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Association of the triglyceride–glucose index with all-cause and cardiovascular mortality among individuals with cardiovascular–kidney–metabolic syndrome: a population-based cohort study using data from the US National Health and Nutrition Examination Survey, 1999–2018

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ABSTRACT

Objective The study investigated the association between the triglyceride–glucose (TyG) index (a surrogate measure for insulin resistance) and all-cause and cardiovascular disease (CVD) mortality among individuals with cardiovascular–kidney–metabolic syndrome.

Design Population-based cohort study.

Setting US National Health and Nutrition Examination Survey, 1999–2018.

Participants A total of 13 585 participants who had valid data were included in this analysis.

Outcome measures Data from the participants were linked to death certificates to obtain follow-up mortality information from the National Death Index. Cox proportional hazards models were used to assess the associations between the TyG index and all-cause and CVD mortality. Non-linear associations and threshold effects were investigated using restricted cubic spline regression and a two-piecewise Cox proportional hazards model.

Results During a median follow-up of 99 months, a total of 2876 (16.24%) deaths occurred, of which 961 were attributed to CVD. Each one-unit increase in the TyG index was associated with an 8.9% relative increase in the hazard of all-cause mortality (HR 1.089, 95% CI 1.013 to 1.171) and a 19.5% relative increase in the hazard of CVD mortality (HR 1.195, 95% CI 1.027 to 1.390). Non-linear relationships were identified between the TyG index and all-cause and CVD mortality, with threshold values of 8.97 and 8.81 for all-cause and CVD mortality, respectively. A significant interaction effect was found between age and the TyG index.

Conclusion There was a U-shaped relationship between the TyG index and both all-cause and CVD mortality. The thresholds of the TyG index may serve as potential tools for managing populations with cardiovascular–kidney–metabolic syndrome to reduce mortality risk.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study used a large-scale, nationally representative population-based cohort.
⇒ The study only included participants with clinical cardiovascular–kidney–metabolic syndrome due to database limitations.
⇒ The triglyceride–glucose (TyG) index was calculated based on blood test results collected at a single point in time, which may not fully capture the effects of dynamic changes in the TyG index over time.

INTRODUCTION

Cardiovascular disease (CVD), chronic kidney disease (CKD) and metabolic diseases are the leading causes of morbidity and mortality worldwide.[1] The American Heart Association (AHA), recognising the complex interplay among these chronic conditions, has recently defined cardiovascular–kidney–metabolic (CKM) syndrome as a systemic disorder encompassing individuals both at risk for and already diagnosed with CVD.[2] CKM syndrome represents a convergence of cardiovascular, renal and metabolic dysfunctions, including hypertension, diabetes and dyslipidaemia.[2]

According to data from the National Health and Nutrition Examination Survey (NHANES) 2011–2020, nearly 90% of US adults met the criteria for CKM syndrome (stage 1 or higher), and 15% were classified in advanced stages.[3] Moreover, the prevalence of one or more CKM conditions in the USA increased from 21.2% to 26.3%, highlighting

a growing public challenge.[4] This underscores the urgent need to identify populations at high risk of mortality among CKM patients and develop clinical strategies to prevent adverse outcomes.

Insulin resistance (IR) is a critical factor in the pathogenesis and progress of CKM syndrome and is associated with adverse cardiovascular outcomes.[5 6] It is considered an independent risk factor for hypertension,[7] obesity,[8] diabetes,[9] CKD[10] and CVD,[11] which are conditions that collectively form CKM syndrome.

The triglyceride–glucose (TyG) index is a well-validated biomarker for IR based on fasting plasma glucose and triglycerides.[12] Pooled evidence has shown that a higher TyG index was associated with the poor prognosis of patients with hypertension,[13 14] diabetes,[15 16] coronary heart disease[17 18] and stroke.[19 20] However, research investigating the predictive ability of the TyG index in the CKM syndrome population remains limited.

To address this gap, we conducted a population-based cohort study to estimate the associations of the TyG index with all-cause and CVD mortality among patients with CKM syndrome, using data from NHANES from 1999 to 2018.

METHODS

Study population

The data were collected from the NHANES database. NHANES is a survey conducted by the National Centre for Health Statistics (NCHS), which is a part of the Centres for Disease Control and Prevention. It is a national representative study that assesses the health and nutritional status of the non-institutional US population. Detailed information is available at https://www.cdc.gov/nchs/nhanes/index.htm.

