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Opposite outcomes of triglyceride-glucose index and associated cardiovascular mortality risk in type 2 diabetes mellitus participants by different obesity criteria

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We investigated the correlation between Triglyceride-glucose (TyG) index and cardiovascular disease (CVD) mortality in type 2 diabetes mellitus (T2DM) population across different obesity classications using a cohort study. We analyzed 7867 T2DM participants from the National Health and Nutrition Examination Survey 1999–2018, categorizing them into obese or non-obese group by body mass index (BMI) and waist circumference (WC). Cox regression models were used to estimate the correlation between TyG index and CVD mortality risk, comparing the results across the two obesity classifications. Over a 9.1-year follow-up, 691 CVD deaths occurred. Among non-obese T2DM participants (BMI-defined), the hazard ration for CVD mortality was 1.73 in the fourth quartile group of TyG index compared with the first quartile group. Conversely, among obese T2DM participants (WC-defined), the fourth quartile group of TyG index held a 1.51-fold risk of CVD mortality compared with the first quartile group. The association between obesity and higher CVD risk was observed in WC-defined obesity but not in BMI-defined obesity. A totally opposite relationship appeared between TyG index and CVD mortality based on how obesity was defined using BMI or WC in the T2DM participants, suggesting a reevaluation of BMI's accuracy in predicting mortality risk.

Keywords Triglyceride-glucose index, Cardiovascular diasease mortality, Obesity, Type 2 diabetes mellitus

Cardiovascular disease (CVD) is a substantial contributor to death in people with type 2 diabetes mellitus (T2DM). T2DM patients had a twofold greater risk of all-cause mortality and a threefold higher risk of CVD-related mortality than non-diabetics[1]. Therefore, lowering the risk of CVD in T2DM patients is of critical importance.

Insulin resistance (IR) constitutes one of the primary mechanisms underlying T2DM. More and more evidence suggest that IR and its associated diseases accelerate the development of CVD in T2DM patients[2]. Homeostatic model assessment of insulin resistance (HOMA-IR) and TyG index are biomarkers of IR and used to evaluate CVD risk. Multiple investigations have indicated that TyG index may serve as a superior predictor of the risk of T2DM and CVD[3–5]. TyG index is calculated using the formula: Ln(fasting triglycerides (mg/dl)×fasting blood glucose (mg/dl)/2)[6]. As TyG is a simple and easily calculable index, it has become an important tool to evaluate the risks of cardiometabolic disorders. Obesity is also an important risk factor for adverse cardiovascular outcomes. T2DM patients with obesity have more obvious IR and significantly increased TyG index[7–10]. However, an increasing body of research has indicated that under different obesity classification criteria, obese people with T2DM do not always maintain a high risk of adverse cardiovascular outcomes. Yang observed a positive linear association between body mass index (BMI) and the incidence of CVD but a non-linear correlation with CVD-related mortality in T2DM patients[11]. The lowest mortality risk was observed around a BMI of approximately 28.4 kg/m^2, with increased risks for mortality at both lower and higher BMI values according to their meta-analysis of previous clinical studies. Xing discovered that waist circumference (WC) is linked to major adverse cardiovascular events in male people with T2DM, but not in female people[12].

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Li found that CVD-related mortality increased monotonically with the increase in a body shape index (ABSI) in T2DM patients[13]. Therefore, we believe that there is a correlation between T2DM individuals' obesity levels and death from CVD. Furthermore, distinct classification criteria may provide varying outcomes and possess their own limitations.

However, there is insufficient research on the correlation between TyG index and CVD-related mortality risk in T2DM patients with or without obesity under different obesity classification criterias at present. As a consequence, we categorized the T2DM participants into non-obese and obese group based on different classifications (BMI/WC) to examine the correlation between TyG index and CVD-related mortality in the above groups of participants.

Research design and methods

Study population

In this study conducted using a cross-sectional design, we integrated data from all National Health and Nutrition Examination Surveys (NHANES) conducted between 1999 and 2018. After excluding pregnant females ($N=43$), participants without monitoring period or with a monitoring period of 0 month ($N=21$) and participants lacking TyG index ($N=812$), a total of 7867 T2DM participants (aged ≥ 20 years) were enrolled in the final data analysis. There were 4144 males and 3723 females.

Measurement and definitions

Definition of T2DM

Diabetes was defined based on the recent American Diabetes Association (ADA) recommendation, where the condition was considered met if any of the following conditions were met[14]: (1) Prior diagnosis of T2DM by physicians (2) HbA1c levels were at least 48 mmol/mol (6.5%) (3) Fasting blood glucose levels were at least 7.0 mmol/L (126 mg/dL) (4) Any blood glucose levels were at least 200 mg/dL (11.1 mmol/L) (5) Postprandial 2 h plasma glucose levels were at least 11.1 mmol/L (200 mg/dL) after a standard 75-g oral glucose tolerance test (6) Treated with insulin or hypoglycemic medications. People potentially diagnosed with type 1 diabetes mellitus (T1DM) were identified as individual under 20 years of age who exclusively received insulin therapy[15].

