Cardiovascular Diabetology

RESEARCH

Open Access

Association between triglyceride-glucose related indices and all-cause and cardiovascular mortality among the population with cardiovascular-kidney-metabolic syndrome stage 0–3: a cohort study

Peng Zhang[1], Degang Mo[1], Wenhua Zeng[2] and Hongyan Dai[1,2*]

Abstract

Background Cardiovascular-Kidney-Metabolic (CKM) syndrome typically commences with the interaction of insulin resistance (IR), excessive or dysfunctional obesity, and the consequent systemic inflammatory response and oxidative stress. The relationship between the triglyceride-glucose (TyG) index and TyG-related indices that may simply assess IR and obesity, as well as the mortality risk in the CKM syndrome population, remains ambiguous.

Methods This study included 6,383 participants from the National Health and Nutrition Examination Survey (NHANES) 2009–2018. The TyG index, TyG-waist-to-height ratio (TyG-WHtR), TyG-waist circumference (TyG-WC), and TyG-body mass index (TyG-BMI) were developed. Cox proportional hazards models, smooth curve fitting, and two-stage Cox proportional hazards models were employed to examine the association of TyG and TyG-related indices with all-cause and cardiovascular mortality in the CKM syndrome population. Subgroup analyses and interaction tests were conducted to evaluate the risk within various demographics.

Results In survey-weighted multifactorial regression analyses, a significant positive association existed between TyG, TyG-related indices, and both all-cause mortality and cardiovascular mortality, except for the TyG index, which did not demonstrate a significant link with all-cause mortality. Of these indices, the TyG-WC index exhibited the strongest correlation with all-cause mortality, with a hazard ratio (HR) of 1.50 and a 95% confidence interval (CI) of 1.18–1.92, followed by the TyG-WHtR index (HR: 1.45, 95%CI 1.13–1.85). The TyG-WHtR index demonstrated the strongest correlation with cardiovascular mortality (HR: 1.85, 95% CI 1.19–2.86), followed by the TyG-WC index(HR: 1.83, 95%CI 1.21–2.78). An L-shaped association was identified between TyG-WHtR, TyG-BMI, and all-cause mortality in CKM syndrome during the examination of nonlinear relationships (both P for log-likelihood ratio < 0.05). The TyG-WHtR, TyG-WC, and TyG-BMI indices exhibited a more pronounced correlation with all-cause mortality in those with CKM syndrome stages 1 and 3 (P value < 0.05, P for interaction < 0.05).

*Correspondence:
Hongyan Dai
DrDaihy@163.com

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

Conclusion Our study emphasizes the association between TyG and TyG-related indices and mortality in individuals with CKM syndrome stages 0–3. Individuals with CKM syndrome stages 1 and 3 should be more vigilant to abnormal alterations in TyG-related indices.

Keywords Cardiovascular-kidney-metabolic syndrome, Triglyceride-glucose index, Waist-to-height ratio, Waist circumference, Body mass index, All-cause mortality, Cardiovascular mortality

Introduction

In 2023, the American Heart Association (AHA) characterized Cardiovascular-Kidney-Metabolic (CKM) syndrome as a systemic condition resulting from the pathophysiological interactions among obesity and metabolic risk factors, such as chronic kidney disease (CKD), diabetes, and the cardiovascular system [1]. The 10-year mortality rate is 11.5% for individuals with diabetes and 31.1% for those with diabetes and CKD [2]. Notably, the predominant causes of death among individuals with diabetes and CKD are heart failure and atherosclerotic cardiovascular disease [3, 4]. CKM syndrome embodies a complex pathophysiology that results in heightened mortality and morbidity, surpassing the mere aggregation of its components [5]. The AHA advises categorizing CKM syndrome into five stages to more distinctly define it as a progressive condition [1]. The study indicates that from 2011 to 2020, approximately 90.8% of individuals satisfied the criteria for CKM syndrome stages 0–3 [6]. At the same time, the AHA Scientific Advisory Panel asserts that management strategies for CKM syndrome stage 0–3 should prioritize the prevention of cardiovascular events [7].

Insulin resistance (IR) is a condition characterized by diminished sensitivity and responsiveness to insulin, leading to the impaired transport of glucose into cells [8, 9]. In response to compensation, the pancreatic beta cells release increased amounts of insulin, resulting in hyperinsulinemia. Hyperinsulinemia enhances renal cell proliferation, increases the expression of angiotensin II receptors in tethered cells, and stimulates the release of several growth factors, all of which are closely related to renal damage and nephropathy progression [10]. Hyperinsulinemia enhances smooth muscle proliferation and the development of atherosclerosis by reducing nitric oxide synthesis [11]. IR results in diminished glucose utilization by cardiomyocytes, thereby causing abnormal myocardial metabolism and myocardial damage [12]. IR also predisposes individuals to metabolic disorders, including hyperglycemia, dyslipidemia, and hypertension [13]. These metabolic anomalies heighten the risk of vascular damage and renal disease, thereby facilitating the development and progression of CKM syndrome [14]. The triglyceride-glucose (TyG) index is a simple, accessible, and economical metric for assessing IR, with high sensitivity and specificity [15, 16]. An increasing amount of studies have demonstrated a substantial connection between the TyG index and the incidence of diabetes, CKD, metabolic syndrome (MeTS), cardiovascular disease (CVD), and consequent unfavourable outcomes [17–21]. Recent research indicates that the integration of the TyG index with obesity metrics, such as TyG-waist-to-height ratio (TyG-WHtR), TyG-waist circumference (TyG-WC), and TyG-body mass index (TyG-BMI), demonstrates superior predictive efficacy for patient survival outcomes compared to the standalone TyG index [22, 23]. However, limited research has been undertaken on the correlation between TyG and TyG-related indices and CKM syndrome [24, 25]. The link between TyG, TyG-related indices, and all-cause, as well as cardiovascular mortality in patients with stages 0–3 of CKM syndrome, is still ambiguous.

Therefore, we performed a study utilizing the National Health and Nutrition Examination Survey (NHANES) database to investigate the correlation between the TyG and TyG-related indices with all-cause mortality and cardiovascular mortality in a group with CKM syndrome stages 0–3. We expect that our work will contribute to the early prevention of CKM syndrome by identifying the relationship between TyG-related indices and mortality.

Methods

Study design and population

NHANES is a nationwide survey aimed at gathering data on the nutrition and health of the American civilian population. NHANES employed a sophisticated, stratified, multistage probability sampling methodology to guarantee a nationally representative sample [26]. The research adhered to the ethical guidelines of the Declaration of Helsinki and received approval from the Ethics Review Board of the National Center for Health Statistics [27]. Every participant executed a written informed consent document. Full details of the NHANES study design and data are freely available on the website (www.cdc.gov/nchs/nhanes/). This study utilized data from five NHANES cycles between 2009 and 2018. People who were pregnant or couldn't use the basic Predicting Risk of CVD EVENTs (PREVENT) equation to figure out their 10-year CVD risk were initially left out of the study. Exclusion criteria 2–7 in Fig. 1 outline the range of values for variables that are incompatible with the basic PREVENT equation [28]. Furthermore, we eliminated persons with clinical CVD. We subsequently removed persons for whom follow-up data were inapplicable.

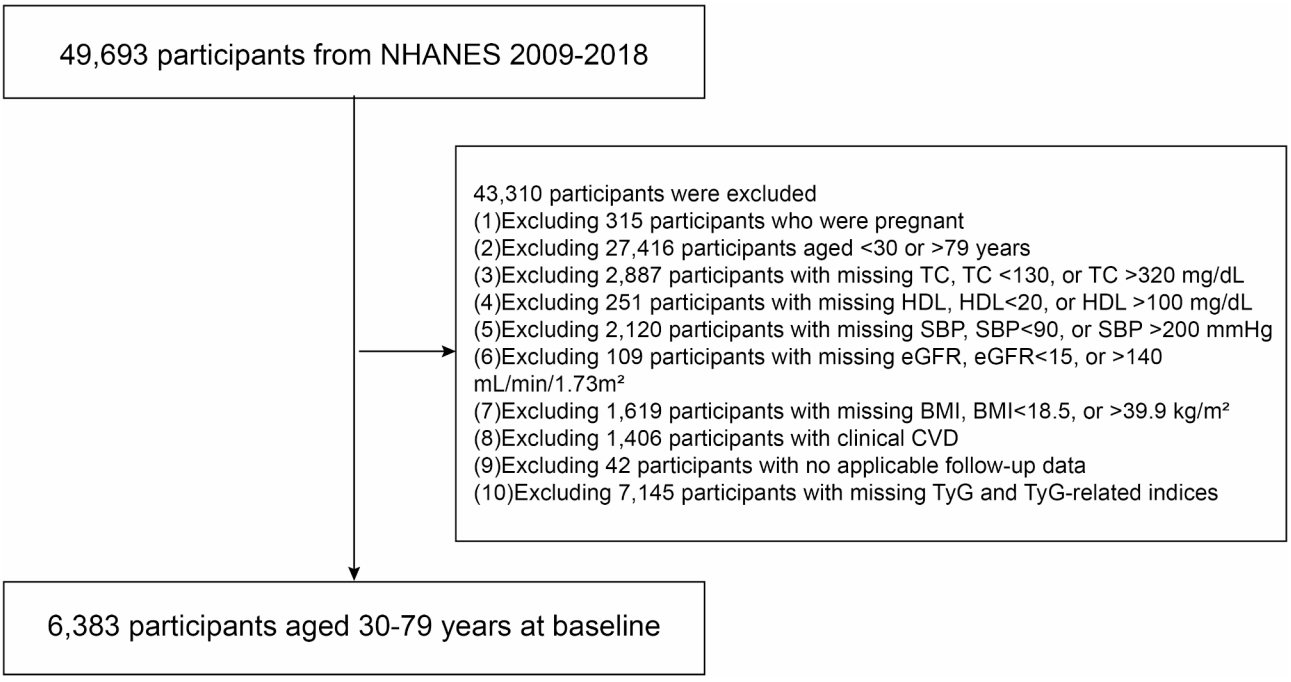

Fig. 1 Flowchart of the study population

Ultimately, we excluded participants without data on the TyG and TyG-related indices (Fig. 1). The final studied sample comprised 6,383 people aged 30 to 79 years.