CKM syndrome is defined as clinical CVD—including coronary heart disease, heart failure (HF), stroke and peripheral artery disease—among individuals with excess or dysfunctional adiposity, other CKM risk factors or CKD, in accordance with the criteria set forth by the AHA presidential advisory.[2] Detailed descriptions of the definitions are shown in the supplementary material.

There are 59 204 individuals aged ≥18 years from 1999 to 2018. Participants without CKM syndrome (n=19 176), without data on the TyG index (n=26 403), and without mortality data (n=40) were excluded. Finally, 13 585 participants with available data were enrolled for further research (figure 1).

The National Health Statistics Research Ethics Review Board approved the NHANES research plan. All participants provided written informed consent. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guideline.[21]

Calculation of triglyceride–glucose index

Blood specimens were collected in the morning after fasting for at least 8.5 hours. Fasting triglycerides were measured enzymatically, whereas fasting glucose levels were measured with the hexokinase method. The TyG index was calculated as ln (fasting triglycerides [mg/dL] × fasting glucose [mg/dL]/2)].[12]

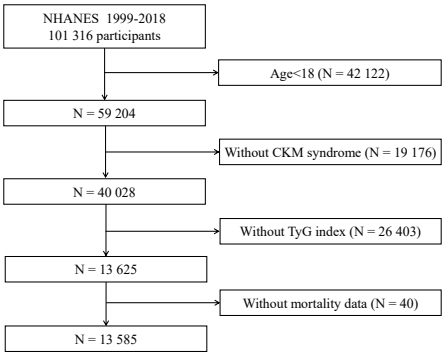

Figure 1 Study participant flowchart. TyG, triglyceride-glucose.

Assessment of outcome

The main outcome of this study was the all-cause mortality, which represents death from any cause. The second outcome was cardiovascular mortality, which refers to deaths caused by heart diseases (International Classification of Diseases 10th Revision [ICD-10] codes I00–I09, I11, I13 and I20–I51) and brain-related diseases (ICD-10 codes I60–I69). Data on deaths were collected from the NHANES and linked to death certificates from the National Death Index using a probability matching algorithm, covering deaths up to December 31, 2019.[22] The probabilistic matching algorithm used by the NCHS incorporates multiple identifying variables to calculate the likelihood of a correct match. These variables include, but are not limited to, the social security number, name, date of birth, sex, race/ethnicity and state of residence. The algorithm assigns weights to these variables based on their reliability and discriminatory power. A composite probability score is then calculated for each potential match, and matches with scores exceeding a predefined threshold are considered valid. This method minimises false positives and false negatives in the linkage process, ensuring high accuracy in mortality data.

Covariates

Covariates included age, sex (male or female), race (Mexican American, non-Hispanic black, non-Hispanic white, other Hispanic or other races), education (less than high school and equal or higher than high school), poverty–income ratio (PIR), body mass index (BMI, kg/m^2), smoking status (never, former or current) and drinking status (never, former or current). BMI was calculated as body weight (kg) divided by the square of height (m). To ensure that multicollinearity among covariates did not influence the results, variance inflation factors (VIFs) were calculated for all variables.

Statistical analysis

The statistical analyses for this study took into account sample weights, clustering and stratification because NHANES uses a complex, multi-stage survey design. The weighted statistical analysis was performed with the R package "survey" conforming to the guidelines of NHANES. These adjustments help ensure that the results accurately represent the US population.

The differences in baseline characteristics across quartiles of the TyG index were compared with one-way ANOVA (continuous variables) and $\chi 2$ tests (categorical variables). The results were displayed as means with SE and proportions for continuous and categorical variables, respectively.

We conducted weighted multivariable Cox proportional hazards regression modelling to explore the relationship of the TyG index with all-cause and CVD mortality. Model 1 was unadjusted. Model 2 was partially adjusted for age, sex and race. Model 3 was further adjusted for education, PIR, BMI, smoking status and drinking status. The results are presented as HRs with 95% CIs. Trends of increasing TyG quartiles were calculated by imputing median TyG levels of each quartile as a continuous variable in the model.

To illustrate the potential non-linear relationship between the TyG index and mortality, restricted cubic spline (RCS) regression models with five knots (at the 5th, 35th, 65th and 95th percentiles) were applied. The non-linearity was tested by using the likelihood ratio test.

Moreover, subgroup analyses were conducted, stratified by age (<60 or ≥60 years), sex (male or female), BMI (<25, 25–29.9 or ≥30 kg/m^2), hypertension (yes or no), diabetes (yes or no) and CKD (yes or no). The interaction effects were tested by incorporating interaction terms into the Cox regression models.

