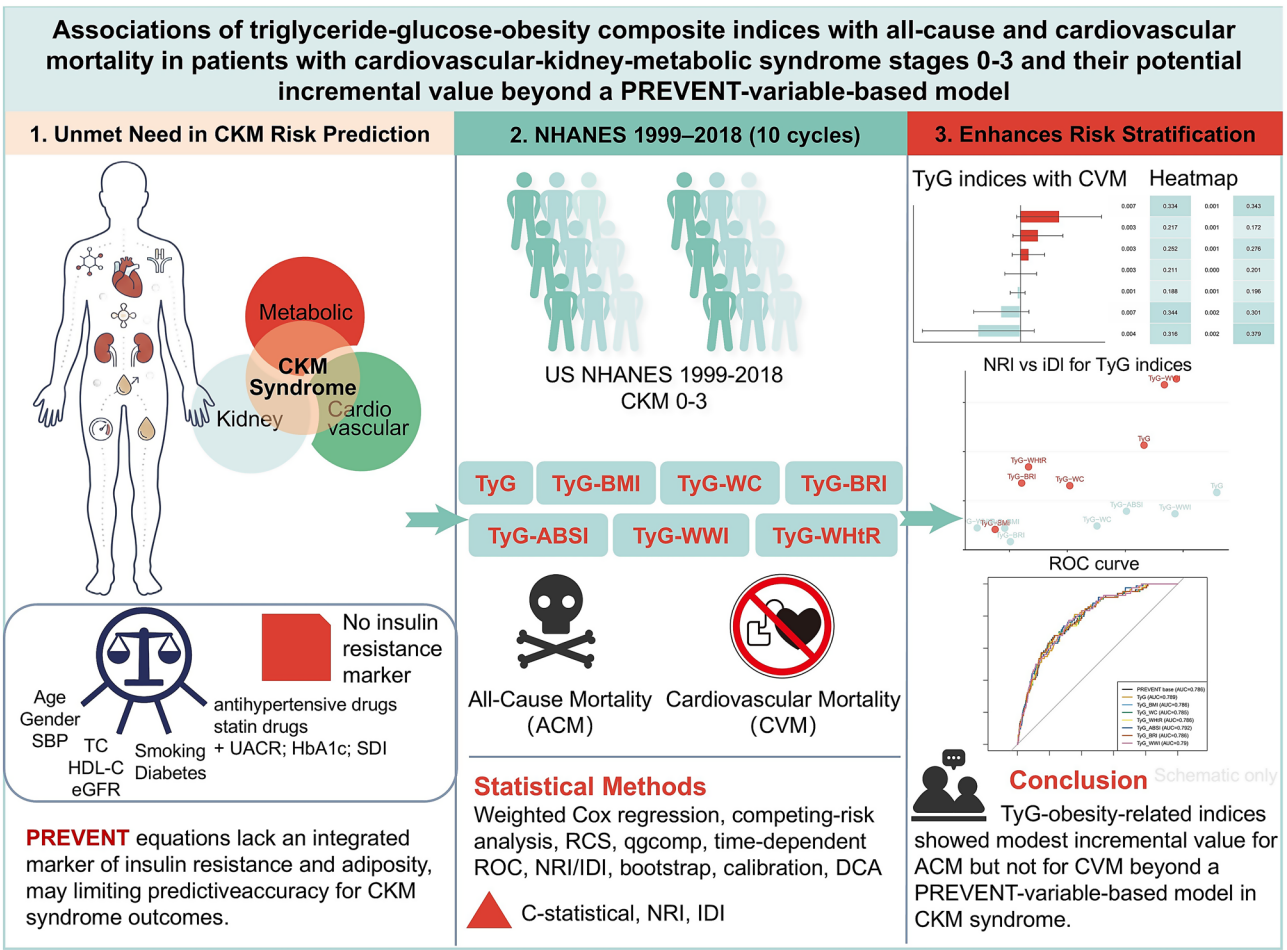
ACM were mainly significant in CKM stage 2; for CVM, significant interactions with CKM stage were observed for TyG-BMI, TyG-WC, and TyG-WHtR ($P<0.05$). RCS analysis suggested nonlinear associations of TyG-BMI and TyG-BRI with ACM. Qgcomp indicated a modest joint effect on CVM. Time-dependent AUC increases were all <0.01. Bootstrap analyses showed small but significant improvements for TyG-ABSI and TyG-WWI in ACM (ΔC=0.0024, 95% CI: 0.0006–0.0055, and 0.0017, 95% CI: 0.0002–0.0046, respectively), but not in CVM. Survival-based NRI/IDI showed modest improvement only for TyG-ABSI (NRI=0.092; IDI=0.003) and TyG-WWI (NRI=0.094; IDI=0.003) in ACM. Sex was a significant effect modifier for several indices ($P<0.001$). Results from multiple imputation sensitivity analyses were consistent with the complete-case analysis. Findings were broadly consistent after excluding deaths within the first 2 years.

Conclusions In individuals with CKM stages 0–3, TyG and TyG-obesity composite indices were independently associated with ACM, with TyG-BMI and TyG-BRI showing the strongest associations. However, no significant associations were observed with CVM. Incremental predictive value beyond a PREVENT-variable-based model was limited, with modest improvement in risk reclassification for ACM only. Their clinical utility warrants further validation.

Graphical Abstract



Research insights

What is currently known about this topic?

TyG and TyG-obesity composite indices have been associated with the development and prognosis of cardiovascular disease. However, their associations with ACM and CVM, and whether they improve mortality

risk prediction beyond a PREVENT-variable-based model, remain insufficiently supported by epidemiological evidence.

What is the key research question?

Beyond the traditional cardiometabolic risk factors already incorporated in a PREVENT-variable-based model, can TyG and TyG-obesity composite indices independently predict ACM and CVM and provide measurable improvements in risk prediction?

What is new?

This study systematically compared seven TyG and TyG-obesity composite indices in a population with CKM stages 0-3. All seven indices were independently associated with ACM, with TyG-BMI and TyG-BRI showing the strongest associations; however, none were significantly associated with CVM after full adjustment. Incremental predictive value beyond a PREVENT-variable-based model was limited (all ΔC and AUC <0.01); only TyG-ABSI and TyG-WWI showed modest improvement in risk reclassification for ACM. Associations with ACM were mainly observed in CKM stage 2, and significant interactions with CKM stage were found for several indices in CVM.

How might this study influence clinical practice?

As low-cost indicators that rely only on routine laboratory tests and simple anthropometric measurements, TyG and TyG-obesity composite indices may help identify individuals at underestimated risk for mortality when used alongside a PREVENT-variable-based model. However, their net clinical benefit still requires further validation in prospective studies.

Introduction

In 2023, the American Heart Association proposed the cardiovascular-kidney-metabolic (CKM) syndrome framework, which ranges from stage 0 (no risk factors) to stage 4-clinical cardiovascular disease (CVD) and reflects progressive pathophysiology and increasing absolute cardiovascular risk [1]. The central insight of this framework is that cardiovascular risk does not simply emerge when traditional risk factors cross a threshold, but rather develops gradually through worsening adipose tissue dysfunction, insulin resistance, and inflammation [2–4]. Risk assessment therefore needs to evolve alongside this integrated and clustered perspective. Stages 0 to 3 cover the entire spectrum from exposure to risk factors alone to subclinical cardiovascular injury. This population is the largest part of clinical practice and also represents a critical window for preventive intervention [5–6]. Once stage 4 is reached, a definite cardiovascular event has already occurred and the benefit of intervention drops substantially. As a result, shifting the focus of risk assessment toward the stage 0 to 3 population and identifying individuals who have not yet developed disease but are already on a high risk trajectory has become a core epidemiological strategy for reducing the overall burden of CKM syndrome.

The PREVENT (Predicting Risk of cardiovascular disease EVENTs) equations represent an important advance in CKM risk assessment. The equations were developed and validated in more than 6.6 million American adults and are sex-specific and race-free, with the ability to estimate 10 year and 30 year risk of total CVD [7]. In clinical practice, clinicians only need to enter routine variables such as age, sex, systolic blood pressure (SBP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), diabetes, smoking status, and use of antihypertensive or lipid-lowering medications to obtain an individualized composite risk score. When available, the optional model can also incorporate urine albumin-to-creatinine ratio, glycated hemoglobin, and social deprivation index [8]. It should be noted that the PREVENT equations were originally designed to predict incident CVD rather than mortality. The present study uses the same variable framework for predicting all-cause mortality (ACM) and cardiovascular mortality (CVM) based on several considerations. First, ACM and CVM are the most definitive clinical hard endpoints in the development of CKM syndrome and are not affected by differences in diagnostic coding practices or access to care, making them suitable for cohort comparisons [9–10]. Second, the variables included in the PREVENT equations are themselves strong predictors of mortality, and previous studies have shown that

the equations also discriminate CVM reasonably well [11]. Finally, the goal of this study is not to develop a new mortality prediction model, but to test whether TyG-related indices can provide additional prognostic information beyond this standardized set of variables. Using the PREVENT variable framework as the base model allows us to examine whether this group of covariates has already fully captured the risk associated with insulin resistance. If TyG and TyG-obesity composite indices can still significantly improve mortality prediction after full adjustment for PREVENT variables, this would indicate that they carry independent prognostic signals beyond those conventional risk factors.

Insulin resistance is a core pathophysiological component in the development and progression of CKM syndrome. Under insulin-resistant conditions, peripheral tissues show reduced sensitivity and responsiveness to insulin, leading to impaired glucose transport and compensatory hyperinsulinemia. Long-standing hyperinsulinemia not only promotes renal cell proliferation and vascular smooth muscle hyperplasia but also aggravates vascular injury by reducing endothelial nitric oxide synthesis, thereby accelerating atherosclerosis and renal function decline [12–13]. In addition, insulin resistance is closely intertwined with visceral fat accumulation, disordered lipid metabolism, and chronic low-grade inflammation, which together form the metabolic basis of CKM syndrome [14–15]. Therefore, even before the diagnostic threshold for diabetes is reached, early identification of insulin resistance and related metabolic abnormalities is important for improving risk stratification in the CKM stage 0–3 population.