Definitions of CKM syndrome stages 0 to 3

CKM syndrome is a systemic disorder defined by pathophysiological interactions among the cardiovascular system, CKD, and metabolic risk factors [7]. We classified the participants into various stages based on their health status: Stage 0: No CKM health risk factors; Stage 1: Presence of excessive or dysfunctional adiposity; Stage 2: Presence of metabolic risk factors or moderate to high-risk CKD; Stage 3: Presence of subclinical CVD. Subclinical CVD was defined as a high predicted 10-year CVD risk or very high-risk CKD stage. A high 10-year CVD risk is characterized as 20% or above, as calculated by the basic PREVENT equation [28]. The base equations are provided in Supplementary Material 1, Table S1. The classification of CKD is established according to Kidney Disease Improving Global Outcomes (KDIGO) criteria, which utilize estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) [29]. The eGFR was computed using the 2021 race and ethnicity-free Chronic Kidney Disease Epidemiology Collaboration creatinine equation [30]. More detailed staging criteria are provided in Supplementary Material 1, Table S2.

Definition of TyG and TyG-related indices

The TyG index, a composite measure of triglycerides (TG) and fasting blood glucose (FBG) is a straightforward and efficient metric for evaluating IR. The TyG and TyG-related indices are computed using the subsequent formula: $TyG = \ln[TG\ (mg/dL) \times FBG\ (mg/dL)/2]$; $TyG\text{-}WHtR = TyG \times WHtR$; $TyG\text{-}WC = TyG \times$ waist circumference; $TyG\text{-}BMI = TyG \times BMI$; $WHtR =$ waist circumference/standing height. Furthermore, we categorized the participants into three groups (T1, T2, and T3) based on the tertiles of the TyG and TyG-related indices, designating the T1 group as the reference group.

Definition of clinical outcomes

We acquired mortality data from the NHANES Public Use Linked Mortality File as of December 31, 2019, which employs a probabilistic matching technique to align with the National Death Index from the National Centre for Health Statistics. Ascertain the cause of death following the International Statistical Classification of Diseases, 10th Revision, and reclassify the specified outcome of death. All-cause mortality refers to deaths attributable to any cause (010). Cardiovascular mortality refers to deaths caused by heart disease (054–068) and cerebrovascular disease (070).

Data collection

Demographic data, physical examinations, laboratory testing, lifestyle habits, and medical conditions of participants were gathered. Demographic data: age, gender, race, education, and poverty income ratio; physical examinations: BMI, waist circumference, standing height, systolic blood pressure (SBP), and diastolic blood pressure

(DBP); laboratory testing data: eGFR, UACR, uric acid, FBG, glycated hemoglobin A1c (HbA1c), TG, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C); lifestyle habits and medical conditions: smoking, drinking, antihypertensive use, antihyperglycemic agent use, insulin use, statin use, hypertension, diabetes, liver disease, cancer, MeTS, CKD. The SDP and DBP were calculated as the mean of three measurements. Hypertension is characterized by an SBP of ≥ 130 mm Hg, a DBP of ≥ 80 mm Hg, a medical diagnosis, or the taking of antihypertensive medication [31]. Diabetes is characterized by FBG levels over 126 mg/dL, HbA1c values of 6.5% or higher, a medical diagnosis, or taking insulin or glucose-lowering medications [32]. MeTS is defined by the presence of ≥ 3 of the following: waist circumference ≥ 102 cm for men or ≥ 88 cm for women; HDL-C < 40 mg/dL for men, < 50 mg/dL for women; TG ≥ 150 mg/dL; elevated blood pressure (SBP ≥ 130 mm Hg, DBP ≥ 80 mm Hg, a medical diagnosis, or taking antihypertensive medication); FBG ≥ 100 mg/dL. CKD is classified as low-risk, moderate to high-risk, and very high-risk according to the KDIGO criteria utilizing eGFR and UACR [29]. All comprehensive measurement procedures for these variables are accessible to the public at www.cdc.gov/nchs/nhanes/.

Statistical analysis

All statistical analyses were conducted according to Centers for Disease Control and Prevention recommendations. Strata, primary sample units, and probability weights are employed to address the intricate multistage stratified probabilistic survey design in NHANES. The characteristics of the study population were classified into three groups according to the three tertiles (T1-T3) of TyG and TyG-related indices. Continuous variables were presented as weighted means, 95% confidence interval (CI), and categorical variables were presented as weighted percentages, 95% CI. Differences in baseline characteristics across groups were analyzed using survey-weighted linear regression for continuous variables and survey-weighted Chi-square test for categorical variables.

Hazard ratios (HRs) and 95% CIs for TyG and TyG-related indices of all-cause and cardiovascular mortality were computed using univariate and multivariate Cox proportional hazards regression models. To facilitate data analysis, the exposure variables were standardized to z-scores, reflecting the change in effect size per 1 standard deviation (SD) rise. In addition, three regression models were developed: model 1: non-adjusted; model 2: adjusted for age, gender, and race; model 3: adjusted for age, gender, race, poverty income ratio, eGFR, UACR, uric acid, SBP, DBP, HDL-C, LDL-C, HbA1c, smoking, drinking, statin use, antihypertensive use, antihyperglycemic agent use, insulin use, liver disease, cancer, hypertension, diabetes, MeTS, CKD, and CKM syndrome. Furthermore, we computed HRs and 95% CIs for the relationships between Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and all-cause as well as cardiovascular mortality utilizing univariate and multivariate Cox proportional hazards regression models. Given the issue of collinearity, we checked the variance inflation factor (VIF) of the covariates so that only covariates with VIF < 5 were included in the model. Comprehensive data for the multicollinearity tests are provided in Tables S1, S2, S3, and S4 in Supplementary Material 2. The median of each tertile was utilized as a continuous variable to evaluate the linear trend among TyG and TyG-related indices tertiles.

We employed generalized additive modelling and smoothed curve fitting (penalized spline method) to depict the dose-response connection between TyG, TyG-related indices, and all-cause, as well as cardiovascular mortality. In the case of a nonlinear relationship, we employed a recursive method to identify potential inflection points and utilized two-segment Cox proportional hazards models to characterize the associations on either side of the inflection point. Subgroup analyses were performed according to age, gender, antihypertensive use, statin use, MeTS, and CKM syndrome, and the above stratifiers were considered as potential effect modifiers, and interaction terms were added to test for heterogeneity of associations between subgroups. Due to the exploratory nature of this study, which aims to develop rather than test hypotheses, no adjustments were implemented for multiple comparisons [33, 34]. All analyses were performed using R 4.2.0 and EmpowerStats 4.2, and a two-tailed $P < 0.05$ was considered statistically significant.

Results

Demographic and clinical attributes of patients with CKM syndrome stages 0–3 regarding all-cause and cardiovascular mortality

Table 1 presents the demographic and clinical characteristics of patients with CKM syndrome stages 0–3 concerning all-cause mortality and cardiovascular mortality. Participants who encountered all-cause or cardiovascular death outcomes were primarily older, male, non-Hispanic white, well-educated, low-risk CKD, and CKM syndrome stage 2, and demonstrated increased levels of waist circumference, SBP, uric acid, FBG, HbA1c, TG, TyG and TyG-related indices, as well as the use of antihypertensive agents, antihyperglycemic agents, insulin, and statins. They exhibited elevated rates of smoking, drinking, hypertension, diabetes, liver disease, cancer, and MeTS, alongside reduced income, DBP, and eGFR.