Measurement of main variables

Height (m) and weight (kg) were measured in the Mobile Examination Center (MEC) by trained health technicians. BMI was computed as weight divided by the square of height (kg/m^2)[16]. Obesity was considered when BMI ≥ 30 kg/m^2. WC was measured to the nearest 0.1 cm at the midpoint between the bottom of the rib cage and the uppermost border of the iliac crests, with participants in a standing position and using an inelastic tape measure at the end of exhalation[16]. Abdominal obesity was defined as WC measurements ≥ 102 cm for males and ≥ 88 cm for females. TyG index is determined by taking the natural logarithm of the product of fasting triglycerides (mg/dl) and fasting blood glucose, divided by two[6].

Ascertainment of mortality

We obtained mortality data directly from NHANES-linked mortality files[17]. Probabilistic matching was performed by the National Centre for Health Statistics to connect NHANES data with death certificate records from the National Death Index (NDI) records to assess mortality status[17]. CVD-related mortality was defined as mortality attributed to heart diseases or cerebrovascular diseases, as documented in prior studies[17].

Definition of other variables

For the demographic variables, race was categorized as Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black and Other Race. Education levels were classified as less than high school, high school, more than high school and not recorded. The poverty to income ratio (PIR) (≤ 1, 1< PIR<4 and ≥ 4) was computed by dividing family (or individual) income by the poverty guidelines applicable to the survey year and state[18]. Smoking habit was categorized as follows: current smokers (average of ≥ 1 cigarette per day), past smokers (average of < 1 cigarette per day or ≥ 100 cigarettes in their lifetime but currently not smoking), and never smokers (fewer than 100 cigarattes in their lifetime or never smoked). Alcohol consumption was categorized into three categories based on whether respondents reported consuming at least 12 drinks per year and whether their responses were recorded[19]. Dietary intake, including total energy, carbonhydrate, protein and fat, was evaluated using two 24-h recalls (one conducted in person and another by telephone 3–10 days later)[19]. Participants were classified into two groups based on whether they had total physical activity ≥ 500 MET- min/week according to established guidelines[20]. eGFR was calculated by the CKD-EPI creatinine equation. The presences of hypertension, hypercholesterolemia, CVD and cancer were defined by self-reporting[21].

Statistical processing and analyses

Unavailable categorical covariates were defined as a separate category as necessary, while unavailable continuous covariates were imputed with group means to mitigate potential bias from missing data. During the initial data assessment phase, the study cohort was stratified into non-obese group and obese group based on BMI or WC. We utilized means ± SEs to summarize continuous variables, and presented numbers (percentages) to depict categorical variables. A t-test or non-parametric test was used to analyze the differences in continuous variables among groups. The categorical variables were evaluated using the chi-square test. TyG index was considered as a variable with continuous data (natural log-transformed) and stratified into four quartile groups(Q1, Q2, Q3 and Q4). Cox proportional hazards models were employed to determine the hazard ratios (HRs) and 95% confidence intervals (CIs) of the TyG index in relation to the CVD-related mortality, adjusting for gender, age,

race, PIR, educational level, smoking status, alcohol consumption, physical activity, diabetes duration, CVD, chronic kidney disease (CKD), cancer, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), and BMI. We utilized a restricted cubic spline regression model to investigate the possible nonlinear relationship between TyG index and CVD-related mortality. Subsequently, a subgroup analysis of participants with or without CVD was performed. Sensitivity analyses were also performed with additional adjustment for the diet-related index and renal function index. Furthermore, we excluded the participants who died within the first 2 years of the survey ($n = 781$) to mitigate potential bias. All statistical analyses were conducted using R (The R Foundation; version 4.1.1) and EmpowerStats software (X&Y Solutions, Inc., Boston, MA, United States).

Results

Study population characteristics

Tables 1 and 2 detail the clinical profiles of the 7867 participants suffering from T2DM included in our study. The participant cohort was classified into two groups based on BMI or WC. TyG index remained consistently high in the obese group whatever the method of estimation. In addition, age, sex, race, education level, smoking status, alcohol consumption, uric acid, blood creatinine, diabetes duration, and history of hypertension remained significantly different in either classification. Except that age was lower in the obese-group defined by BMI and higher in the obese-group defined by WC, the above indicators were consistent. The prevalence of CVD did not show significantly differences between the two groups defined by BMI; however, this was notably elevated among participants classified as obese based on WC.

Association of TyG Index with CVD-related mortality

The average follow-up duration for the entire cohort was 9.1 years. By the end of the monitoring period, 691 participants had died from CVD. Among 3,569 obese and 4,298 non-obese T2DM participants defined by BMI, 316 and 375 participants died due to CVD respectively. Among obese and non-obese T2DM participants defined by WC, 524 and 167 participants died due to CVD respectively.