The TyG index is a surrogate marker of insulin resistance, calculated from fasting triglycerides and fasting glucose. Compared with the hyperinsulinemic-euglycemic clamp technique and HOMA-IR, the TyG index has the advantages of simplicity, low cost, and reliance only on routine laboratory tests. In recent years, researchers have developed composite indices that combine TyG with obesity measures: TyG-BMI integrates overall obesity; TyG-WC reflects central obesity; TyG-WHtR reflects height-adjusted fat distribution; TyG-ABSI reflects body shape; TyG-BRI reflects body roundness; and TyG-WWI reflects weight-adjusted central obesity, thereby capturing insulin resistance together with different dimensions of fat accumulation [16]. In theory, these composite indices better reflect the interaction between abnormal fat distribution and insulin resistance than TyG alone, and previous studies have also suggested stronger associations with cardiovascular events and mortality [17–19]. However, existing studies have mainly assessed the association of TyG and some obesity-composite indices with mortality in CKM stage 0–3 populations, and have limitations such as a narrow range of included indices, relatively short study periods, restricted populations, and lack of formal assessment of clinical utility [18–20]. As a result, the association of these low-cost and readily available indices with mortality outcomes in CKM stage 0–3 remains uncertain, and whether they can provide measurable improvements in mortality risk prediction beyond the PREVENT equations, which already incorporate multiple traditional risk factors, still lacks direct evidence. Based on this background, the present study aims to comprehensively evaluate the associations of TyG alone and six TyG-obesity composite indices with ACM and CVM in the CKM syndrome population, and to quantify the incremental predictive value of each index beyond the PREVENT equations using statistical metrics.

Methods

Study design and population

This study used a pooled cohort design based on data from the National Health and Nutrition Examination Survey (NHANES) across 10 consecutive cycles from 1999 to 2018 (https://www.cdc.gov/nchs/nhanes/index.htm). NHANES is a nationally representative, complex, multistage probability survey conducted by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC), with data collected every two years to assess the health and nutritional status of the noninstitutionalized civilian population in the United States. Written informed consent was obtained from all participants. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Table S1).

Participants aged 31–78 years with complete information on CKM syndrome stage were included. Exclusion criteria were: (1) age ≤ 30 or ≥ 79 years; (2) pregnancy or indeterminate pregnancy status, baseline diagnosed CVD, or malignancy; (3) missing data needed for CKM staging; (4) missing data required for calculation of TyG and TyG-obesity indices; and (5) lack of valid mortality follow-up data. After stepwise exclusion, 12,947 participants with CKM stages 0–3 were included. The participant selection process is shown in Fig. 1.

Study variables and definitions

CKM syndrome reflects the multifaceted interactions among metabolic disorders, chronic kidney disease (CKD), and CVD. Based on the 2023 American Heart Association Presidential Advisory on CKM syndrome, participants were classified into stages 0–3, with stage 4 (clinical CVD at baseline) excluded. Stage 0 was defined by the absence of metabolic abnormalities. Stage 1 was characterized by obesity (BMI ≥ 25 kg/m^2, or waist circumference ≥ 102 cm in men or ≥ 88 cm in women) or prediabetes (HbA1c 5.7%-6.4% or fasting plasma glucose 100–124 mg/dL). Stage 2 included individuals with at least one of the following: hypertension [SBP ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 80 mmHg, self-reported diagnosis, or use of antihypertensive medication], diabetes [fasting plasma glucose (FBG) ≥ 126 mg/dL, HbA1c ≥ 6.5%, self-reported diagnosis, or use of insulin/oral hypoglycemic agents], hypertriglyceridemia [triglycerides (TG) ≥ 135 mg/dL], metabolic syndrome (at least three of five components: central obesity, TG ≥ 150 mg/dL, HDL-C < 40 mg/dL in men and < 50 mg/dL in women, blood pressure ≥ 130/80 mmHg, FBG ≥ 100 mg/dL), or moderate-to-high-risk CKD (eGFR 30–59 mL/min/1.73 m²). Stage 3 was defined as very-high-risk CKD (eGFR < 30 mL/min/1.73 m^2). Subclinical CVD could not be directly ascertained because UACR and imaging markers were unavailable. Because the NHANES race/ethnicity classification cannot reliably identify Asian populations, all anthropometric and metabolic cutoffs were defined using non-Asian criteria, including those used for obesity, abdominal obesity, metabolic syndrome, and TyG-related indices. Details of the CKM staging criteria are provided in Table S2.

For exposure variables, anthropometric and laboratory measurements were performed by trained health professionals under standardized conditions. Venous blood samples were collected after at least 8 h of fasting for measurement of FBG, TG, TC, HDL-C, and serum creatinine (Scr). Height, weight, and waist circumference were measured using standardized protocols. BMI was calculated as weight in kilograms divided by height in meters squared. Seven TyG-related indices were calculated: TyG, TyG-BMI, TyG-WC, TyG-WHtR, TyG-ABSI, TyG-BRI, and TyG-WWI, to capture the combined effects of insulin resistance and different dimensions of obesity. Formulas for these indices are provided in Table S3.

ACM was defined as death from any cause during follow-up. In NHANES, mortality status was ascertained through probabilistic linkage to the National Death Index (NDI), with follow-up through December 31, 2019. CVM was defined as death with an underlying cause coded as UCOD_LEADING = 1 (diseases of the heart, corresponding to ICD-10 I00–I09, I11, I13, I20–I51) or UCOD_LEADING = 5 (cerebrovascular diseases, corresponding to I60–I69). Cause-of-death classification was performed according to standardized procedures by the data providers.

Covariates were selected based on prior literature and causal considerations. They included: (1) sociodemographic variables: age, sex, race/ethnicity, marital status, education level, and family income-to-poverty ratio (PIR); (2) lifestyle variables: smoking status, alcohol consumption, and physical activity; and (3) clinical variables: SBP, DBP, TC, HDL-C, low-density lipoprotein cholesterol (LDL-C), HbA1c, Scr, estimated glomerular filtration rate (eGFR, calculated using the 2021 CKD-EPI creatinine equation without race), BMI, antihypertensive medication use, lipid-lowering medication use, TG, and FBG.

In NHANES, race/ethnicity was categorized into five groups: Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race/ethnicity. Education level was classified as less than high school, high school or equivalent, some college, and college graduate or above. Marital status was categorized as married, widowed, divorced, separated, never married, or living with a partner. PIR was divided into three groups (< 1.3, 1.3–3.5, ≥ 3.5). Hypertension was defined as systolic blood pressure ≥ 130 mmHg and/or DBP ≥ 80 mmHg based

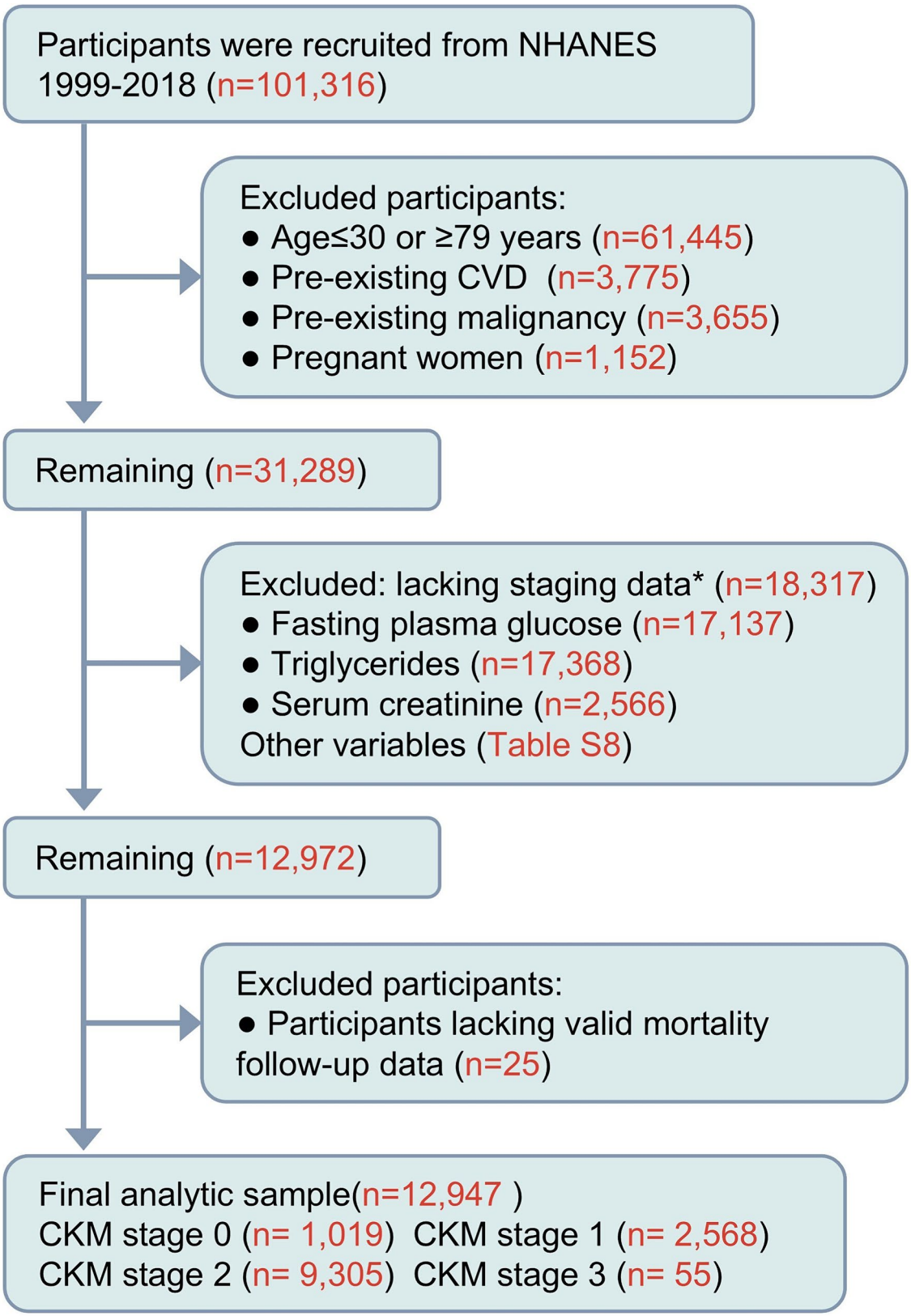

Participants were recruited from NHANES 1999-2018 (n=101,316)
Excluded participants:
● Age≤30 or ≥79 years (n=61,445)
● Pre-existing CVD (n=3,775)
● Pre-existing malignancy (n=3,655)
● Pregnant women (n=1,152)
Remaining (n=31,289)
Excluded: lacking staging data* (n=18,317)
● Fasting plasma glucose (n=17,137)
● Triglycerides (n=17,368)
● Serum creatinine (n=2,566)
Other variables (Table S8)
Remaining (n=12,972)
Excluded participants:
● Participants lacking valid mortality follow-up data (n=25)
Final analytic sample(n=12,947)
CKM stage 0 (n= 1,019) CKM stage 1 (n= 2,568)
CKM stage 2 (n= 9,305) CKM stage 3 (n= 55)