Table 1 The characteristics of patients with CKM syndrome stage 0–3 concerning all-cause mortality and cardiovascular mortality, weighted for representativeness

	All-cause mortality			Cardiovascular mortality		*P* value
	Censored outcomes	All-cause death outcomes	*P* value	Censored outcomes	Cardiovascular death outcomes	
Age, years	49.98 (49.50,50.47)	61.64 (58.67, 64.62)	< 0.001	50.22 (49.74,50.70)	64.66 (60.96,68.37)	< 0.001
Male, %	50.51 (48.80,52.22)	58.81 (49.84, 67.23)	0.069	50.59 (48.93,52.25)	73.28 (54.46,86.28)	0.005
Race, %			< 0.001			0.030
Mexican American	8.87 (7.32,10.72)	4.46 (2.48,7.89)		8.77 (7.24,10.60)	4.83 (1.08,19.10)	
Other Hispanic	6.32 (5.03,7.91)	3.53 (2.02,6.10)		6.26 (4.99,7.82)	3.36 (1.02,10.53)	
Non-Hispanic white	66.75 (63.48,69.86)	74.97 (67.89,80.93)		67.03 (63.78,70.13)	60.89 (40.95,77.76)	
Non-Hispanic black	9.58 (8.19,11.17)	12.99 (9.17,18.07)		9.59 (8.21,11.17)	21.50 (11.19,37.31)	
Other Race	8.49 (7.37,9.75)	4.04 (2.08,7.71)		8.35 (7.25,9.60)	9.42 (3.27,24.21)	
Education, %			0.106			0.043
Less than high school	14.88 (13.24,16.67)	20.51 (14.95,27.48)		14.97 (13.35,16.74)	25.64 (12.69,44.99)	
High school	21.38 (19.51,23.37)	24.54 (17.36,33.49)		21.39 (19.59,23.31)	32.71 (14.71,57.81)	
Above high school	63.75 (61.04,66.37)	54.95 (44.76,64.73)		63.65 (60.99,66.23)	41.65 (23.76,62.05)	
Poverty income ratio	3.14 (3.04,3.24)	2.78 (2.46,3.10)	0.035	3.13 (3.04,3.23)	2.77 (2.15,3.39)	0.267
BMI, kg/m^2	28.28 (28.08,28.47)	29.07 (28.22,29.93)	0.078	28.29 (28.10,28.49)	29.57 (27.83,31.31)	0.155
WC, cm	98.31 (97.76,98.86)	104.12 (101.66,106.58)	< 0.001	98.42 (97.88,98.97)	106.72 (101.68,111.75)	0.002
Standing height, cm	169.18 (168.77,169.60)	170.21 (168.71,171.71)	0.208	169.20 (168.80,169.61)	170.80 (167.74,173.87)	0.320
Smoking, %	14.30 (12.84,15.90)	27.46 (19.41,37.30)	< 0.001	14.62 (13.16,16.21)	24.08 (11.42,43.83)	0.116
Drinking, %	13.40 (12.00,14.94)	26.22 (18.49,35.76)	< 0.001	13.72 (12.34,15.23)	22.37 (9.63,43.80)	0.159
eGFR, ml/min/1.73m^2	95.91 (95.21,96.61)	87.55 (84.23,90.87)	< 0.001	95.75 (95.05,96.45)	84.16 (77.95,90.37)	< 0.001
UACR, mg/g	18.44 (15.29,21.59)	91.36 (7.56,175.17)	0.091	19.30 (16.10,22.50)	199.02 (-113.80,511.85)	0.264
Uric acid, mg/dL	5.40 (5.36,5.45)	5.55 (5.25,5.84)	0.336	5.40 (5.36,5.45)	6.08 (5.61,6.55)	0.005
SBP, mm Hg	121.18 (120.61,121.75)	126.39 (123.60,129.18)	< 0.001	121.24 (120.67,121.80)	134.68 (128.10,141.26)	< 0.001
DBP, mm Hg	71.36 (70.84,71.88)	68.66 (66.60,70.71)	0.014	71.29 (70.76,71.81)	70.41 (65.04,75.79)	0.757
FBG, mg/dL	105.81 (104.84,106.79)	110.71 (106.30,115.12)	0.045	105.85 (104.90,106.81)	120.33 (107.39,133.27)	0.034
HbA1c, %	5.62 (5.59,5.64)	5.87 (5.68,6.05)	0.014	5.62 (5.59,5.65)	6.16 (5.61,6.71)	0.061
Insulin, uU/mL	11.45 (11.08,11.81)	14.49 (11.91,17.08)	0.026	11.48 (11.12,11.84)	19.68 (11.57,27.80)	0.051
TG, mg/dL	123.22 (120.05,126.39)	131.65 (120.31,143.00)	0.170	123.28 (120.20,126.36)	149.38 (126.68,172.08)	0.026
TC, mg/dL	198.82 (197.57,200.07)	198.66 (192.39, 204.93)	0.960	198.79 (197.56,200.01)	203.08 (189.66,216.49)	0.525
HDL-C, mg/dL	54.57 (54.06,55.08)	52.78 (50.22,55.33)	0.169	54.52 (54.01,55.04)	53.49 (49.40,57.58)	0.621
LDL-C, mg/dL	120.00 (118.98,121.02)	119.33 (113.80,124.87)	0.815	119.99 (118.98,121.00)	118.86 (108.43,129.28)	0.830
Antihypertensive use, %	22.46 (20.75,24.26)	37.01 (28.18,46.80)	< 0.001	22.80 (21.13,24.56)	35.09 (19.49,54.71)	0.074
Antihyperglycemic agent use, %	6.58 (5.85,7.40)	10.08 (6.28,15.79)	0.080	6.63 (5.92,7.42)	15.23 (6.49,31.75)	0.021
Insulin use, %	1.51 (1.16,1.97)	3.85 (1.97,7.37)	0.009	1.55 (1.20,2.01)	5.55 (1.12,23.28)	0.065
Statin use, %	16.05 (14.71,17.49)	28.37 (21.52,36.40)	< 0.001	16.19 (14.88,17.60)	47.43 (26.87,68.91)	< 0.001
Hypertension, %	47.51 (45.58,49.44)	64.12 (55.13,72.21)	< 0.001	47.80 (45.93,49.67)	75.64 (55.29,88.63)	0.001
Diabetes, %	11.69 (10.62,12.86)	20.44 (14.26,28.41)	0.003	11.83 (10.78,12.97)	28.33 (12.75,51.67)	0.009
Liver disease, %	3.95 (3.19,4.88)	10.41 (5.88,17.78)	0.001	4.14 (3.38,5.06)	3.89 (0.72,18.54)	0.933
Cancer, %	9.00 (8.01,10.10)	20.39 (13.67,29.28)	< 0.001	9.36 (8.38,10.44)	5.65 (1.31,21.31)	0.394
MeTS, %	37.85 (36.17,39.57)	51.61 (43.95,59.20)	< 0.001	38.07 (36.40,39.77)	63.99 (44.86,79.51)	< 0.001
CKD, %			< 0.001			0.006
Low-risk	88.62 (87.59,89.57)	79.98 (70.37,85.61)		88.44 (87.43,89.37)	74.08(45.84,90.61)	
Moderate to high-risk	11.15 (10.20,12.18)	17.48 (11.35,25.94)		11.26 (10.33,12.26)	22.39(7.58,50.38)	
Very high-risk	0.23 (0.14,0.36)	3.54 (1.55,7.88)		0.30(0.20,0.45)	3.53(0.35,27.57)	
CKM syndrome, %			< 0.001			< 0.001
Stage 0	12.74 (11.49,14.10)	6.33 (3.40,11.49)		12.64 (11.39,14.00)	0.00 (0.00,0.00)	
Stage 1	20.92 (19.43,22.49)	11.59 (6.64,19.47)		20.74 (19.27,22.29)	7.33 (2.31,20.96)	
Stage 2	63.63 (61.91,65.31)	62.88 (53.17,71.66)		63.61 (61.90,65.28)	63.47 (44.42,79.06)	
Stage 3	2.72 (2.23,3.31)	19.19 (13.79,26.07)		3.02 (2.51,3.62)	29.20 (15.22,48.66)	
HOMA-IR	3.14 (3.03,3.26)	4.42 (3.01,5.83)	0.084	3.15(3.04,3.27)	7.13(1.87,12.39)	0.143

Table 1 (continued)

	All-cause mortality			Cardiovascular mortality		*P* value
	Censored outcomes	All-cause death outcomes	*P* value	Censored outcomes	Cardiovascular death outcomes	
TyG	8.58 (8.56,8.60)	8.76 (8.67,8.85)	< 0.001	8.58 (8.56,8.60)	8.97 (8.81,9.13)	< 0.001
TyG-WHtR	5.01 (4.98,5.04)	5.38 (5.25,5.50)	< 0.001	5.02 (4.98,5.05)	5.61 (5.34,5.89)	< 0.001
TyG-WC	846.61 (840.81,852.41)	914.04 (890.13,937.96)	< 0.001	847.80 (842.12,853.48)	959.11 (904.80,1013.42)	< 0.001
TyG-BMI	243.59 (241.64,245.53)	255.14 (247.28,263.01)	0.007	243.77 (241.85,245.68)	265.87 (247.54,284.20)	0.021

CKM syndrome, Cardiovascular-Kidney-Metabolic syndrome; BMI, body mass index; WC, waist circumference; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CKD, chronic kidney disease; HOMA-IR, homeostatic model assessment of insulin resistance; TyG, triglyceride-glucose index; WHtR, waist-to-height ratio; WC, waist circumference

Continuous variables were presented as weighted means (95% CI), and *P* values were obtained from survey-weighted linear regression. Categorical variables were presented as weighted percentages (95% CI), and *P* values were obtained from the survey-weighted Chi-square test

Baseline characteristics of participants categorized by the tertile of TyG-WHtR, TyG, TyG-WC, and TyG-BMI index

Table 2 and Supplementary Material 3, Tables S1, S2, and S3 present participant characteristics categorized by tertiles of TyG-WHtR, TyG, TyG-WC, and TyG-BMI. Participants exhibiting elevated TyG-WHtR index levels were predominantly older, non-Hispanic white, well-educated, low-risk CKD, and CKM syndrome stage 2. They demonstrated heightened metrics in BMI, waist circumference, SBP and DBP, UACR, uric acid, FBG, HbA1c, TG, TC, and LDL-C, alongside increased use of antihypertensive agents, antihyperglycemic agents, insulin, and statins. Furthermore, they presented higher incidences of hypertension, diabetes, and MeTS, coupled with diminished income and HDL-C. A comparable trend was noted for baseline parameters across tertiles of TyG, TyG-WC, and TyG-BMI.