Missing values were input based on the random forest algorithm with the R package 'missForest'.[23] Statistical analyses were conducted using R software (version 3.6.1). A two-tailed P value<0.05 was considered statistically significant.

Patient and public involvement

None.

RESULTS

Baseline characteristics

The baseline characteristics of CKM participants across TyG quartiles (Q1, 5.65≤TyG index<8.39; Q2, 8.39≤TyG index<8.81; Q3, 8.81≤TyG index<9.23; Q4, 9.23≤TyG index≤13.40) are shown in table 1. Among 13 585 participants, the mean age was 53.35 years, and 49.67% of them were male. Participants with a higher TyG index were more likely to be male, current smokers and have higher BMI levels and lower family income and educational levels. The baseline characteristics of the excluded participants are shown in online supplemental table S1.

Our analysis revealed significant differences across all variables, indicating that the excluded participants may have distinct characteristics compared with those retained in the analysis.

Association of the TyG index with all-cause and CVD mortality

During a median follow-up of 99 months, a total of 2876 (16.24%) deaths occurred, of which 961 were attributed to CVD. In the univariable Cox analysis, a significantly positive association was found between the TyG index and all-cause and CVD mortality. The positive relationship remained after adjustment of covariates. VIFs for all covariates were below 10, indicating that multicollinearity was unlikely to influence the results. The fully adjusted HRs for the TyG index for all-cause and CVD mortality were 1.089 (1.013, 1.171) and 1.195 (1.027, 1.390), respectively. No significant association was found between quartiles of the TyG index and mortality (table 2).

Restricted cubic spline regression

RCS analyses revealed U-shaped associations between the TyG index and both all-cause and CVD mortality (P for non-linear <0.001, figure 2). Using a two-piecewise Cox proportional hazards regression model, we identified inflection points for the TyG index of 8.97 for all-cause mortality and 8.81 for CVD mortality. After adjusting for various covariates, we found that with the TyG index below these thresholds, the risk of all-cause mortality decreased by 20.9% (HR 0.791, 95% CI 0.662 to 0.945) per unit increase. Conversely, with the TyG index above the thresholds, the risk of all-cause mortality increased by 37.2% (HR 1.372, 95% CI 1.208 to 1.559) per unit increase. For CVD mortality, no significant association was observed with the TyG index below the threshold. However, for the TyG index above the threshold, the risk of CVD mortality increased by 56.7% (HR 1.567, 95% CI 1.311 to 1.877) per unit increase (table 3).

Subgroup analyses

To further explore the association between the TyG index and mortality across diverse subgroups, we stratified the CKM population by age, sex, BMI, hypertension, diabetes and CKD. After controlling for variables included in model 3, stratified analyses revealed that the TyG index was significantly associated with all-cause mortality in participants younger than 60 years, male participants, those with a BMI of 25–29.9 kg/m^2 and those with hypertension (figure 3A). A positive association between the TyG index and CVD mortality was found among participants younger than 60 years, maleparticipants, those with a BMI of 25–29.9 kg/m^2 and those with hypertension or diabetes (figure 3B). Additionally, significant interaction effects were found between the TyG index and age for both outcomes (p<0.001 for all-cause mortality, p=0.001 for CVD mortality).

Table 1 Weighted baseline characteristics of participants with CKM syndrome according to TyG quantiles