Fig. 1 Flowchart of participant selection. A total of 101,316 participants were recruited from NHANES 1999-2018. Participants were excluded for age≤30 or≥79 years (n = 61,445), pregnancy or indeterminate pregnancy status (n = 1,152), pre-existing malignancy (n = 3,655), and pre-existing cardiovascular disease (n = 3,775). After these exclusions, 31,289 participants remained. A further 18,317 participants were excluded because of missing data on CKM staging variables; the most frequently missing variables were fasting plasma glucose (n = 17,137) and triglycerides (n = 17,368), and detailed variable-specific missingness is provided in Table S8. An additional 25 participants were excluded because of lack of valid mortality follow-up data. The final analytic sample comprised 12,947 participants with CKM stages 0-3: stage 0 (n = 1,019), stage 1 (n = 2,568), stage 2 (n = 9,305), and stage 3 (n = 55). Covariate missingness was handled in the analysis stage using complete-case analysis and multiple imputation.* Participants with multiple missing data will be counted multiple times, so the total sum of the missing values exceeds the total number of those excluded

on the average of three consecutive measurements, or a previous diagnosis of hypertension. Hyperlipidemia was defined as self-reported diagnosis of high cholesterol, current use of lipid-lowering medication, TC ≥ 240 mg/dL, TG ≥ 200 mg/dL, LDL-C ≥ 160 mg/dL, or HDL-C < 40 mg/dL in men and < 50 mg/dL in women. Smoking status was grouped into never (< 100 cigarettes in lifetime), former (≥ 100 cigarettes in lifetime but currently quit), and current (≥ 100 cigarettes in lifetime and currently smoking). Alcohol consumption was classified as none (never drinker), moderate (≤ 1 drink/day for women and ≤ 2 drinks/day for men), and heavy (> 1 drink/day for women and > 2 drinks/day for men). Because physical activity questionnaires differed across NHANES cycles, leisure-time physical activity (LTPA) was used as the harmonized indicator. For 1999–2006, LTPA was classified as None, Some, or Active based on self-reported vigorous and moderate leisure-time activities. For 2007–2018, LTPA was calculated from the Global Physical Activity Questionnaire as MET-min/week and classified using equivalent thresholds.

Statistical analysis

Baseline characteristics were described by quartiles of the TyG index (Q1-Q4). Continuous variables were presented as weighted mean ± standard error (SE), and categorical variables as unweighted frequency (weighted percentage). Group comparisons were performed using weighted Kruskal-Wallis rank sum tests for continuous variables and weighted Rao-Scott χ^2 tests for categorical variables. All weighted analyses used the fasting subsample weight (WTSAF2YR), combined across the 10 cycles by dividing by 10, and incorporated clustering (SDMVPSU) and stratification (SDMVSTRA) via the survey package. For ACM, Kaplan-Meier curves were constructed by quartiles of each TyG-related index, and differences were tested using the log-rank test. For CVM, cumulative incidence functions were estimated using the Aalen-Johansen method, and competing-risk analyses were performed using cause-specific Cox models and Fine-Gray subdistribution hazard models, with non-cardiovascular death treated as a competing event. Weighted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for ACM and CVM associated with each TyG index, modeled as continuous variables (per 1-SD increase) and as quartiles (Q1-Q4 with Q1 as reference). All Cox models used the full available follow-up time, and censored participants were treated as censored observations rather than survivors. Three sequential models were fitted: Model 1 adjusted for age, sex, and race/ethnicity; Model 2 additionally adjusted for marital status, education, PIR, smoking status, and alcohol consumption; Model 3 further adjusted for BMI, eGFR, HbA1c, TC, HDL-C, antihypertensive medication use, and lipid-lowering medication use. To avoid collinearity, BMI was not adjusted in Model 3 when analyzing obesity-related TyG indices other than TyG alone; in quartile and subgroup analyses, BMI was also removed when BMI was the stratification variable.

Restricted cubic splines (RCS) were used to assess nonlinear associations. qgcomp based on Cox proportional hazards models was used to evaluate the joint effect of the TyG and TyG-obesity composite indices, with each exposure discretized into quartiles (q = 4) to estimate the hazard ratio for a simultaneous one-quartile increase on mortality risk during follow-up, adjusting for Model 3 covariates without BMI; the primary aim was to assess the overall mixture effect rather than to identify independent contributions of individual indices, because the seven

indices are mathematically interrelated and share underlying variables. In addition, standardized logistic regression was performed to assess the independent contribution of each index. Complete-case analysis was used for the main models, and multiple imputation by chained equations (MICE) was performed as a sensitivity analysis. RCS, NRI/IDI, qgcomp, standardized logistic regression, and competing-risk analyses did not fully incorporate the complex sampling design and were considered exploratory.

Incremental predictive value was assessed as the core analysis. It should be noted that the published PREVENT equations were not directly applied to calculate predicted mortality risk in this study. Because the PREVENT equations were developed to predict incident cardiovascular disease rather than mortality, we constructed a Cox proportional hazards model using variables that overlap with the PREVENT predictors as the base model, referred to as the PREVENT-variable-based model. Each TyG-obesity related index was added individually to a PREVENT-variable-based model, and changes in C-statistic were used to evaluate improvement in discrimination, with C-statistic > 0.01 considered clinically meaningful. Time-dependent ROC curves at 10 years were used to evaluate discrimination, with censoring accounted for by inverse probability of censoring weighting. Survival-based continuous NRI and IDI were used to assess risk reclassification and overall discrimination improvement, with censoring similarly accounted for. Bootstrap resampling (1000 replicates) was used to estimate 95% confidence intervals for the change in C-statistic. Calibration curves and decision curve analysis were performed to assess model calibration and net clinical benefit. Subgroup analyses were stratified by age, sex, eGFR, and BMI. Stage-specific analyses were also performed by CKM stage (0–1, 2). Sensitivity analyses excluded deaths occurring within the first 2 years of follow-up to test robustness. All analyses were performed using R 4.3.1, and $P < 0.05$ was considered statistically significant. For exploratory visualization, a standardized combined score was calculated for each index by summing the z-scores of its NRI and IDI values (averaged across ACM and CVM). It should be interpreted descriptively.

Results

Baseline characteristics

A total of 12,947 participants with CKM stage 0–3 were included and divided into four groups by TyG index quartiles: Q1 ($n = 3,239$), Q2 ($n = 3,237$), Q3 ($n = 3,235$), and Q4 ($n = 3,236$). The weighted mean age was 49.16 years (SE 0.16), and 49.8% were men. From Q1 to Q4, age, male proportion, BMI, waist circumference, FBG, HbA1c, and TG increased gradually ($P < 0.001$), whereas HDL-C and eGFR declined ($P < 0.001$ or $P = 0.003$). The proportion of current smokers increased from 19.0% to 30.9% ($P < 0.001$), and the proportion of participants with no physical activity increased from 43.2% to 56.3% ($P < 0.001$). Alcohol consumption did not differ significantly across groups ($P = 0.422$). During a median follow-up of 10.25 years, 1,284 ACM (7.5%) and 342 CVM (1.9%) occurred. Baseline characteristics are presented in Table 1. Both outcomes increased across TyG quartiles.

Included participants were older and had a higher cardiometabolic risk burden than excluded participants, who more often had missing laboratory data (Table S4). In the final analytic population, missingness was confined to questionnaire-based covariates (marital status 0.98%, education 0.06%, PIR 8.57%, smoking 25.03%, alcohol use 40.47%); all TyG-related indices, key laboratory variables and mortality outcomes were complete (Table S5). Complete-case analysis was used for the main models. In MICE sensitivity analyses (20 imputed datasets), TyG-WC, TyG-WHtR, TyG-ABSI, TyG-BRI and TyG-WWI remained significantly associated with ACM, whereas TyG and TyG-BMI did not; no TyG-related index was significantly associated with CVM (Table S6).