Association of TyG, TyG-related indices, and HOMA-IR with all-cause mortality and cardiovascular mortality

Figure 2 demonstrates the relationship of TyG and TyG-related indices to all-cause and cardiovascular mortality. In survey-weighted multifactorial regression analyses, when TyG and TyG-related indices were examined as continuous variables (each SD), the findings indicated significant positive associations between TyG, TyG-related indices, and both all-cause and cardiovascular mortality, except for the TyG index, which showed no significant correlation with all-cause mortality. The TyG-WC index demonstrated the strongest correlation with all-cause mortality, signifying a 50% increase in mortality risk for each extra SD (HR: 1.50, 95% CI 1.18–1.92), followed by the TyG-WHtR index(HR: 1.45, 95%CI 1.13–1.85). The TyG-WHtR index exhibited the strongest correlation with cardiovascular mortality, with an 85% elevation in death risk for each extra SD (HR: 1.85, 95% CI 1.19–2.86), followed by the TyG-WC index(HR: 1.83, 95%CI 1.21–2.78). We subsequently categorized the TyG and TyG-related indices into tertiles, revealing significant positive correlations with all-cause mortality and cardiovascular mortality, except for the TyG index, which did not demonstrate a significant association with all-cause mortality, and the TyG-WC index, which lacked a significant association with cardiovascular mortality. In comparison to the initial tertiary group (T1), the TyG-WC index T3 exhibited the greatest elevation in all-cause mortality risk at 178% (HR: 2.78, 95% CI 1.53–5.06), followed by the WHtR index(HR: 2.73, 95% CI 1.42–5.23); the TyG index T3 demonstrated the highest increase in cardiovascular mortality risk at 483% (HR: 5.83, 95% CI 1.70-19.95), followed by the WHtR index (HR: 4.58, 95% CI 1.29–16.21).

We also constructed three models for the unweighted data illustrating the correlation between the TyG and TyG-related indices and all-cause as well as cardiovascular mortality, which are presented in Supplementary Material 3, Tables S4 and S5. In Model 3, all indices exhibited a significant positive correlation or trend with all-cause mortality (P value < 0.05, P for trend < 0.05), except for the TyG index, which demonstrated no significant association; and for cardiovascular mortality, all indices indicated a significant positive correlation or trend(P value < 0.05, P for trend < 0.05), except for the TyG-WC index, which demonstrated a weak correlation(P value = 0.064). These results remain generally consistent with the weighted regression results described above.

Table S6 in Supplementary Material 3 illustrates the correlation between HOMA-IR and both all-cause and cardiovascular mortality. In the survey-weighted multifactor regression analysis, HOMA-IR was assessed as a continuous variable (each SD), revealing positive correlations with both all-cause mortality (HR: 1.13, 95% CI 1.06–1.21) and cardiovascular mortality (HR: 1.21, 95% CI 1.09–1.33). The findings indicated that the relationship between HOMA-IR and mortality was significantly lower than those of the TyG and TyG-related indices.

Table 2 The baseline characteristics stratified by TyG-WHtR index tertiles, weighted for representativeness

	TyG-WHtR index			*P* value
	Tertile 1(<4.67)	Tertile 2(4.67–5.42)	Tertile 3(>5.42)	
Age, years	47.02 (46.23, 47.82)	51.03 (50.27, 51.80)	53.36 (52.67, 54.06)	< 0.001
Male, %	48.99 (46.02, 51.97)	54.63 (51.44, 57.77)	48.63 (45.69, 51.57)	0.010
Race, %				< 0.001
Mexican American	4.88 (3.83, 6.21)	9.45 (7.59, 11.71)	12.42 (10.07, 15.23)	
Other Hispanic	5.49 (4.20, 7.15)	5.97 (4.68, 7.59)	7.39 (5.71, 9.51)	
Non-Hispanic white	68.17 (64.88, 71.29)	65.89 (62.19, 69.39)	66.81 (62.44, 70.91)	
Non-Hispanic black	11.35 (9.69, 13.25)	9.95 (8.20, 12.04)	7.46 (6.10, 9.08)	
Other race	10.11 (8.54, 11.94)	8.74 (7.25, 10.49)	5.92 (4.57, 7.64)	
Education, %				< 0.001
Less than high school	9.93 (8.41, 11.69)	16.11 (13.72, 18.84)	19.77 (17.21, 22.60)	
High school	17.61 (14.98, 20.58)	23.31 (21.14, 25.63)	23.93 (21.29, 26.79)	
Above high school	72.46 (68.61, 76.00)	60.58 (57.33, 63.74)	56.30 (52.72, 59.81)	
Poverty income ratio	3.40 (3.28, 3.52)	3.10 (2.99, 3.22)	2.85 (2.73, 2.97)	< 0.001
BMI, kg/m^2	24.15 (23.96, 24.34)	28.46 (28.27, 28.64)	32.90 (32.68, 33.12)	< 0.001
WC, cm	86.86 (86.38, 87.34)	99.20 (98.76, 99.64)	111.07 (110.43, 111.72)	< 0.001
Standing height, cm	170.45 (169.83, 171.07)	169.31 (168.75, 169.87)	167.69 (167.02, 168.36)	< 0.001
Smoking, %	14.25 (12.08, 16.73)	15.46 (13.31, 17.89)	14.37 (12.52, 16.43)	0.628
Drinking, %	11.58 (9.44, 14.12)	14.70 (12.48, 17.23)	15.32 (13.57, 17.26)	0.024
eGFR, $ml/min/1.73m^2$	97.41 (96.40, 98.42)	94.99 (93.96, 96.03)	94.38 (93.36, 95.41)	< 0.001
UACR, mg/g	12.32 (9.73, 14.91)	17.05 (13.03, 21.07)	33.88 (22.37, 45.39)	0.002
Uric acid, mg/dL	4.94 (4.87, 5.01)	5.48 (5.40, 5.55)	5.87 (5.80, 5.94)	< 0.001
SBP, mm Hg	116.20 (115.35, 117.06)	122.65 (121.81, 123.49)	125.82 (124.89, 126.75)	< 0.001
DBP, mm Hg	69.60 (68.98, 70.21)	72.03 (71.25, 72.81)	72.41 (71.70, 73.12)	< 0.001
FBG, mg/dL	97.16 (96.41, 97.90)	104.53 (103.01, 106.04)	117.61 (115.83, 119.40)	< 0.001
HbA1c, %	5.37 (5.34, 5.39)	5.57 (5.53, 5.62)	5.97 (5.92, 6.03)	< 0.001
Insulin, uU/mL	6.71(6.45, 6.97)	11.00(10.63, 11.37)	17.66(16.82, 18.49)	< 0.001
TG, mg/dL	76.55 (74.27, 78.83)	121.10 (117.11, 125.08)	179.95 (171.86, 188.05)	< 0.001
TC, mg/dL	190.98 (189.22, 192.74)	203.11 (200.97, 205.25)	203.22 (200.93, 205.52)	< 0.001
HDL-C, mg/dL	62.02 (61.31, 62.73)	53.24 (52.40, 54.08)	47.26 (46.47, 48.05)	< 0.001
LDL-C, mg/dL	113.68 (112.08, 115.28)	125.51 (123.77, 127.24)	121.29 (119.20, 123.37)	< 0.001
Antihypertensive use, %	9.95 (8.27, 11.93)	23.55 (20.87, 26.46)	37.05 (33.71, 40.53)	< 0.001
Antihyperglycemic agent use, %	1.34 (0.90, 2.00)	4.31 (3.38, 5.48)	15.39 (13.65, 17.30)	< 0.001
Insulin use, %	0.42 (0.18, 1.00)	1.42 (0.92, 2.19)	3.08 (2.29, 4.14)	< 0.001
Statin use, %	9.57 (7.88, 11.59)	16.73 (14.29, 19.49)	23.95 (21.57, 26.50)	< 0.001
Hypertension, %	30.01 (27.44, 32.73)	50.95 (47.45, 54.43)	65.51 (62.74, 68.17)	< 0.001
Diabetes, %	2.68 (1.82, 3.92)	8.97 (7.42, 10.81)	25.81 (23.56, 28.20)	< 0.001
Liver disease, %	2.91 (2.20, 3.82)	3.99 (2.93, 5.40)	5.72 (4.33, 7.52)	0.001
Cancer, %	9.46 (7.79, 11.45)	9.13 (7.40, 11.22)	9.40 (7.51, 11.72)	0.970
MeTS, %	3.94 (2.88, 5.38)	38.82 (35.12, 42.65)	77.12 (74.37, 79.65)	< 0.001
CKD, %				< 0.001
Low-risk	92.63 (90.79,94.13)	89.92 (88.25,91.38)	81.69 (79.64,83.57)	
Moderate to high-risk	7.32 (5.84,9.15)	9.82 (8.38,11.49)	17.59 (15.73,19.62)	
Very high-risk	0.04 (0.01,0.32)	0.26 (0.13,0.49)	0.72 (0.43,1.21)	
CKM syndrome, %				< 0.001
Stage 0	34.36 (31.39, 37.46)	0.87 (0.44, 1.73)	0.00 (0.00,0.00)	
Stage 1	25.23 (22.93, 27.67)	26.51 (23.77, 29.45)	9.07 (7.40, 11.07)	
Stage 2	39.30 (36.41, 42.27)	70.02 (67.00, 72.87)	84.67 (82.40, 86.69)	
Stage 3	1.11 (0.72, 1.70)	2.60 (1.96, 3.44)	6.26 (5.03, 7.76)	
HOMA-IR	1.63(1.56, 1.71)	2.85(2.74, 2.96)	5.32(5.02, 5.61)	< 0.001