Characteristics	Overall	Quartile of the TyG index				P value
		Q1 (5.65–8.39)	Q2 (8.39–8.81)	Q3 (8.81–9.23)	Q4 (9.23–13.40)	
Age, years	53.35 (0.22)	52.18 (0.43)	54.55 (0.38)	53.87 (0.35)	52.77 (0.36)	<0.001
Sex, n (%)						<0.001
Female	6806 (50.33)	1844 (56.51)	1715 (50.95)	1767 (52.08)	1480 (41.82)	
Male	6779 (49.67)	1559 (43.49)	1674 (49.05)	1629 (47.92)	1917 (58.18)	
Race/ethnicity, n (%)						<0.001
Mexican American	2368 (7.73)	358 (5.69)	532 (7.31)	646 (7.81)	832 (10.08)	
Non-Hispanic black	2707 (11.29)	1198 (20.94)	677 (10.88)	475 (7.60)	357 (5.97)	
Non-Hispanic white	6210 (69.12)	1338 (62.69)	1585 (69.58)	1670 (72.13)	1617 (71.90)	
Other Hispanic	1154 (5.12)	228 (4.30)	292 (4.83)	325 (6.02)	309 (5.28)	
Other races	1146 (6.75)	281 (6.38)	303 (7.40)	280 (6.45)	282 (6.76)	
Education						0.012
Lower than high school	4111 (20.30)	879 (17.95)	978 (19.38)	1059 (20.42)	1195 (23.40)	
Equal or higher than high school, n (%)	9474 (79.70)	2524 (82.05)	2411 (80.62)	2337 (79.58)	2202 (76.60)	
PIR	2.88 (0.03)	2.96 (0.04)	2.89 (0.05)	2.85 (0.05)	2.84 (0.04)	0.060
BMI, kg/m^2	30.61 (0.10)	28.43 (0.20)	30.21 (0.15)	31.61 (0.18)	32.13 (0.15)	<0.001
Smoking status, n (%)						<0.001
Never	6947 (50.37)	1880 (54.92)	1763 (51.35)	1739 (49.98)	1565 (45.30)	
Former	3994 (29.29)	924 (26.55)	983 (29.34)	1004 (28.87)	1083 (32.38)	
Current	2644 (20.34)	599 (18.52)	643 (19.31)	653 (21.15)	749 (22.32)	
Drinking status, n (%)						<0.001
Never	2391 (14.41)	617 (14.96)	594 (14.22)	599 (14.42)	581 (14.05)	
Former	2784 (17.63)	624 (15.96)	667 (15.90)	707 (17.98)	786 (20.63)	
Current	8410 (67.96)	2162 (69.08)	2128 (69.88)	2090 (67.61)	2030 (65.32)	
Hypertension, n (%)	9059 (63.95)	2430 (66.82)	2350 (67.83)	2163 (60.50)	2116 (60.83)	<0.0001
Diabetes, n (%)	4047 (24.54)	523 (11.94)	755 (17.56)	1058 (25.94)	1711 (42.46)	<0.0001
CKD, n (%)	3882 (23.73)	983 (25.37)	947 (24.05)	897 (20.42)	1055 (25.20)	<0.0001
All-cause death, n (%)	2876 (16.24)	625 (14.00)	767 (16.38)	708 (15.90)	776 (18.67)	<0.0001
CVD-related death, n (%)	961 (5.12)	199 (4.16)	268 (5.42)	241 (4.89)	253 (6.01)	<0.0001

CKD, chronic kidney disease; CVD, cardiovascular disease; PIR, poverty–income ratio; TyG index, triglyceride–glucose index.

DISCUSSION

This study investigated the relationship between the TyG index and all-cause and CVD mortality among participants with CKM syndrome using data from NHANES 1999–2018. The RCS analysis revealed a non-linear, U-shaped association between the TyG index and mortality risks. Specifically, inflection points were identified at TyG indices of 8.97 for all-cause mortality and 8.81 for CVD mortality. Our findings suggest that the TyG index could serve as a potential surrogate biomarker for IR, aiding in the management of patients with clinical CKM syndrome.

Previous studies have reported that a higher TyG index was associated with increased risk of adverse events in patients with hypertension,[24] CVD,[25] diabetes[26] and CKD.[27] Our study extends this knowledge by providing a detailed analysis of the U-shaped relationship and establishing precise inflection points pertinent to CKM syndrome (all-cause mortality, 8.97; CVD mortality, 8.81). The observed U-shaped association is intriguing and warrants further exploration.

The TyG index has emerged as a reliable biomarker for assessing IR and metabolic disorders. Although higher levels of the TyG index are commonly associated with worse IR, extremely low levels have also been linked to metabolic impairment. The underlying mechanism may be related to the fact that an extremely low TyG index could reflect insufficient energy substrates for normal metabolic processes, as the index is calculated using both triglyceride and glucose levels. It is plausible that moderate levels of the TyG index reflect optimal metabolic function, whereas both high and low levels indicate underlying metabolic dysregulation, thereby contributing to increased mortality risks.