Table 1 Baseline characteristics of participants according to TyG index quartiles

Variable	Overall (*n* = 12947)	Q1 (*n* = 3239)	Q2 (*n* = 3237)	Q3 (*n* = 3235)	Q4 (*n* = 3236)	*p*
Sex, n (%)						< 0.001
Male	6,431 (49.8)	1,259 (38.5)	1,550 (48.2)	1,719 (53.6)	1,903 (60.0)	
Female	6,516 (50.2)	1,980 (61.5)	1,687 (51.8)	1,516 (46.4)	1,333 (40.0)	
Age, years, mean (SE)	49.16 (0.16)	46.77 (0.32)	48.93 (0.26)	50.38 (0.26)	50.76 (0.27)	< 0.001
Race/Ethnicity, n (%)						< 0.001
Mexican American	2,466 (7.9)	377 (5.5)	537 (7.3)	700 (8.7)	852 (10.6)	
Other Hispanic	1,213 (5.7)	237 (4.7)	301 (5.6)	332 (6.0)	343 (6.6)	
Non-Hispanic White	5,374 (69.4)	1,268 (67.7)	1,346 (69.3)	1,404 (71.1)	1,356 (69.5)	
Non-Hispanic Black	2,637 (10.2)	1,032 (16.2)	742 (11.3)	485 (7.1)	378 (5.8)	
Other Race	1,257 (6.8)	325 (6.0)	311 (6.6)	314 (7.1)	307 (7.6)	
Marital status, n (%)						0.003
Married	7,752 (65.0)	1,879 (65.3)	1,897 (63.8)	2,001 (65.9)	1,975 (64.7)	
Widowed	718 (3.7)	124 (2.2)	186 (3.9)	200 (4.4)	208 (4.6)	
Divorced	1,560 (12.1)	392 (12.0)	411 (12.7)	351 (10.9)	406 (12.8)	
Separated	510 (2.8)	133 (2.5)	129 (3.2)	140 (3.2)	108 (2.3)	
Never married	1,411 (10.0)	437 (10.8)	359 (9.7)	307 (9.7)	308 (9.9)	
Living with partner	869 (6.4)	246 (7.2)	230 (6.7)	200 (6.0)	193 (5.6)	
Education level, n (%)						< 0.001
< 9th grade	1,651 (6.1)	238 (3.9)	365 (5.6)	458 (6.6)	590 (8.6)	
9–11th grade	1,872 (10.7)	426 (8.4)	430 (10.5)	518 (12.3)	498 (11.8)	
High school grad	2,899 (23.5)	664 (19.7)	753 (23.1)	712 (24.1)	770 (27.3)	
Some college	3,473 (29.5)	939 (30.4)	892 (29.8)	803 (27.3)	839 (30.6)	
College grad or above	3,044 (30.2)	971 (37.6)	796 (31.0)	740 (29.7)	537 (21.6)	
Income-to-poverty ratio, n (%)						< 0.001
< 1.3	3,300 (17.4)	713 (14.7)	804 (17.2)	834 (17.3)	949 (20.8)	
1.3–3.5	4,372 (34.4)	1,089 (32.9)	1,069 (33.1)	1,101 (35.7)	1,113 (35.9)	
≥ 3.5	4,166 (48.2)	1,156 (52.4)	1,101 (49.7)	1,016 (47.0)	893 (43.2)	
BMI (kg/m^2), mean (SE)	29.00 (0.10)	26.54 (0.16)	28.31 (0.15)	30.17 (0.17)	31.25 (0.17)	< 0.001
WC (cm), mean (SE)	99.33 (0.24)	91.62 (0.38)	97.52 (0.39)	102.59 (0.39)	106.40 (0.39)	< 0.001
SBP(mmHg), mean (SE)	122.21 (0.22)	117.39 (0.37)	121.07 (0.40)	123.77 (0.36)	127.15 (0.41)	< 0.001
DBP (mmHg), mean (SE)	72.43 (0.17)	70.06 (0.25)	72.04 (0.31)	73.21 (0.27)	74.67 (0.28)	< 0.001
Smoking status, n (%)						< 0.001
Never	6,929 (71.8)	1,960 (77.4)	1,766 (72.5)	1,717 (71.5)	1,486 (64.4)	
Former	428 (3.8)	98 (3.7)	88 (2.7)	110 (4.2)	132 (4.7)	
Current	2,349 (24.4)	496 (19.0)	627 (24.9)	573 (24.3)	653 (30.9)	
Alcohol use, n (%)						0.422
None	2,421 (25.2)	623 (24.6)	604 (24.4)	592 (25.1)	602 (27.0)	
Moderate	2,524 (36.9)	641 (37.5)	661 (37.4)	658 (38.6)	564 (33.9)	
Heavy	2,762 (37.8)	699 (37.9)	685 (38.2)	673 (36.3)	705 (39.0)	
Physical activity, n (%)						< 0.001
None	6,522 (50.1)	1,375 (43.2)	1,606 (49.1)	1,711 (52.5)	1,830 (56.3)	
Some	1,396 (10.1)	385 (10.7)	350 (10.1)	352 (10.9)	309 (8.7)	
Meeting	1,286 (10.1)	383 (11.8)	329 (9.8)	303 (9.6)	271 (8.9)	
Exceeding	3,743 (29.7)	1,096 (34.3)	952 (30.9)	869 (26.9)	826 (26.2)	
Diabetes, n (%)	2,191 (12.2)	172 (3.7)	288 (5.8)	519 (11.2)	1,212 (29.6)	< 0.001
Hyperlipidemia, n (%)	8,284 (83.3)	1,186 (60.0)	1,816 (80.0)	2,298 (88.7)	2,984 (97.7)	< 0.001
Antihypertensive medication, n (%)	3,448 (23.8)	598 (14.6)	786 (21.1)	942 (27.3)	1,122 (33.3)	< 0.001
Lipid-lowering medication, n (%)	1,940 (14.2)	273 (7.8)	419 (12.1)	544 (16.5)	704 (21.2)	< 0.001
FBG (mg/dL), mean (SE)	105.67 (0.34)	94.76 (0.27)	99.47 (0.29)	104.41 (0.36)	125.94 (1.13)	< 0.001
HbA1c (%), mean (SE)	5.60 (0.01)	5.32 (0.01)	5.43 (0.01)	5.55 (0.01)	6.14 (0.03)	< 0.001
TG (mg/dL), mean (SE)	137.00 (1.52)	59.53 (0.37)	95.03 (0.34)	137.60 (0.58)	268.29 (4.33)	< 0.001
TC (mg/dL), mean (SE)	201.41 (0.57)	184.61 (0.83)	197.78 (0.87)	205.96 (0.95)	219.26 (1.15)	< 0.001
LDL(mg/dL), mean (SE)	120.92 (0.45)	108.41 (0.73)	122.60 (0.78)	127.92 (0.85)	126.17 (0.93)	< 0.001

Table 1 (continued)

Variable	Overall (*n* = 12947)	Q1 (*n* = 3239)	Q2 (*n* = 3237)	Q3 (*n* = 3235)	Q4 (*n* = 3236)	*p*
HDL (mg/dL), mean (SE)	49.01 (0.40)	59.28 (0.63)	50.84 (0.66)	45.82 (0.57)	38.94 (0.38)	< 0.001
Scr (mg/dL), mean (SE)	0.86 (0.00)	0.83 (0.01)	0.85 (0.00)	0.86 (0.01)	0.88 (0.01)	< 0.001
eGFR (mL/min/1.73 m²), mean (SE)	96.68 (0.26)	97.94 (0.43)	96.60 (0.38)	96.08 (0.38)	95.97 (0.44)	0.003
CRP (mg/L), mean (SE)	3.69 (0.21)	3.03 (0.35)	3.79 (0.30)	3.86 (0.26)	4.43 (0.51)	< 0.001
BUN (mg/dL), mean (SE)	13.29 (0.06)	13.11 (0.11)	13.04 (0.11)	13.31 (0.11)	13.77 (0.12)	< 0.001
UA (mg/dL), mean (SE)	5.44 (0.02)	4.85 (0.03)	5.31 (0.03)	5.70 (0.04)	5.98 (0.03)	< 0.001
TyG, mean (SE)	8.67 (0.01)	7.91 (0.01)	8.44 (0.00)	8.85 (0.00)	9.56 (0.01)	< 0.001
TyG-BMI, mean (SE)	252.53 (1.00)	210.05 (1.30)	239.02 (1.30)	267.15 (1.56)	298.92 (1.72)	< 0.001
TyG-WC, mean (SE)	864.55 (2.60)	725.10 (3.20)	823.29 (3.35)	908.34 (3.47)	1,018.09 (4.27)	< 0.001
TyG-WHtR, mean (SE)	5.11 (0.02)	4.31 (0.02)	4.86 (0.02)	5.38 (0.02)	5.99 (0.03)	< 0.001
TyG-ABSI, mean (SE)	0.71 (0.00)	0.63 (0.00)	0.68 (0.00)	0.72 (0.00)	0.79 (0.00)	< 0.001
TyG-BRI, mean (SE)	46.46 (0.33)	34.65 (0.40)	42.52 (0.44)	50.91 (0.50)	59.13 (0.61)	< 0.001
TyG-WWI, mean (SE)	94.86 (0.17)	83.72 (0.17)	91.58 (0.16)	98.16 (0.15)	107.31 (0.24)	< 0.001
ACM, n (%)	1,284 (7.5)	192 (4.2)	302 (6.5)	332 (8.3)	458 (11.6)	
CVM, n (%)	342 (1.9)	39 (0.8)	86 (1.7)	90 (2.3)	127 (2.9)	

Note: Continuous variables are presented as weighted mean (standard error); categorical variables are presented as unweighted frequency (weighted percentage). P values were derived from weighted Kruskal–Wallis rank sum tests for continuous variables and weighted Rao–Scott χ^2 tests for categorical variables. TyG quartiles: Q1 (lowest) to Q4 (highest). ACM, all-cause mortality; CVM, cardiovascular mortality; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting plasma glucose; HbA1c, glycated hemoglobin; TG, triglycerides; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; BUN, blood urea nitrogen; UA, uric acid; TyG, triglyceride-glucose index; TyG-BMI, TyG-body mass index; TyG-WC, TyG-waist circumference; TyG-WHtR, TyG-waist-to-height ratio; TyG-ABSI, TyG-body shape index; TyG-BRI, TyG-body roundness index; TyG-WWI, TyG-weight-adjusted waist index. *P* for ACM and CVM are not shown because these are outcome events rather than baseline characteristics

Associations of TyG and TyG-obesity composite indices with ACM: continuous, quartile and nonlinear analyses

In the primary complete-case weighted Cox models, all seven indices were positively associated with ACM after full adjustment (Model 3; Table 2). The strongest estimates were observed for TyG-BMI (HR = 1.99, 95% CI: 1.21–3.28) and TyG-BRI (HR = 1.89, 95% CI: 1.38–2.59), followed by TyG-WHtR (HR = 1.58, 95% CI: 1.21–2.05), TyG-WC (HR = 1.34, 95% CI: 1.04–1.75), TyG-WWI (HR = 1.32, 95% CI: 1.12–1.56), TyG-ABSI (HR = 1.25, 95% CI: 1.07–1.46) and TyG alone (HR = 1.19, 95% CI: 1.01–1.39). Kaplan-Meier curves showed lower survival across increasing TyG quartiles (log-rank $P < 0.001$; Fig. 2).