Table 2 (continued)

	TyG-WHtR index			*P* value
	Tertile 1(<4.67)	Tertile 2(4.67–5.42)	Tertile 3(>5.42)	
All-cause mortality, %	1.35 (0.96, 1.92)	3.62 (2.80, 4.68)	4.03 (3.08, 5.26)	< 0.001
Cardiovascular mortality, %	0.18 (0.08, 0.37)	0.74 (0.43, 1.28)	1.31 (0.76, 2.22)	< 0.001

TyG, triglyceride-glucose index; WHtR, waist-to-height ratio; BMI, body mass index; WC, waist circumference; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MeTS, metabolic syndrome; CKD, chronic kidney disease; CKM syndrome, Cardiovascular-Kidney-Metabolic syndrome; HOMA-IR, homeostatic model assessment of insulin resistance

Continuous variables were presented as weighted means (95% CI), and *P* values were obtained from survey-weighted linear regression. Categorical variables were presented as weighted percentages (95% CI), and *P* values were obtained from the survey-weighted Chi-square test

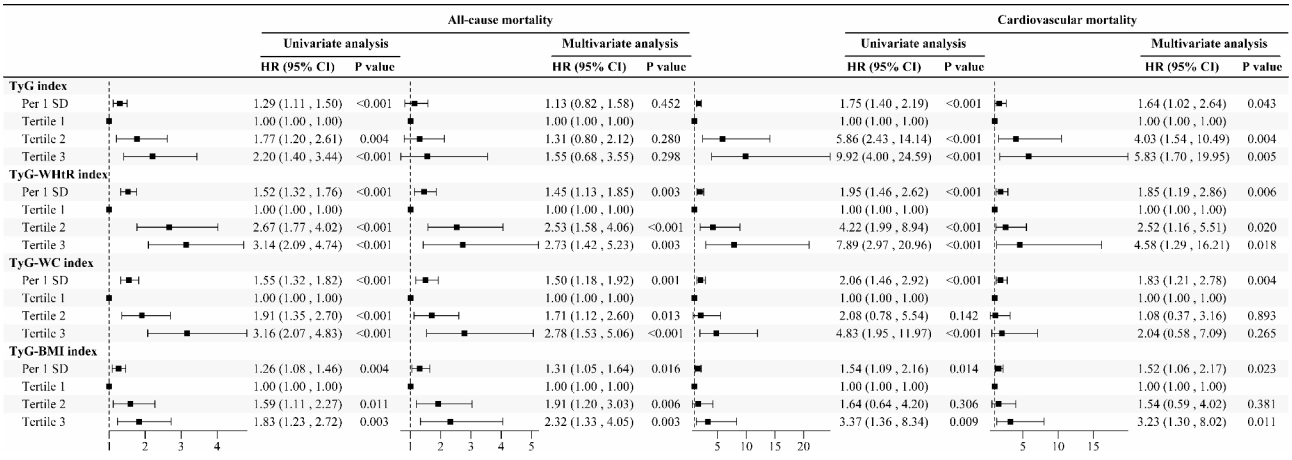

Fig. 2 Cox proportional hazards regression analysis of TyG and TyG-related indices concerning all-cause and cardiovascular mortality in a CKM syndrome stage 0–3 population, weighted for representativeness. Abbreviations: HR, hazard ratio; CI, confidence interval; SD, standard deviation; CKM syndrome, Cardiovascular-Kidney-Metabolic syndrome; TyG, triglyceride-glucose index; WHtR, waist-to-height ratio; WC, waist circumference; BMI, body mass index. The model was adjusted for age, gender, race, poverty income ratio, eGFR, UACR, uric acid, SBP, DBP, HDL-C, LDL-C, HbA1c, smoking, drinking, statin use, antihypertensive use, antihyperglycemic agent use, insulin use, liver disease, cancer, hypertension, diabetes, MeTS, CKD, and CKM syndrome.

Nonlinear relationship of TyG and TyG-related indices with all-cause mortality and cardiovascular mortality

Figure 3 illustrates the dose-response association between TyG and TyG-related indices and all-cause as well as cardiovascular mortality. A significant nonlinear association existed between the TyG-WHtR index and both all-cause and cardiovascular mortality, with inflection points at 3.74 and 6.38, respectively, exhibiting an L-shaped correlation concerning all-cause mortality (both P for log-likelihood ratio < 0.05). Table 3 illustrates the nonlinear association between the TyG-WHtR index and all-cause as well as cardiovascular mortality. When the TyG-WHtR level is below 3.74, the risk of all-cause mortality rises by 92% for each unit increase (HR: 0.08, 95% CI 0.01, 0.85). Conversely, when the TyG-WHtR level exceeds 3.74, the risk of all-cause mortality rises by 34% per unit increase (HR: 1.34, 95% CI 1.07, 1.67). Additionally, the risk of cardiovascular mortality increases by 109% per unit increase when TyG-WHtR levels are below 6.38 (HR: 0.08, 95% CI 0.01, 0.85) and shows no association with cardiovascular mortality risk when TyG-WHtR levels are above 6.38. The nonlinear relationships of the TyG, TyG-WC, and TyG-BMI indices were examined in Supplementary Material 3, S7, S8, and S9; only the TyG-BMI index exhibited a significant nonlinear correlation with all-cause mortality, demonstrating an L-shaped relationship with an inflection point at 169.05(P for log-likelihood ratio < 0.05). When TyG-BMI fell below 169.05, each unit increase in TyG-BMI was associated with a 5% reduction in risk (HR: 0.95, 95% CI: 0.92–0.99). When TyG-BMI exceeded 169.05, it was not correlated with cardiovascular mortality.

Subgroup analysis of the association between TyG, TyG-related indices and mortality

Subgroup analyses were conducted based on age, gender, antihypertensive use, statin use, MeTS, and CKM syndrome after adjusting for covariates. A significant interaction existed between TyG and TyG-related indices concerning CKM syndrome and all-cause mortality (all P for interaction < 0.05); however, no significant interaction was seen between TyG and TyG-related indices and cardiovascular mortality (all P for interaction > 0.05). Furthermore, subgroup analyses of the TyG-related indices revealed that individuals with CKM syndrome stages 1 and 3 exhibited a more pronounced association

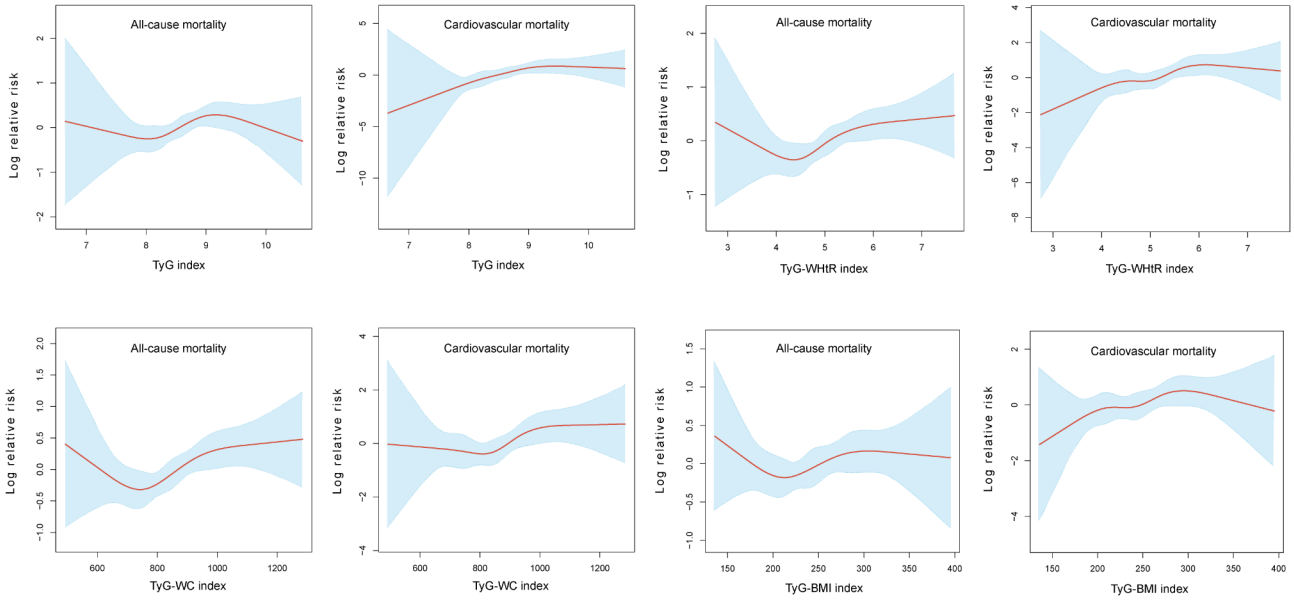

Fig. 3 Smooth curve fitting of the association between TyG and TyG-related indices and all-cause and cardiovascular mortality in a group with CKM syndrome stage 0–3. Abbreviations: CKM syndrome, Cardiovascular-Kidney-Metabolic syndrome; TyG, triglyceride-glucose index; WHtR, waist-to-height ratio; WC, waist circumference; BMI, body mass index. The solid red line at the center represents a smooth curve fit, while the blue-shaded regions on either side show 95% confidence intervals. The model was adjusted for age, gender, race, poverty income ratio, eGFR, UACR, uric acid, SBP, DBP, HDL-C, LDL-C, HbA1c, smoking, drinking, statin use, antihypertensive use, antihyperglycemic agent use, insulin use, liver disease, cancer, hypertension, diabetes, MeTS, CKD, and CKM syndrome.