Table 2 HRs (95% CIs) for mortality according to the TyG index quartiles

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
All-cause mortality			
Continuous	**1.077 (1.004, 1.154)**	**1.161 (1.080, 1.249)**	**1.089 (1.013, 1.171)**
Categories			
Q1	Reference	Reference	Reference
Q2	1.050 (0.910, 1.211)	0.900 (0.794, 1.020)	0.866 (0.757, 0.991)
Q3	0.922 (0.798, 1.066)	**0.905 (0.784, 1.043)**	0.836 (0.726, 0.962)
Q4	1.070 (0.932, 1.228)	**1.115 (0.980, 1.268)**	0.988 (0.866, 1.129)
P for trend	0.573	0.042	0.837
CVD mortality			
Continuous	**1.124 (0.989, 1.278)**	**1.292 (1.119, 1.492)**	**1.195 (1.027, 1.390)**
Categories			
Q1	Reference	Reference	Reference
Q2	1.171 (0.914, 1.499)	1.021 (0.807, 1.291)	0.983 (0.770, 1.254)
Q3	0.954 (0.759, 1.199)	1.003 (0.808, 1.245)	0.913 (0.729, 1.143)
Q4	1.163 (0.900, 1.503)	**1.323 (1.037, 1.687)**	1.143 (0.883, 1.481)
P for trend	0.470	0.022	0.302

Model 1: unadjusted.
Model 2: adjusted for age, sex and race.
Model 3: further adjusted for education, poverty–income ratio, body mass index, smoking status and drinking status.
Bold values indicated statistical significance.
CVD, cardiovascular disease.

Similar to our study, other studies have also illustrated similar non-linear patterns in the relationship between the TyG index and mortality risk across various populations, including those with metabolic syndrome,[28] CVD[25] and diabetes.[26] These consistent findings reinforce the potential utility of the TyG index as a general biomarker for metabolic health and mortality risk. Understanding this common pathway provides a robust foundation for further research and may inform comprehensive risk assessment strategies aimed at improving clinical outcomes across a broad spectrum of metabolism-related diseases.

Moreover, our analysis revealed a significant interaction effect between the TyG index and age. Specifically,

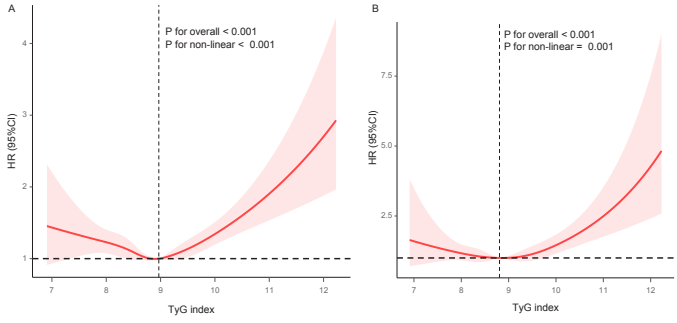

Figure 2 Multivariable adjusted restricted cubic spline curves for the associations of the TyG index with all-cause (A) and CVD mortality (B) in individuals with cardiovascular–kidney–metabolic syndrome. Adjusted for age, sex, race, education, poverty–income ratio, body mass index, smoking status and drinking status. The solid line and red area represent the estimated values and their corresponding 95% CI. TyG index, triglyceride-glucose index.

Table 3 Threshold effect analysis of the TyG index on all-cause and CVD mortality in participants with CKM syndrome

	HR (95% CI)
All-cause mortality	
Total	**1.089 (1.013, 1.171)**
Inflection point	8.97
TyG index <8.97	**0.791 (0.662, 0.945)**
TyG index >8.97	**1.372 (1.208, 1.559)**
P for log-likelihood ratio	<0.001
CVD mortality	
Continuous	**1.195 (1.027, 1.390)**
Inflection point	8.81
TyG index 8.81	0.811 (0.542, 1.212)
TyG index >8.81	**1.567 (1.311, 1.872)**
P for log-likelihood ratio	<0.001

Cox proportional hazards models were used to estimate the HR and 95% CI. Adjusted for age, sex, race, education, poverty–income ratio, body mass index, smoking status and drinking status.
Bold values indicated significance.
CKM syndrome, cardiovascular–kidney–metabolic syndrome; CVD, cardiovascular disease; TyG index, triglyceride–glucose index.

the association between the TyG index and mortality was evident only in participants younger than 60 years. This age-dependent variation is consistent with previous research on diabetic patients, which found that the TyG index did not hold significant prognostic value for older participants.[26] Moreover, we observed that approximately one-fourth of the participants with CKM syndrome were diabetic, with an average haemoglobin A1c level of 7.00%. This finding highlights the need for close monitoring and management of blood glucose levels in this population. Several factors may explain why older individuals with CKM syndrome do not exhibit a similar association. First, age-related physiological changes, such as alterations in body composition and metabolic function, might attenuate the relationship between the TyG index and mortality in older adults. Additionally, older individuals often have multiple comorbidities and are more likely to be on various medications that could influence metabolic markers, thereby obscuring the specific impact of the TyG index.