In quartile analyses, TyG-ABSI showed a significant trend with ACM (*P* for trend = 0.008), with the highest risk in Q4 (HR = 2.72, 95% CI: 1.24–5.97). TyG-WWI showed a weaker, non-significant trend ($P = 0.080$), and its risk estimates were not strictly monotonic. Restricted cubic spline analysis suggested nonlinear associations of TyG-BMI (*P* for nonlinearity = 0.006; *P* for overall association = 0.016) and TyG-BRI (*P* for nonlinearity = 0.034; *P* for overall association = 0.062) with ACM, whereas the other indices were largely linear (Fig. 3; Table S7).

Associations of TyG and TyG-obesity composite indices with CVM: continuous, quartile, competing-risk, and joint mixture analyses

For CVM, none of the seven indices remained significantly associated in Model 3 ($P > 0.05$; Table 3). Aalen-Johansen cumulative incidence curves for TyG-WWI and TyG-ABSI showed an increasing trend across quartiles (Fig. 2), but neither cause-specific Cox models nor Fine-Gray subdistribution hazard models identified significant associations after full adjustment (Table S8). For TyG-ABSI, the cause-specific and Fine-Gray HRs were 1.19 (95% CI: 0.93–1.52) and 1.18 (95% CI: 0.92–1.51), respectively; for TyG-WWI, the corresponding estimates were 1.21 (95% CI: 0.92–1.58) and 1.19 (95% CI: 0.90–1.57).

Table 2 Association of TyG-related indices with ACM: continuous and quartile analyses

Variable	Model 1 HR (95% CI)	*P* value	Model 2 HR (95% CI)	*P* value	Model 3 HR (95% CI)	*P* value
TyG	1.27 (1.19–1.35)	<0.001	1.19 (1.05–1.34)	0.019	1.19 (1.01–1.39)	0.033
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	0.99 (0.79–1.23)	0.920	0.90 (0.61–1.33)	0.633	1.00 (0.66–1.51)	0.992
Q3	1.14 (0.92–1.41)	0.355	1.25 (0.85–1.82)	0.362	1.60 (1.04–2.48)	0.068
Q4	1.58 (1.29–1.94)	<0.001	1.24 (0.85–1.83)	0.372	1.00 (0.62–1.63)	0.988
P-trend		<0.001		0.165		0.210
TyG-ABSI	1.40 (1.31–1.49)	<0.001	1.25 (1.10–1.41)	0.004	1.25 (1.07–1.46)	0.012
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.43 (1.11–1.84)	0.013	1.35 (0.86–2.13)	0.274	1.49 (0.92–2.40)	0.182
Q3	1.57 (1.21–2.03)	0.002	1.62 (1.02–2.56)	0.110	1.72 (1.05–2.81)	0.083
Q4	2.51 (1.97–3.20)	<0.001	1.72 (1.12–2.64)	0.068	1.57 (0.96–2.56)	0.192
P-trend		<0.001		0.012		0.015
TyG-BMI	1.13 (1.06–1.21)	0.003	1.08 (0.95–1.22)	0.375	1.99 (1.21–3.28)	0.005
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	0.86 (0.71–1.03)	0.090	1.23 (0.87–1.73)	0.313	2.98 (1.77–5.02)	<0.001
Q3	0.99 (0.83–1.19)	0.950	1.07 (0.75–1.53)	0.772	4.17 (1.99–8.76)	<0.001
Q4	1.13 (0.94–1.35)	0.234	1.20 (0.84–1.71)	0.356	1.01 (0.46–2.22)	0.970
P-trend		0.077		0.530		0.589
TyG-BRI	1.22 (1.15–1.30)	<0.001	1.14 (1.01–1.29)	0.125	1.89 (1.38–2.59)	<0.001
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	0.85 (0.69–1.03)	0.141	0.97 (0.67–1.41)	0.867	1.69 (1.00–2.88)	0.073
Q3	0.91 (0.75–1.11)	0.486	0.88 (0.60–1.28)	0.617	2.52 (1.29–4.93)	0.018
Q4	1.37 (1.14–1.64)	0.003	1.22 (0.86–1.74)	0.330	1.29 (0.63–2.61)	0.484
P-trend		0.001		0.262		0.144
TyG-WC	1.23 (1.15–1.31)	<0.001	1.12 (0.99–1.27)	0.195	1.34 (1.04–1.75)	0.046
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	0.94 (0.77–1.16)	0.529	1.15 (0.80–1.65)	0.477	1.70 (1.07–2.72)	0.050
Q3	0.96 (0.78–1.17)	0.682	1.00 (0.68–1.46)	0.985	2.14 (1.16–3.96)	0.013
Q4	1.33 (1.09–1.62)	0.006	1.11 (0.76–1.61)	0.641	0.87 (0.45–1.71)	0.730
P-trend		<0.001		0.488		0.681
TyG-WHtR	1.25 (1.17–1.34)	<0.001	1.15 (1.02–1.31)	0.102	1.58 (1.21–2.05)	0.001
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	0.90 (0.73–1.10)	0.296	0.93 (0.65–1.35)	0.734	1.59 (0.98–2.60)	0.087
Q3	0.97 (0.79–1.18)	0.806	0.88 (0.60–1.29)	0.599	2.18 (1.15–4.11)	0.009
Q4	1.48 (1.22–1.78)	<0.001	1.24 (0.87–1.75)	0.317	1.41 (0.73–2.73)	0.390
P-trend		<0.001		0.228		0.112
TyG-WWI	1.39 (1.30–1.49)	<0.001	1.25 (1.10–1.42)	0.006	1.32 (1.12–1.56)	0.003
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.08 (0.85–1.36)	0.538	0.84 (0.55–1.27)	0.471	0.96 (0.61–1.53)	0.879
Q3	1.34 (1.07–1.69)	0.027	1.09 (0.72–1.63)	0.772	1.57 (0.95–2.59)	0.137
Q4	2.24 (1.80–2.78)	<0.001	1.15 (0.78–1.70)	0.555	0.95 (0.56–1.62)	0.857
P-trend		<0.001		0.097		0.080

Weighted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality. Model 1 adjusted for age, sex, and race/ethnicity. Model 2 additionally adjusted for marital status, education, income-to-poverty ratio, smoking status, and alcohol consumption. Model 3 further adjusted for BMI, eGFR, HbA1c, total cholesterol, HDL-C, antihypertensive medication use, and lipid-lowering medication use. For obesity-related TyG composite indices (TyG-ABSI, TyG-BMI, TyG-BRI, TyG-WC, TyG-WHtR, TyG-WWI), BMI was not included in Model 3 to avoid collinearity; for TyG alone, BMI was included in Model 3. All models incorporated the fasting subsample weight (WTSAF2YR), divided by 10 to combine the 10 NHANES cycles, with clustering (SDMVPSU) and stratification (SDMVSTRA). P-trend was calculated by modeling the median value of each quartile as a continuous variable. ACM, all-cause mortality; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; SD, standard deviation; TyG, triglyceride-glucose index; TyG-ABSI, TyG-body shape index; TyG-BMI, TyG-body mass index; TyG-BRI, TyG-body roundness index; TyG-WC, TyG-waist circumference; TyG-WHtR, TyG-waist-to-height ratio; TyG-WWI, TyG-weight-adjusted waist index

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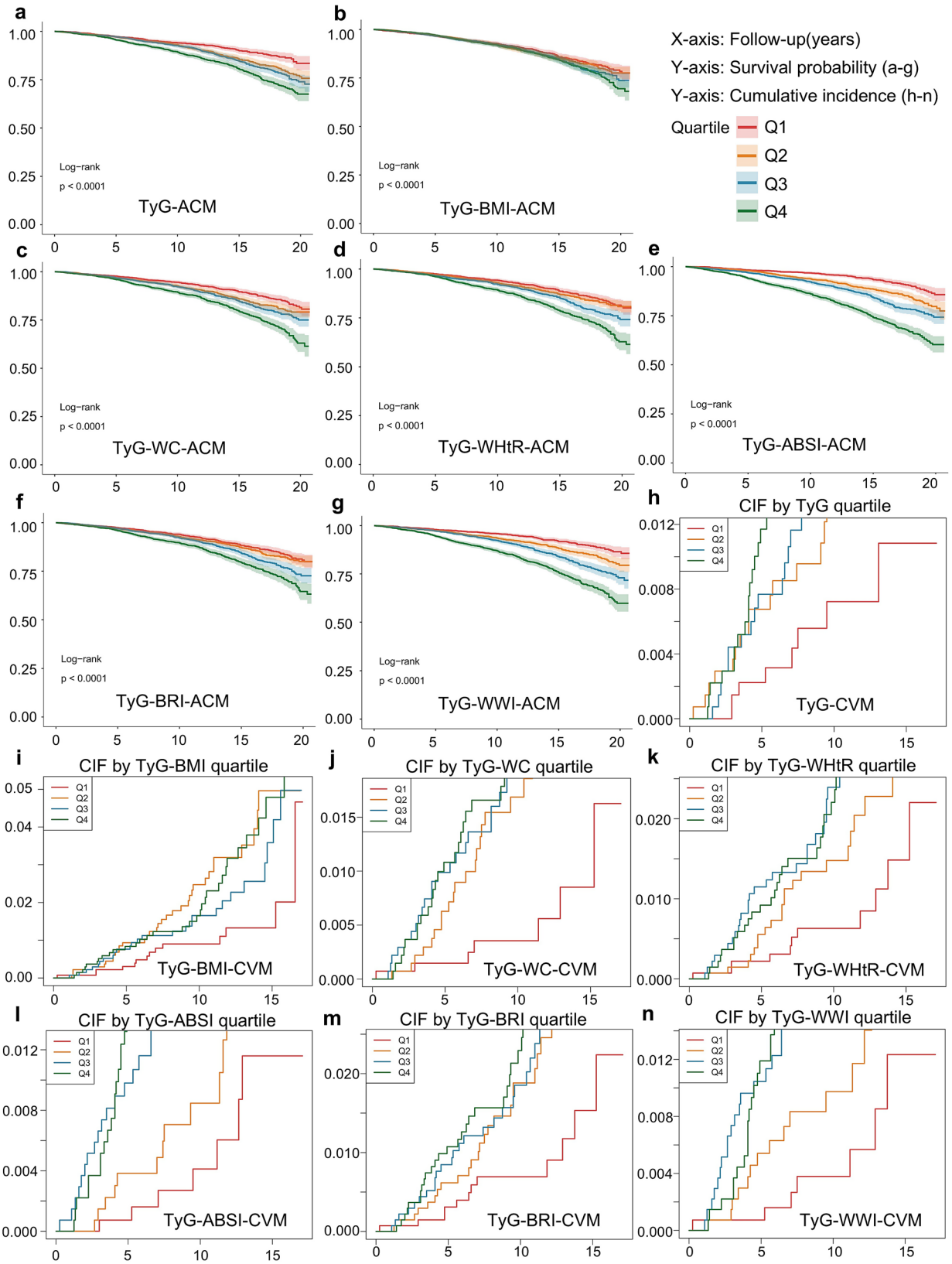