Table 3 Analysis of the threshold effect of TyG-WHtR index on all-cause and cardiovascular mortality in patients with CKM syndrome stage 0–3

	Adjusted HR (95% CI)	*P* value
All-cause mortality		
Fitting by the standard linear model	1.29 (1.03, 1.61)	0.027
Fitting by the two-piecewise linear model		
I nflection point	3.74	
TyG-WHtR<3.74	0.08 (0.01, 0.85)	0.036
TyG-WHtR ≥ 3.74	1.34 (1.07, 1.67)	0.012
P for Log-likelihood ratio	**0.046**	
Cardiovascular mortality		
Fitting by the standard linear model	1.56 (1.01, 2.41)	0.047
Fitting by the two-piecewise linear model		
Inflection point	6.38	
TyG-WHtR<6.38	2.09 (1.23, 3.53)	0.006
TyG-WHtR ≥ 6.38	0.24 (0.02, 2.34)	0.219
P for Log-likelihood ratio	**0.044**	

Bold font indicates that the log likelihood ratio test is statistically significant ($P < 0.05$)

HR, hazard ratio; CI, confidence interval; TyG, triglyceride-glucose index; WHtR, waist-to-height ratio; CKM syndrome, Cardiovascular-Kidney-Metabolic syndrome

The model was adjusted for age, gender, race, poverty income ratio, eGFR, UACR, uric acid, SBP, DBP, HDL-C, LDL-C, HbA1c, smoking, drinking, statin use, antihypertensive use, antihyperglycemic agent use, insulin use, liver disease, cancer, hypertension, diabetes, MeTS, CKD, and CKM syndrome

with all-cause mortality (P value < 0.05, P for interaction < 0.05). Table 4 presents the subgroup analyses of the TyG-WHtR index, revealing a stronger correlation with all-cause mortality in individuals aged ≥ 60 years, men, those using antihypertensive medicines and statins, as well as in the absence of MeTS and CKM syndrome stages 1 and 3. The correlation with cardiovascular mortality is more pronounced in individuals who do not use statins. Supplementary Material 3, Tables S10, S11, and S12 provide a detailed presentation of the subgroup analyses for TyG, TyG-WC, and TyG-BMI indices.

Discussion

Based on the results of the literature search, we initiated the first investigation examining the association between TyG and TyG-related indices with all-cause and cardiovascular mortality in a cohort with CKM syndrome. Our findings indicated that [1] a significant positive association existed between TyG, TyG-related indices, and both all-cause mortality and cardiovascular mortality, except for the TyG index, which did not demonstrate a significant link with all-cause mortality [2]. Significant nonlinear correlations were seen between the TyG-WHtR index and both all-cause and cardiovascular mortality, as well as between the TyG-BMI index and all-cause mortality, with both the TyG-WHtR and TyG-BMI exhibiting an L-shaped association with all-cause mortality [3]. The TyG-WHtR, TyG-WC, and TyG-BMI indices exhibited a

Table 4 Subgroup analysis of the association between TyG-WHtR index and all-cause and cardiovascular mortality in patients with CKM syndrome stage 0–3

TyG-WHtR per 1 SD	All-cause mortality			Cardiovascular mortality		
	HR(95% CI)	*P* value	*P* interaction	HR(95% CI)	*P* value	*P* interaction
Age			0.069			0.740
<60 years	1.00 (0.72, 1.39)	0.994		1.67 (0.79, 3.51)	0.176	
≥60 years	**1.42 (1.14, 1.78)****	**0.002**		1.46 (0.96, 2.20)	0.076	
Gender			0.096			0.602
Male	**1.39 (1.09, 1.78)****	**0.008**		1.60 (0.98, 2.61)	0.058	
Female	1.05 (0.81, 1.37)	0.698		1.30 (0.69, 2.44)	0.419	
Antihypertensive use			0.066			0.706
Yes	**1.55 (1.17, 2.06)****	**0.002**		1.59 (0.92, 2.74)	0.098	
No	1.08 (0.82, 1.41)	0.589		1.38 (0.84, 2.28)	0.199	
Statin use			0.197			0.996
Yes	**1.48 (1.08, 2.03)***	**0.015**		1.58 (0.85, 2.94)	0.150	
No	1.17 (0.93, 1.46)	0.184		**1.57 (1.01, 2.46)***	**0.045**	
Metabolic syndrome			0.645			0.844
Yes	1.22 (0.96, 1.56)	0.109		1.56 (0.96, 2.54)	0.075	
No	**1.33 (1.00, 1.75)***	**0.047**		1.44 (0.78, 2.66)	0.240	
CKM syndrome			**0.029**			0.919
Stage 0	1.00 (0.18, 5.58)	0.999		0.95 (0.00, Inf)	1.000	
Stage 1	**3.26 (1.44, 7.37)****	**0.005**		3.19 (0.09, 119.19)	0.529	
Stage 2	1.07 (0.84, 1.37)	0.583		1.43 (0.86, 2.37)	0.166	
Stage 3	**1.63 (1.13, 2.36)****	**0.009**		1.84 (0.93, 3.66)	0.081	

Bold font indicates statistically significant differences ($P < 0.05$)

*$P < 0.05$, **$P < 0.01$

HR, hazard ratio; CI, confidence interval; SD, standard deviation; TyG, triglyceride-glucose index; WHtR, waist-to-height ratio; CKM syndrome, Cardiovascular-Kidney-Metabolic syndrome

The model was adjusted for age, gender, race, poverty income ratio, eGFR, UACR, uric acid, SBP, DBP, HDL-C, LDL-C, HbA1c, smoking, drinking, statin use, antihypertensive use, antihyperglycemic agent use, insulin use, liver disease, cancer, hypertension, diabetes, MeTS, CKD, and CKM syndrome

more pronounced correlation with all-cause mortality in those with CKM syndrome stages 1 and 3.

Our findings indicated significant positive correlations between TyG, TyG-related indices, and both all-cause and cardiovascular mortality in stages 0–3 of CKM syndrome, except for the TyG index, which exhibited no significant association with all-cause mortality. This positive association is consistent with the findings of previous investigations [23, 35]. In a prospective urban-rural epidemiologic investigation, the TyG index exhibited no significant association with non-cardiovascular mortality following the adjustment for confounding variables [36]. A cohort research based on an Iranian population also found no significant association between the TyG index and mortality after controlling for the influence of diabetes [37]. Despite this, much research has shown positive results regarding the association between the TyG index and mortality [38–40]. However, the TyG index combined with the obesity index showed better correlation and diagnostic efficacy for illnesses and mortality. Our findings indicated that the TyG-WC index exhibited the strongest correlation with all-cause mortality, while the TyG-WHtR index demonstrated the strongest correlation with cardiovascular mortality. A study on the mortality risk associated with metabolic dysfunction-associated steatotic liver disease (MASLD) revealed that the TyG-WHtR and TyG-WC indices exhibited a much superior predictive value compared to the single TyG index for mortality outcomes in persons with MASLD [41]. A cohort study from the UK Biobank showed that the TyG-WC was more effective than other TyG-related indices in diagnosing various types of myocardial infarction [42]. WHtR and WC are anthropometric indicators of central obesity and are more effective in screening for cardiometabolic disorders than BMI, which indicates overall obesity [43, 44]. WHtR and WC are equally proficient in identifying IR [45, 46], and the integration of TyG with these obesity indices provides a more precise evaluation of IR compared to TyG in isolation [23, 47, 48]. Similarly, central obesity is significantly linked to the development of IR, systemic inflammation, and oxidative stress, all of which facilitate the progression of CKM syndrome [49, 50]. Therefore, it is essential to integrate the TyG index with the obesity index to investigate the detrimental effects of CKM syndrome.

Our findings revealed substantial nonlinear associations between the TyG-WHtR index and both all-cause and cardiovascular mortality, as well as between the

TyG-BMI index and all-cause mortality. A study utilizing NHANES data revealed a substantial L-shaped correlation between the TyG-WHtR index and both all-cause and cardiovascular mortality in the general population [35]. A separate analysis of NHANES data revealed a U-shaped correlation between the TyG-WHtR index and CKD, demonstrating greater predictive efficacy for CKD mortality compared to other TyG-related indices [51]. A retrospective study of patients with diabetes revealed a U-shaped correlation between TyG-BMI and both all-cause death and cardiovascular mortality [52]. This indicates that both elevated and diminished TyG and TyG-related indices correlate with mortality risk in the CKM syndrome population and that sustaining these indices within the optimal range may reduce mortality incidence.