This study benefits from a robust design, leveraging nationally representative NHANES data and employing rigorous statistical methods to elucidate complex relationships. The comprehensive adjustment for a wide array of covariates enhances the credibility of our findings.

However, several limitations need to be acknowledged. First, the observational nature of the study precludes causal inferences. Second, due to the limited information in the NHANES database, we only included participants with clinical CKM syndrome. Further research should aim to explore the relationship between the TyG index and mortality in various statuses of CKM syndrome, therefore providing more evidence for clinical management and treatment of CKM patients. Third, the TyG index was calculated based on blood test results collected at a single point in time, which may not fully capture the effects of dynamic changes in the TyG index over time. Fourth, residual confounding cannot be entirely ruled out despite extensive adjustments. Fifth, the comparison between the included and excluded participants indicated that the missing data may not be completely

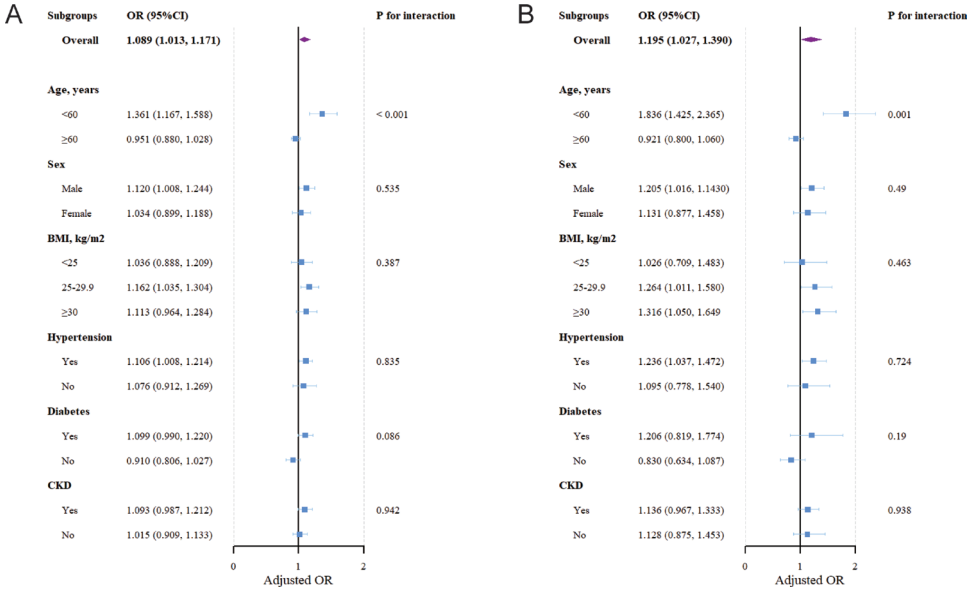

Figure 3 Subgroup analysis of the association between the TyG index and all-cause (A) and CVD mortality (B) in individuals with CKM syndrome. Adjusted for age, sex, race, education, poverty–income ratio, body mass index, smoking status, and drinking status. CKD, chronic kidney disease; TyG index, triglyceride–glucose index.

random, and the exclusion of these participants could potentially introduce selection bias. This may affect the generalisability of the results.

CONCLUSION

This study elucidates the intricate, non-linear relationship between the TyG index and mortality outcomes in individuals with CKM syndrome. The discerned U-shaped associations highlight critical inflection points that are instrumental in refining risk stratification and guiding clinical management. These results suggest the necessity for age-specific assessments and tailored interventions to mitigate mortality risks associated with varying TyG index levels. Further research is warranted to unravel the mechanistic underpinnings and explore the utility of the TyG index in broader clinical contexts.

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Contributors SZ: data analysis, software, writing original draft, writing—reviewing and editing. JD: conceptualisation, funding acquisition and writing—reviewing and editing. All authors have contributed to the article and approved the submitted version. JD is the guarantor. Yes, AI was used for polishing the manuscript and checking grammar.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The protocol for NHANES was approved by the National Center for Health Statistics and Ethics Review Board. All participants provided written informed consent. As this is a secondary analysis, no further ethics approval was required for the present analysis.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Publicly available datasets were analysed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/

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