Fig. 2 Cumulative event curves for all-cause mortality and cardiovascular mortality by TyG index quartiles. (**a**-**g**) Kaplan-Meier curves for all-cause mortality. (**h**-**n**) Aalen-Johansen cumulative incidence functions for cardiovascular mortality, with non-cardiovascular death treated as a competing event. Follow-up time is shown for the full available period (median 10.25 years). The 10-year time point was used for time-dependent ROC and NRI/IDI analyses. Q1 to Q4 denote quartiles of the TyG index. ACM, all-cause mortality; CVM, cardiovascular mortality

In quartile analyses, TyG-WWI was associated with increased CVM risk in Q3 (HR = 4.53, 95% CI: 1.41–14.58) but not in Q4, indicating a non-monotonic pattern. In the joint mixture analysis, a simultaneous one-quartile increase across all seven indices was associated with a modest increase in CVM risk (HR = 1.02, 95% CI: 1.00-1.04), whereas the corresponding association with ACM was not significant. Component-specific weights from this model were exploratory because the indices are mathematically interrelated.

Incremental predictive value beyond the PREVENT-variable-based model

To evaluate the independent contribution of each index beyond the base model, standardized logistic regression was performed. Several indices, particularly TyG-WWI, TyG-BMI, and TyG-BRI, demonstrated positive standardized coefficients for both 10-year ACM and CVM when added to the PREVENT-variable framework (Fig. 4a, b). However, time-dependent ROC curves at 10 years revealed limited improvement in discrimination, with all ΔAUC values falling below the prespecified 0.01 threshold (Fig. 4c, d; Table S9). Bootstrap analyses (1,000 replicates) showed small but statistically significant increases in the C-statistic for TyG-ABSI (ΔC = 0.0024, 95% CI: 0.0006–0.0055) and TyG-WWI (ΔC = 0.0017, 95% CI: 0.0002–0.0046) for ACM, but not for CVM. For CVM, the largest point estimate was observed for TyG-WWI (ΔC = 0.0043, 95% CI: 0.0000-0.0115), but the lower confidence bound reached the null and the estimate remained below the clinical significance threshold.

Survival-based continuous NRI and IDI showed modest improvement only for TyG-ABSI (NRI = 0.092, 95% CI: 0.012–0.127; IDI = 0.003, 95% CI: 0.000-0.007) and TyG-WWI (NRI = 0.094, 95% CI: 0.023–0.136; IDI = 0.003, 95% CI: 0.000-0.006) for ACM (Fig. 4e, f; Table S10). For CVM, TyG-WC showed a nominal NRI (0.104, 95% CI: 0.007–0.193), but its IDI was not significant; no consistent incremental value was observed for CVM. A standardized combined score of NRI and IDI further visualized this pattern, highlighting TyG-WWI and TyG-ABSI as the top-performing indices, albeit with modest absolute gains (Fig. 4g). Calibration curves for TyG-WWI and TyG-ABSI showed reasonable agreement between predicted and observed 10-year mortality (Figure S1), whereas decision curve analysis indicated limited additional net benefit across clinically relevant thresholds (Figure S2).

Subgroup, stage-specific and sensitivity analyses

Sex was the most consistent effect modifier: interactions between sex and all TyG-related indices were significant for both ACM and CVM (P for interaction < 0.001; Table S11). For ACM, significant interactions were also observed with eGFR for TyG, TyG-BMI, TyG-WC, TyG-WHtR, TyG-BRI and TyG-WWI, and with BMI for TyG-BMI; no significant age interactions were evident.

In CKM stage-specific analyses, associations with ACM were most apparent in stage 2, where TyG-BRI remained significantly associated (HR = 1.57, 95% CI: 1.16–2.13); other stage 2 estimates were directionally positive but did not reach statistical significance (Table S12). Stage 0–1 estimates were imprecise because of sparse events, and stage 3 (n = 55) was not analyzed separately. For CVM, significant interactions with CKM stage were observed for TyG-BMI (P = 0.047), TyG-WC (P = 0.015) and TyG-WHtR (P = 0.034), but not for the other indices.

After excluding deaths within the first 2 years of follow-up, ACM estimates were attenuated; TyG-ABSI (HR = 1.14, 95% CI: 1.00-1.31) and TyG-BRI (HR = 1.49, 95% CI: 1.11–1.99) remained nominally significant,

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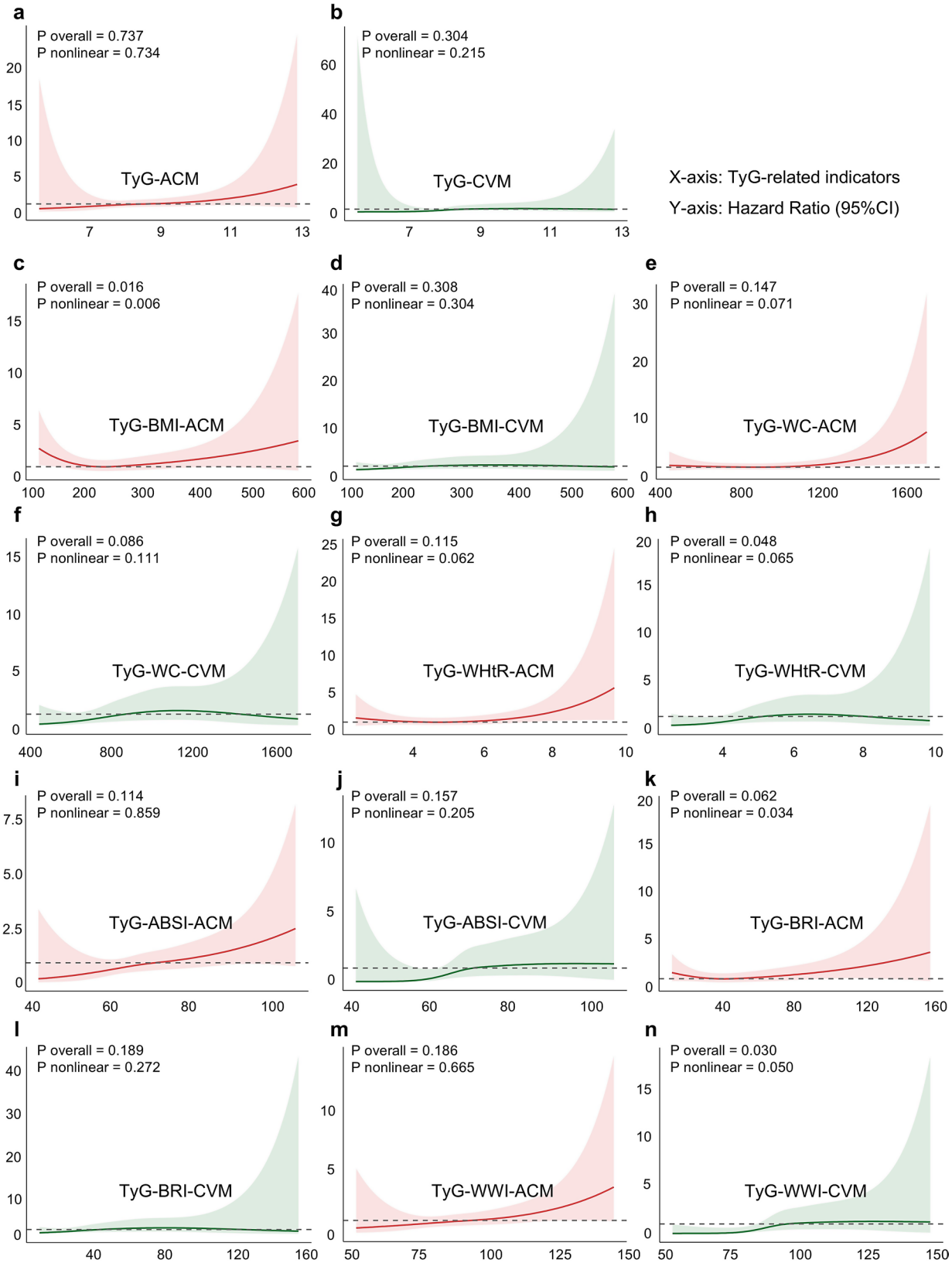

Fig. 3 Restricted cubic spline curves for the association of TyG and TyG-obesity composite indices with all-cause mortality (red) and cardiovascular mortality (green). The reference value was the median of each index. Two interior knots were placed at the 33rd and 67th percentiles; specific knot locations and reference values are reported in Table S14. P values for overall association and nonlinearity are shown in each panel. Confidence intervals were wide at the extremes due to sparse data in those regions, and these findings should be interpreted with caution

whereas CVM associations remained null (Fig. 4h; Table S13). These sensitivity analyses indicate that the ACM findings were not driven by early deaths, although the magnitude of association was modest and index-dependent.