In subgroup analyses and interaction tests, as the TyG-WHtR, TyG-WC, and TyG-BMI indices increased, their correlations with all-cause mortality grew more pronounced in patients with CKM syndrome stages 1 and 3. This indicates that integrating the TyG index with obesity metrics may enhance the prediction of all-cause mortality in excessively or dysfunctionally obese populations and those with subclinical CVD. A cohort analysis utilizing the China Health and Retirement Longitudinal Study revealed no statistically significant association between the TyG-BMI index and long-term CVD outcomes in the CKM syndrome stages 0–3 group [25]. Compared to the previous study, our research employed the most recent AHA-recommended PREVENT equation for forecasting subclinical CVD and utilized the new race-free eGFR equation for eGFR calculation, consequently enhancing the reliability of our findings. The variability in staging methods for CKM syndrome, together with social determinants such as geographic location, lifestyle choices, and the participant's economic position, may have influenced the discrepancies in outcomes. Given the contradictory results in different stages of CKM syndrome, further studies and analysis of the relationship of TyG and TyG-related indices with clinical outcomes in different stages of CKM syndrome are necessary. No interaction was observed between TyG and TyG-related indices of CKM syndrome and cardiovascular mortality, indicating the generalizability of our findings across all populations in the context of cardiovascular mortality analysis. However, in our study, we did not use multiple comparison adjustments like Bonferroni corrections, which increase the risk of Type I errors (false positives) [34]. Therefore, we believe that these results should be interpreted with caution and independently verified in future confirmatory research. Furthermore, we offer P values for all subgroups without adjustment, allowing readers to evaluate the evidence based on their significant criteria.

CKM syndrome is a widespread, multisystemic, chronic systemic disorder. Current evidence indicates that CKM syndrome typically evolves due to the interaction of various variables, including IR, excessive or dysfunctional obesity, and the resulting systemic inflammatory response and oxidative stress. Hyperinsulinemia resulting from IR enhances renal cell proliferation, elevates angiotensin II receptor expression in tethered cells, and triggers the release of several growth factors, hence facilitating nephropathy [10]. Furthermore, IR disrupts the equilibrium between the phosphatidylinositol-3-kinase and protein kinase B pathways, resulting in diminished endothelial nitric oxide synthesis, which subsequently causes vascular endothelial injury and metabolic dysfunction [53, 54]. These changes additionally facilitate the progression of cardiovascular and metabolic diseases. Pro-inflammatory factors that are overexpressed in obesity, including tumour necrosis factor-α, interleukin-6, and monocyte chemotactic protein-1, induce localized inflammation and oxidative stress in tissues and organs, thereby indirectly facilitating cardiovascular dysfunction and metabolic irregularities [55]. Fatty acids resulting from lipolysis trigger the pro-inflammatory serine kinase cascade and release inflammatory mediators such as C reactive protein while simultaneously correlating with diminished β-cell activity and heightened IR [56, 57]. An elevation in lipocalin diminishes in cases of severe obesity, resulting in a reduction of the body's anti-inflammatory and anti-atherogenic properties while also facilitating the advancement of IR [58]. Moreover, many studies have demonstrated a strong association between IR, secondary hyperinsulinemia, and both all-cause and cardiovascular mortality across many conditions [59–61]. Consequently, TyG and TyG-related indices linked to dysfunctional obesity or IR serve as valid and efficient surrogates for identifying the risk of adverse outcomes in CKM syndrome populations.

However, certain limitations persist. Due to its nature as an observational study, we could not ascertain causality. Secondly, even adjusting for some relevant confounders, there may still be aspects that were overlooked. Furthermore, we only included patients for whom the PREVENT equation was relevant, thereby limiting the generalizability of our study. Ultimately, NHANES evaluated data for participants just once at a certain time, which may have diminished the risk relationship in this prospective analysis due to regression dilution [62]. This work employed a typical statistical method for analysis, appropriate for small datasets, while its generalization ability is limited. Future research may explore the incorporation of machine learning methods to enhance the model's stability and accuracy [63–65].

Conclusion

This study emphasizes the association between TyG and TyG-related indices and mortality in individuals with CKM syndrome stages 0–3. TyG-WHtR and TyG-BMI exhibit L-shaped nonlinear correlations with all-cause mortality. TyG-WHtR, TyG-WC, and TyG-BMI had a stronger correlation with the probability of all-cause mortality in stages 1 and 3 of CKM syndrome. These findings indicate the significance of TyG and TyG-related indices for the simple and efficient evaluation of mortality risk in CKM syndrome stages 0–3 populations.

Abbreviations

AHA	American Heart Association
CKM syndrome	Cardiovascular-kidney-metabolic syndrome
CKD	Chronic kidney disease
IR	Insulin resistance
TyG	Triglyceride-glucose index
MeTS	Metabolic syndrome
CVD	Cardiovascular disease
WHtR	Waist-to-height ratio
WC	Waist circumference
BMI	Body mass index
NHANES	National Health and Nutrition Examination Survey
PREVENT equation	Predicting risk of CVD EVENTs equation
KDIGO	Kidney Disease Improving Global Outcomes
eGFR	Estimated glomerular filtration rate
UACR	Urine albumin-to-creatinine ratio
TG	Triglycerides
FBG	Fasting blood glucose
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
HbA1c	Glycated hemoglobin A1c
TC	Total cholesterol
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
HR	Hazard ratio
CI	Confidence interval
SD	Standard deviation
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
VIF	Variance inflation factor
MASLD	Metabolic dysfunction-associated steatotic liver disease

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02642-7 .

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements

We express our gratitude to all participants in the NHANES study and the project team.

Author contributions

PZ was responsible for the design and conceptualization of the study, as well as drafting and revising the manuscript. PZ and DM contributed to data collecting, statistical analysis, and result interpretation. WZ was responsible for the data results visualization. HD read and revised the manuscript. All authors read and approved the final manuscript.

Funding

This study was funded by the Qingdao Outstanding Health Professional Development Fund 2025–2027.

Data availability

The datasets produced and analyzed in this research are accessible in the NHANES database (https://wwwn.cdc.gov/nchs/nhanes/default.aspx).

Declarations

Ethics approval and consent to participate

The NHANES study protocol received approval from the Ethics Review Board of the National Center for Health Statistics. All participants executed a written informed consent form before their involvement.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Cardiology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China
[2]Department of Cardiology,Qingdao Municipal Hospital, Shandong Second Medical University, Weifang, China

Received: 6 January 2025 / Accepted: 10 February 2025
Published online: 28 February 2025

References

1. Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, et al. A synopsis of the evidence for the science and clinical management of cardiovascular-kidney-metabolic (CKM) syndrome: a scientific statement from the American Heart Association. Circulation. 2023;148(20):1636–64.
2. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol JASN. 2013;24(2):302–8.
3. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet (London, England). 2015;385(9963):117–71.
4. Packham DK, Alves TP, Dwyer JP, Atkins R, de Zeeuw D, Cooper M, et al. Relative incidence of ESRD versus cardiovascular mortality in proteinuric type 2 diabetes and nephropathy: results from the DIAMETRIC (Diabetes Mellitus Treatment for Renal Insufficiency Consortium) database. Am J Kidney Dis Off J Natl Kidney Found. 2012;59(1):75–83.
5. Ahmad FB, Anderson RN. The leading causes of death in the US for 2020. JAMA. 2021;325(18):1829–30.
6. Aggarwal R, Ostrominski JW, Vaduganathan M. Prevalence of cardiovascular-kidney-metabolic syndrome stages in US adults, 2011–2020. JAMA. 2024;331(21):1858–60.
7. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, et al. Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. Circulation. 2023;148(20):1606–35.
8. Defronzo RA. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58(4):773–95.
9. Faerch K, Vaag A, Holst JJ, Hansen T, Jørgensen T, Borch-Johnsen K. Natural history of insulin sensitivity and insulin secretion in the progression from normal glucose tolerance to impaired fasting glycemia and impaired glucose tolerance: the Inter99 study. Diabetes Care. 2009;32(3):439–44.
10. Sarafidis PA, Ruilope LM. Insulin resistance, hyperinsulinemia, and renal injury: mechanisms and implications. Am J Nephrol. 2006;26(3):232–44.
11. Reaven GM. Insulin resistance, the insulin resistance syndrome, and cardiovascular disease. Panminerva Med. 2005;47(4):201–10.
12. Fahed G, Aoun L, Bou Zerdan M, Allam S, Bou Zerdan M, Bouferraa Y et al. Metabolic syndrome: updates on pathophysiology and management in 2021. Int J Mol Sci. 2022;23(2).
13. Hill MA, Yang Y, Zhang L, Sun Z, Jia G, Parrish AR, et al. Insulin resistance, cardiovascular stiffening and cardiovascular disease. Metab Clin Exp. 2021;119:154766.

14. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation. 2005;112(20):3066–72.
15. Ramdas Nayak VK, Satheesh P, Shenoy MT, Kalra S. Triglyceride glucose (TyG) index: a surrogate biomarker of insulin resistance. JPMA J Pak Med Assoc. 2022;72(5):986–8.
16. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, Martínez-Abundis E, Ramos-Zavala MG, Hernández-González SO, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab. 2010;95(7):3347–51.
17. Park HM, Lee HS, Lee YJ, Lee JH. The triglyceride-glucose index is a more powerful surrogate marker for predicting the prevalence and incidence of type 2 diabetes mellitus than the homeostatic model assessment of insulin resistance. Diabetes Res Clin Pract. 2021;180:109042.
18. Liu C, Liang D. The association between the triglyceride-glucose index and the risk of cardiovascular disease in US population aged ≤ 65 years with prediabetes or diabetes: a population-based study. Cardiovasc Diabetol. 2024;23(1):168.
19. Kunutsor SK, Seidu S, Kurl S, Laukkanen JA. Baseline and usual triglyceride-glucose index and the risk of chronic kidney disease: a prospective cohort study. GeroScience. 2024;46(3):3035–46.
20. Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Triglyceride-glucose index is a predictor of incident chronic kidney disease: a population-based longitudinal study. Clin Exp Nephrol. 2019;23(7):948–55.
21. Liu Q, Zhang Y, Chen S, Xiang H, Ouyang J, Liu H, 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.
22. Dang K, Wang X, Hu J, Zhang Y, Cheng L, Qi X, et al. The association between triglyceride-glucose index and its combination with obesity indicators and cardiovascular disease: NHANES 2003–2018. Cardiovasc Diabetol. 2024;23(1):8.
23. Wei X, Min Y, Song G, Ye X, Liu L. Association between triglyceride-glucose related indices with the all-cause and cause-specific mortality among the population with metabolic syndrome. Cardiovasc Diabetol. 2024;23(1):134.
24. Wu L, Huang Z. Elevated triglyceride glucose index is associated with advanced cardiovascular kidney metabolic syndrome. Sci Rep. 2024;14(1):31352.
25. Li W, Shen C, Kong W, Zhou X, Fan H, Zhang Y, et al. Association between the triglyceride glucose-body mass index and future cardiovascular disease risk in a population with cardiovascular-kidney-metabolic syndrome stage 0–3: a nationwide prospective cohort study. Cardiovasc Diabetol. 2024;23(1):292.
26. Patel CJ, Pho N, McDuffie M, Easton-Marks J, Kothari C, Kohane IS, et al. A database of human exposomes and phenomes from the US National Health and Nutrition Examination Survey. Sci data. 2016;3:160096.
27. htm NCfHSJHNCfHSAoahwcgnni. Centers for Disease control and prevention NCHS research ethics review board (ERB) approval. 2023.
28. Khan SS, Matsushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A, et al. Development and validation of the American Heart Association's PREVENT equations. Circulation. 2024;149(6):430–49.
29. KDIGO 2024 Clinical Practice Guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105(4s):S117–314.
30. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737–49.
31. Whelton PK, Carey RM. The 2017 American College of Cardiology/American Heart Association Clinical Practice Guideline for high blood pressure in adults. JAMA Cardiol. 2018;3(4):352–3.
32. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S17–38.
33. Cao J, Zhang S. Multiple comparison procedures. JAMA. 2014;312(5):543–4.
34. Perneger TV. What's wrong with Bonferroni adjustments. BMJ (Clin Res ed). 1998;316(7139):1236–8.
35. Li S, An L, Fu Z, Zhang W, Liu H. Association between triglyceride-glucose related indices and all-cause and cause-specific mortality in the general population: a cohort study. Cardiovasc Diabetol. 2024;23(1):286.
36. Lopez-Jaramillo P, Gomez-Arbelaez D, Martinez-Bello D, Abat MEM, Alhabib KF, Avezum Á, 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.
37. Alavi Tabatabaei G, Mohammadifard N, Rafiee H, Nouri F, Maghami Mehr A, Najafian J, et al. Association of the triglyceride glucose index with all-cause and cardiovascular mortality in a general population of Iranian adults. Cardiovasc Diabetol. 2024;23(1):66.
38. Park K, Ahn CW, Lee SB, Kang S, Nam JS, Lee BK, et al. Elevated TyG index predicts progression of coronary artery calcification. Diabetes Care. 2019;42(8):1569–73.
39. He G, Zhang Z, Wang C, Wang W, Bai X, He L, et al. Association of the triglyceride-glucose index with all-cause and cause-specific mortality: a population-based cohort study of 3.5 million adults in China. Lancet Reg Health Western Pac. 2024;49:101135.
40. 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.
41. Min Y, Wei X, Wei Z, Song G, Zhao X, Lei Y. Prognostic effect of triglyceride glucose-related parameters on all-cause and cardiovascular mortality in the United States adults with metabolic dysfunction-associated steatotic liver disease. Cardiovasc Diabetol. 2024;23(1):188.
42. Zhou J, Huang H, Huang H, Peng J, Chen W, Chen F et al. Association of triglyceride-glucose index and its combination with adiposity-related indices with the incidence of myocardial infarction: a cohort study from the UK Biobank. Int J Obes (2005). 2024;48(10):1498–505.
43. 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 Off J Int Assoc Study Obes. 2012;13(3):275–86.
44. Yang D, Ma L, Cheng Y, Shi H, Liu Y, Shi C. Utility of anthropometric indexes for detecting metabolic syndrome in Resource-Limited regions of Northwestern China: cross-sectional study. JMIR Public Health Surveill. 2024;10:e57799.
45. Ramírez-Manent JI, Jover AM, Martinez CS, Tomás-Gil P, Martí-Lliteras P, López-González. Á A. Waist circumference is an essential factor in Predicting insulin resistance and early detection of metabolic syndrome in adults. Nutrients. 2023;15(2).
46. Zhu M, Wang K, Feng J, Liu Y, Guan M, Wang Y, et al. The waist-to-height ratio is a good predictor for insulin resistance in women with polycystic ovary syndrome. Front Endocrinol. 2024;15:1502321.
47. Yan S, Wang D, Jia Y. Comparison of insulin resistance-associated parameters in US adults: a cross-sectional study. Hormones (Athens Greece). 2023;22(2):331–41.
48. Lim J, Kim J, Koo SH, Kwon GC. Comparison of triglyceride glucose index, and related parameters to predict insulin resistance in Korean adults: an analysis of the 2007–2010 Korean National Health and Nutrition Examination Survey. PLoS ONE. 2019;14(3):e0212963.
49. Rangaswami J, Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation. 2019;139(16):e840–78.
50. Longo M, Zatterale F, Naderi J, Parrillo L, Formisano P, Raciti GA et al. Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. Int J Mol Sci. 2019;20(9).
51. Shen R, Lin L, Bin Z, Qiao X. The U-shape relationship between insulin resistance-related indexes and chronic kidney disease: a retrospective cohort study from National Health and Nutrition Examination Survey 2007–2016. Diabetol Metab Syndr. 2024;16(1):168.
52. Xiao S, Zhang Q, Yang HY, Tong JY, Yang RQ. The association between triglyceride glucose-body mass index and all-cause and cardiovascular mortality in diabetes patients: a retrospective study from NHANES database. Sci Rep. 2024;14(1):13884.
53. Pei J, Wang B, Wang D. Current studies on molecular mechanisms of insulin resistance. J Diabetes Res. 2022;2022:1863429.
54. Islam MS, Wei P, Suzauddula M, Nime I, Feroz F, Acharjee M, et al. The interplay of factors in metabolic syndrome: understanding its roots and complexity. Mol Med (Cambridge Mass). 2024;30(1):279.
55. Soták M, Clark M, Suur BE, Börgeson E. Inflammation and resolution in obesity. Nat Rev Endocrinol. 2025;21(1):45–61.
56. Gastaldelli A, Gaggini M, DeFronzo RA. Role of adipose tissue insulin resistance in the natural history of type 2 diabetes: results from the San Antonio Metabolism Study. Diabetes. 2017;66(4):815–22.
57. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. Nat Rev Cardiol. 2009;6(6):399–409.
58. Goldstein BJ, Scalia R, Adiponectin. A novel adipokine linking adipocytes and vascular function. J Clin Endocrinol Metab. 2004;89(6):2563–8.

59. Ni W, Jiang R, Xu D, Zhu J, Chen J, Lin Y, et al. Association between insulin resistance indices and outcomes in patients with heart failure with preserved ejection fraction. Cardiovasc Diabetol. 2025;24(1):32.
60. Sun R, Wang J, Li M, Li J, Pan Y, Liu B, et al. Association of insulin resistance with cardiovascular disease and all-cause mortality in type 1 diabetes: systematic review and meta-analysis. Diabetes Care. 2024;47(12):2266–74.
61. Peng J, Zhang Y, Zhu Y, Chen W, Chen L, Ma F, et al. Estimated glucose disposal rate for predicting cardiovascular events and mortality in patients with non-diabetic chronic kidney disease: a prospective cohort study. BMC Med. 2024;22(1):411.
62. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. Am J Epidemiol. 1999;150(4):341–53.
63. Dharmarathne G, Bogahawaththa M, Rathnayake U, Meddage DPP. Integrating explainable machine learning and user-centric model for diagnosing cardiovascular disease: a novel approach. Intell Syst Appl. 2024;23:200428.
64. Dharmarathne G, Bogahawaththa M, McAfee M, Rathnayake U, Meddage DPP. On the diagnosis of chronic kidney disease using a machine learning-based interface with explainable artificial intelligence. Intell Syst Appl. 2024;22:200397.
65. Dharmarathne G, Jayasinghe TN, Bogahawaththa M, Meddage DPP, Rathnayake U. A novel machine learning approach for diagnosing diabetes with a self-explainable interface. Healthc Anal. 2024;5:100301.

Publisher's note