Discussion

In this study based on a nationally representative sample integrating 10 NHANES cycles from 1999 to 2018, we systematically evaluated the associations of seven TyG-obesity composite indices with ACM and CVM among individuals with CKM stages 0–3, and further quantified their incremental predictive value beyond the PREVENT-variable-based model. All seven indices were independently and positively associated with ACM, with TyG-BMI and TyG-BRI exhibiting the strongest effect sizes. However, none retained an independent association with CVM after rigorous multivariable and competing-risk adjustments. Quartile analyses showed a non-monotonic risk increase for TyG-WWI, and qgcomp indicated a modest synergistic effect across all indices. Regarding predictive performance, although these indices did not materially improve global discrimination ($\Delta C < 0.01$), TyG-ABSI and TyG-WWI provided modest but statistically significant improvements in risk reclassification for ACM.

The robust, linear associations with ACM align with the central pathological role of insulin resistance in driving multisystem decompensation [21–18]. Long-standing hyperinsulinemia, coupled with visceral adiposity, promotes systemic inflammation, endothelial dysfunction, and renal impairment, thereby establishing a trajectory toward early mortality. Notably, TyG-BMI and TyG-BRI exhibited the strongest effect sizes in our cohort, which contrasts with previous literature. A recent systematic review of 70 cohorts emphasized central adiposity indices, reporting that TyG-WHtR and TyG-ABSI were the strongest predictors of CVM and ACM, respectively, while TyG-BMI increased ACM risk by only 5% [22–23]. Our findings suggest that in a population restricted to early-to-intermediate CKM stages, the synergistic burden of generalized obesity and overall body geometry (captured by BMI and BRI) may be more lethal than central adiposity alone. Physiologically, BRI captures the geometric distribution of adipose tissue and muscle mass, reflecting the combined effects of visceral fat accumulation and muscle loss [24–25]. In the absence of overt cardiovascular disease, this profound metabolic exhaustion may drive ACM (including non-cardiovascular causes such as frailty and infection) more strongly than traditional risk factors.

In contrast to ACM, the relationship between TyG-related indices and CVM is characterized by non-linearity and synergistic effects rather than simple linear gradients. The null continuous associations in the cause-specific and Fine-Gray models (e.g., Fine-Gray HR for TyG-WWI: 1.19, 95% CI: 0.90–1.57) might be partially attributed to the highly calibrated PREVENT-variable-based base model, which already incorporates blood pressure, lipids, renal function, and diabetes, thereby absorbing the majority of the specific cardiovascular risk signal. Moreover, the relatively lower number of CVM events ($n = 342$) restricted statistical power. The significant risk increase for TyG-WWI in the third quartile (HR = 4.53, 95% CI: 1.41–14.58), but not the fourth, suggests a threshold effect complicated by competing risks. Individuals in the highest quartile likely suffer from severe, end-stage metabolic frailty or occult malignancies, rendering them highly susceptible to non-cardiovascular death [26–28]. The competing-risk framework correctly accounts for this, suppressing the apparent CVM signal in Q4. Furthermore, the joint mixture analysis demonstrated that a simultaneous one-quartile increase across all indices modestly increased CVM risk (HR = 1.02, 95% CI: 1.00-1.04). This highlights a synergistic effect, wherein the cumulative

Table 3 Association of TyG-related indices with CVM: continuous and quartile analyses

Variable	Model 1 HR (95% CI)	*P* value	Model 2 HR (95% CI)	*P* value	Model 3 HR (95% CI)	*P* value
TyG	1.30 (1.15–1.47)	<0.001	1.23 (0.96–1.58)	0.066	0.98 (0.70–1.37)	0.903
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.27 (0.79–2.06)	0.286	1.55 (0.64–3.74)	0.366	1.21 (0.48–3.05)	0.762
Q3	1.61 (1.00–2.57)	0.056	2.09 (0.88–4.99)	0.103	2.46 (0.92–6.57)	0.176
Q4	2.00 (1.26–3.17)	0.012	1.66 (0.66–4.15)	0.295	0.42 (0.13–1.34)	0.166
P-trend		0.006		0.375		0.729
TyG-ABSI	1.38 (1.21–1.58)	<0.001	1.34 (1.03–1.74)	0.009	1.15 (0.84–1.58)	0.365
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.50 (0.85–2.63)	0.168	1.56 (0.47–5.24)	0.527	0.98 (0.27–3.63)	0.985
Q3	2.08 (1.19–3.64)	0.029	4.10 (1.38–12.16)	0.035	4.50 (1.38–14.67)	0.108
Q4	2.85 (1.67–4.88)	<0.001	2.53 (0.87–7.29)	0.150	1.59 (0.49–5.21)	0.599
P-trend		<0.001		0.007		0.122
TyG-BMI	1.47 (1.30–1.66)	<0.001	1.34 (1.06–1.70)	0.052	0.82 (0.30–2.25)	0.723
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.31 (0.86–2.01)	0.168	2.21 (1.05–4.67)	0.036	2.51 (0.80–7.90)	0.193
Q3	1.46 (0.96–2.21)	0.097	1.20 (0.52–2.77)	0.738	1.66 (0.27–10.08)	0.598
Q4	2.34 (1.57–3.48)	<0.001	2.26 (1.06–4.81)	0.052	0.91 (0.19–4.23)	0.880
P-trend		<0.001		0.132		0.631
TyG-BRI	1.53 (1.36–1.72)	<0.001	1.42 (1.12–1.79)	0.009	1.51 (0.79–2.88)	0.196
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.16 (0.73–1.83)	0.471	1.99 (0.82–4.84)	0.076	2.75 (0.79–9.54)	0.063
Q3	1.21 (0.78–1.88)	0.407	1.53 (0.63–3.69)	0.410	4.61 (0.95–22.25)	0.044
Q4	2.99 (2.00–4.48)	<0.001	2.71 (1.21–6.07)	0.020	1.49 (0.35–6.32)	0.512
P-trend		<0.001		0.036		0.360
TyG-WC	1.54 (1.35–1.75)	<0.001	1.39 (1.09–1.78)	0.021	1.10 (0.65–1.84)	0.733
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.49 (0.93–2.38)	0.070	2.66 (1.03–6.91)	0.048	2.36 (0.75–7.42)	0.116
Q3	1.09 (0.67–1.77)	0.748	2.17 (0.83–5.70)	0.143	2.95 (0.71–12.32)	0.079
Q4	2.60 (1.67–4.04)	<0.001	2.89 (1.10–7.60)	0.028	1.03 (0.24–4.38)	0.961
P-trend		<0.001		0.045		0.817
TyG-WHtR	1.57 (1.38–1.79)	<0.001	1.44 (1.12–1.85)	0.009	1.28 (0.74–2.22)	0.351
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.19 (0.75–1.90)	0.368	2.14 (0.90–5.09)	0.016	2.81 (0.88–8.93)	0.100
Q3	1.24 (0.79–1.94)	0.327	1.38 (0.55–3.47)	0.545	3.19 (0.74–13.70)	0.077
Q4	2.82 (1.87–4.26)	<0.001	2.71 (1.22–6.00)	0.024	1.66 (0.42–6.56)	0.435
P-trend		<0.001		0.061		0.573
TyG-WWI	1.51 (1.33–1.73)	<0.001	1.45 (1.12–1.89)	<0.001	1.21 (0.85–1.72)	0.254
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.75 (1.01–3.06)	0.043	1.68 (0.57–4.95)	0.480	1.43 (0.44–4.63)	0.585
Q3	2.37 (1.37–4.10)	0.001	3.42 (1.28–9.13)	0.012	4.53 (1.41–14.58)	0.023
Q4	4.07 (2.41–6.86)	<0.001	2.29 (0.83–6.29)	0.138	0.80 (0.23–2.77)	0.704
P-trend		<0.001		0.004		0.291

Weighted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for cardiovascular mortality. Model 1 adjusted for age, sex, and race/ethnicity. Model 2 additionally adjusted for marital status, education, income-to-poverty ratio, smoking status, and alcohol consumption. Model 3 further adjusted for BMI, eGFR, HbA1c, total cholesterol, HDL-C, antihypertensive medication use, and lipid-lowering medication use. For obesity-related TyG composite indices (TyG-ABSI, TyG-BMI, TyG-BRI, TyG-WC, TyG-WHtR, TyG-WWI), BMI was not included in Model 3 to avoid collinearity; for TyG alone, BMI was included in Model 3. All models incorporated the fasting subsample weight (WTSAF2YR), divided by 10 to combine the 10 NHANES cycles, with clustering (SDMVPSU) and stratification (SDMVSTRA). P-trend was calculated by modeling the median value of each quartile as a continuous variable. CVM, cardiovascular mortality; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; SD, standard deviation; TyG, triglyceride-glucose index; TyG-ABSI, TyG-body shape index; TyG-BMI, TyG-body mass index; TyG-BRI, TyG-body roundness index; TyG-WC, TyG-waist circumference; TyG-WHtR, TyG-waist-to-height ratio; TyG-WWI, TyG-weight-adjusted waist index

burden of multiple metabolic abnormalities-rather than any single marker-drives CVM, explaining the significant stage-specific interactions observed for TyG-BMI, TyG-WC, and TyG-WHtR [29–32].

The dichotomy between prognostic association and predictive utility is a common challenge when adding novel markers to an already robust framework [33–34]. The limited improvement in the C-statistic ($\Delta C < 0.01$) is expected, as the PREVENT equations are highly discriminative; a single surrogate marker is unlikely to shift the AUC substantially. However, NRI and IDI evaluate net risk reclassification, capturing subtler clinical utility [35–37]. For ACM, TyG-ABSI and TyG-WWI demonstrated significant NRI improvements (0.092 and 0.094, respectively; Table S10). Remarkably, despite its null continuous association, TyG-WC showed a significant NRI of 0.104 for CVM (95% CI 0.007–0.193). This implies that even when the linear HR is not significant, adding TyG-WC can still correctly reclassify a meaningful proportion of individuals, pushing high-risk patients above clinical thresholds. Nevertheless, the absolute IDI values were small, and decision curve analysis indicated limited additional net benefit across all thresholds, suggesting that routine clinical adoption should be approached with caution.

Subgroup and stage-specific analyses provided further clinical context. Sex was a pervasive effect modifier (all P for interaction < 0.001). This reflects fundamental differences in fat distribution, insulin sensitivity, and sex hormone regulation. Women generally exhibit more peripheral subcutaneous fat, whereas men are more prone to visceral accumulation; the protective metabolic effects of estrogen may also diminish after menopause [38–39]. Additionally, the stage-specific analyses localized the strongest ACM associations to CKM stage 2. This is a critical window where metabolic risk factors are firmly established but clinical cardiovascular disease has not yet manifested. Sensitivity analyses using multiple imputation and excluding early deaths confirmed that the associations were not driven by reverse causality.

This study has several notable strengths. First, the use of 10 consecutive NHANES cycles (1999–2018) provides a large, nationally representative sample with standardized data collection, allowing for robust weighted analyses that account for the complex survey design. Second, the systematic comparison of seven TyG-related indices within a single cohort minimizes inter-study heterogeneity and provides direct comparative evidence for selecting the most informative index in future research. Third, anchoring the evaluation within a PREVENT-variable-based framework ensures that the incremental predictive value assessed is highly relevant to contemporary clinical risk stratification.

However, several limitations must be acknowledged. First, as an observational study, residual confounding and unmeasured covariates inherent to the NHANES dataset cannot be entirely excluded. Second, the lack of UACR and imaging markers may have led to an underestimation of subclinical CVD, potentially affecting CKM staging accuracy. Third, cardiovascular mortality was ascertained via probabilistic linkage to the National Death Index based on ICD-10 codes on death certificates. Although this is a standard epidemiological approach, some CVM may have been underestimated or misclassified, which may have partly attenuated the observed CVM associations. Fourth, the median follow-up of 10.25 years restricts our ability to evaluate the very-long-term effects of TyG-related indices. While the PREVENT framework can estimate up to 30-year risks, whether the prognostic value of these indices remains stable over a much longer horizon (beyond 10 years) requires further validation using extended follow-up cohorts. Fifth, the relatively low number of cardiovascular deaths ($n = 342$) and the extremely small sample size of CKM stage 3 ($n = 55$) restricted statistical power for cause-specific analyses and precluded stage-specific CVM evaluations. Sixth, all TyG-related indices were derived from a single baseline examination; thus, our findings reflect the predictive value of baseline measurements rather than dynamic trajectories or cumulative exposure. Seventh, while the primary Cox models properly handled censoring and follow-up time, some exploratory analyses (e.g., RCS, qgcomp, NRI/IDI) did not fully incorporate the complex sampling weights or account for censoring, which may affect standard error estimation. These analyses should therefore be interpreted as hypothesis-generating rather than definitive. Finally, because the NHANES race/ethnicity classification cannot reliably identify Asian populations, all anthropometric and metabolic cutoffs were defined using non-Asian criteria, which may limit the generalizability of our findings to Asian populations.

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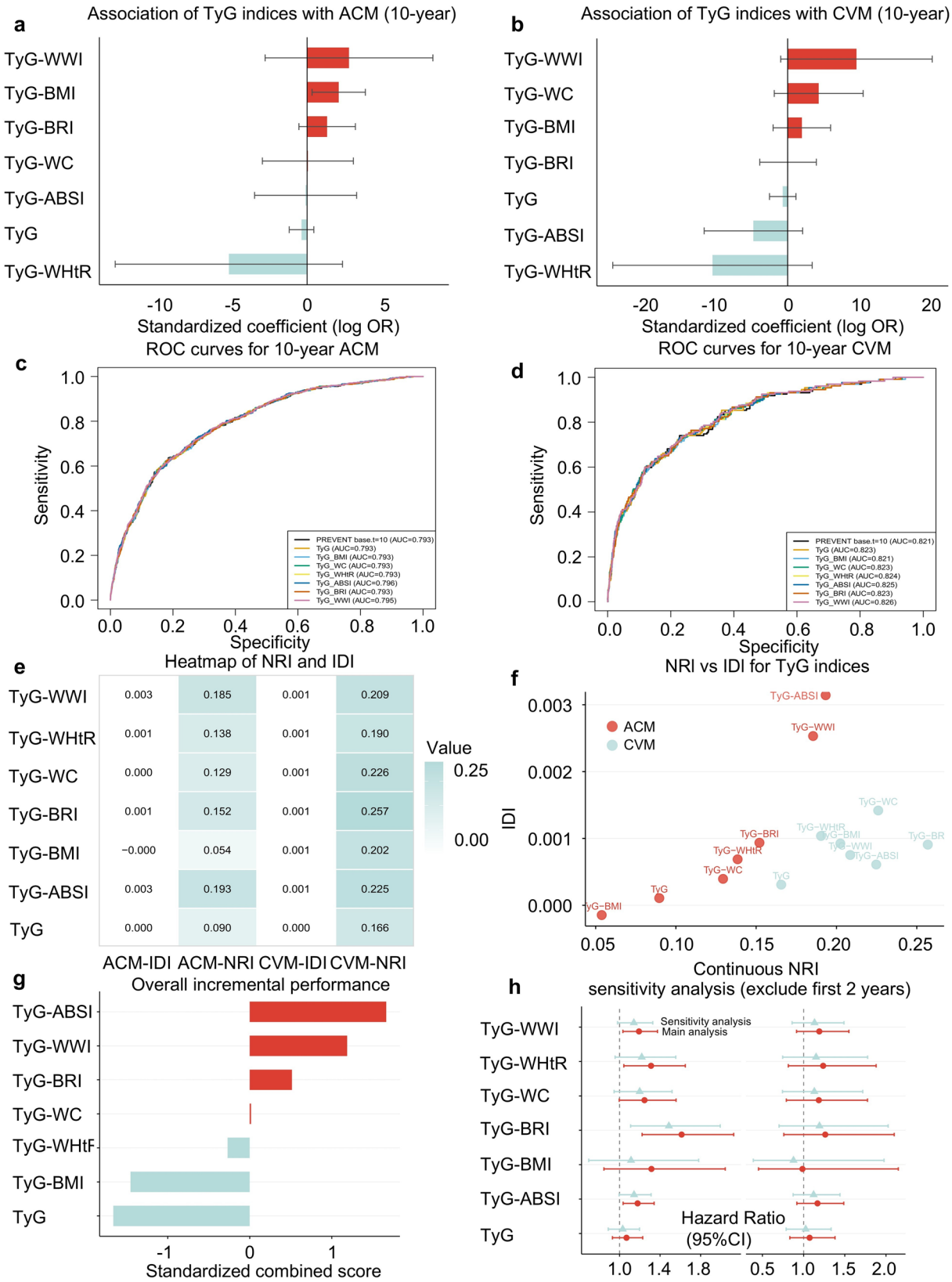

Fig. 4 Incremental predictive value of TyG-related indices beyond the PREVENT-variable-based model. (**a**, **b**) Standardized logistic regression coefficients (log OR) assessing the independent contribution of each TyG-related index to the 10-year risk of all-cause mortality (ACM) (**a**) and cardiovascular mortality (CVM) (**b**). (**c**, **d**) Time-dependent receiver operating characteristic (ROC) curves for 10-year ACM (**c**) and CVM (**d**), comparing the PREVENT-variable-based base model (black line) with models incorporating each individual TyG-related index. (**e**) Heatmap displaying the continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) for each index across both mortality outcomes. (**f**) Scatter plot comparing the continuous NRI and IDI for ACM (red dots) and CVM (blue dots). (**g**) Standardized combined score summarizing the overall incremental performance of each index, calculated by summing the z-scores of NRI and IDI values averaged across ACM and CVM. Positive scores (red bars) indicate better overall incremental performance. (**h**) Forest plot comparing the hazard ratios (HRs) and 95% confidence intervals (CIs) for ACM from the main analysis (red dots) versus the sensitivity analysis excluding deaths within the first 2 years of follow-up (blue dots)

Conclusion

In adults with CKM syndrome stages 0–3, TyG and TyG-obesity composite indices are robustly associated with ACM, while their relationship with CVM is complex and non-linear. Although these indices provide minimal improvement in global discrimination beyond a PREVENT-variable-based model ($\Delta C < 0.01$), they offer modest enhancements in risk reclassification. As low-cost, routinely available tools, they may serve as valuable adjuncts to standard risk stratification to identify high-risk individuals, warranting further prospective validation.

Abbreviations

ACM	All-cause mortality
CVM	Cardiovascular mortality
NHANES	National Health and Nutrition Examination Survey
TyG	Triglyceride-glucose index
TyG-ABSI	Triglyceride-glucose-body shape index
TyG-BMI	Triglyceride-glucose-body mass index
TyG-WC	Triglyceride-glucose-waist circumference
TyG-WHtR	Triglyceride-glucose-waist-to-height ratio
TyG-BRI	Triglyceride-glucose-body roundness index
TyG-WWI	Triglyceride-glucose-weight-adjusted waist index

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Author contributions Hongwei Wang and Caizheng Yang designed the study, performed the data extraction and statistical analysis, and drafted the initial manuscript. Shanshan Ge, Xinyu Wang, and Zhonglin Hao independently verified the extracted data, resolved discrepancies during data cleaning, and contributed to the variable definitions and CKM staging. Xueyu Wang and Ming Zhao conducted the formal statistical analyses, generated the figures and tables, and performed the subgroup and sensitivity analyses. Hua He, Fangying Tian, and Ruihua Jin provided senior methodological supervision, interpreted the results in their clinical and epidemiological context, and critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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Data availability The NHANES data can be freely downloaded via https://www.cdc.gov/nchs/nhanes/. The analysis codes for this study can be requested from the corresponding author (Caizheng Yang) upon reasonable request.

Declarations

Ethical approval and consent to participate This study used publicly available, de-identified data from the National Health and Nutrition Examination Survey (NHANES). NHANES was approved by the National Center for Health Statistics Research Ethics Review Board, and written informed consent was obtained from all participants before data collection. All procedures involving human participants were conducted in accordance with the ethical principles of the Declaration of Helsinki. The present study did not require separate ethical approval because it involved secondary analysis of de-identified public-use data.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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