Cox regression analyses were performed to investigate the correlation between TyG index and mortality related to CVD in participants with T2DM. The results showed that in the non-obese group of T2DM participants defined by BMI, the HR and 95%CI of CVD-related mortality across the quartiles of TyG index was 1.0 (reference), 1.05 (0.77, 1.43), 1.05 (0.77, 1.43) and 1.73 (1.26, 2.40) ($p < 0.001$). When examining TyG index as a variable with continuous values, each 1 unit increase in TyG index was associated with a 36% higer risk of mortality related to CVD. Nevertheless, in the obese T2DM group defined by BMI, TyG index, either as continuous or categorical variables, showed no association with CVD-related mortality (Table 3).

When grouped by WC, the outcome was strikingly opposite. In obese group of T2DM participants defined by WC, the HR of CVD-related mortality across the quartiles of TyG index was 1.0 (reference), 1.12 (0.86, 1.45), 1.23 (0.95, 1.59) and 1.51 (1.14, 1.99) ($p = 0.004$). When examining TyG index as a variable with continuous values, every 1 unit increase in TyG index was associated with a 28% increase in CVD-related mortality. No significant correlations were observed in non-obese T2DM participants defined by WC (Table 4).

Non-linearity of TyG Index with CVD-related mortality

Non-linear associations were noted between the log-transformed TyG index and CVD-related mortality in both non-obese T2DM participants categorized by BMI and obese participants categorized by WC after covariate adjustments (log likelihood ratio test, both $p < 0.05$) (Fig. 1). Based on the results of the two-piecewise Cox proportional hazards regression models, we obtained the inflection points for CVD-related mortality as 8.5 and 8.2, respectively. When TyG index < 8.5, CVD-related mortality decreased with the increase of TyG index among non-obese T2DM participants defined by BMI. When TyG index < 8.2, no apparent correlation observed among obese T2DM participants defined by WC. When TyG index ≥ 8.5/8.2, the increase of TyG index was significantly positively associated with CVD-related mortality (Table 5). With regard to subgroup analysis, the results obtained remained consistent with the above study. The associations of TyG index with CVD-related mortality were not modified by CVD comorbidities (Table 6).

Sensitivity analyses

We performed additional adjustments for total energy intake (kcal), carbohydrate percentage (Car%), and fat percentage (Fat%) to account for potential confounding effects of dietary habits. Despite these adjustments, the relationship between TyG index and CVD-related mortality remained largely unchanged, indicating that dietary factors did not significantly influence the observed association (as detailed in Supplementary Tables 1 and Table 2). We also adjusted for renal function markers such as uric acid (UA), serum creatinine (Scr), and estimated glomerular filtration rate (eGFR) to control for the impact of renal health on CVD mortality risk. The results showed consistency, further validating the robustness of our findings. After further excluding paiticipants who died within two years of follow-up, the overall results were not significantly changed (Supplementary Table 3).

Discussion

T2DM is a metabolic disorder with a high prevalence, which has become a global health problem. Reducing the exponential increase in CVD-related mortality remains challenging. IR is a critical factor in the onset of CVD among people with T2DM[2]. TyG index, derived from TG-FPG, is currently being studied as a reliable alternative to IR. Considering the relationship between obesity and IR, we aim to elucidate the predictive value of TyG index for CVD-related mortality in T2DM people with different types of obesity.

Characteristic	T2DM participants defined by BMI		*p* value
	Non-obese (*n* = 3569)	Obese (*n* = 4298)	
Age (years)	60.82 ± 0.36	56.50 ± 0.28	< 0.001
Male (%)	2128 (59.62)	1441 (40.38)	< 0.001
Race (%)			< 0.001
Mexican American	735 (20.59)	871 (20.27)	
Other Hispanic	336 (9.41)	404 (9.40)	
Non-Hispanic White	1250 (35.02)	1627 (37.85)	
Non-Hispanic Black	709 (19.87)	1180 (27.45)	
Other Race	539 (15.11)	216 (5.03)	
Education level (%)			< 0.001
Less than high school	1390 (38.95)	1493 (34.74)	
High school	793 (22.21)	982 (22.85)	
More than high school	1379 (38.64)	1819 (42.32)	
Not recorded	7 (0.20)	4 (0.09)	
PIR (%)			0.087
≤1	732 (20.51)	891 (20.73)	
>1, <4	1816 (50.88)	2201 (51.21)	
≥4	633 (17.74)	809 (18.82)	
Not recorded	388 (10.87)	397 (9.24)	
Smoking status (%)			0.001
Current	620 (17.37)	622 (14.47)	
Past	1246 (34.91)	1500 (34.90)	
Never	1703 (47.72)	2176 (50.63)	
Alcohol consumption (%)			< 0.001
Yes	2029 (56.85)	2410 (56.07)	
No	1265 (35.44)	1637 (38.09)	
Not recorded	275 (7.71)	251 (5.84)	
Nutritional intake			
Total energy (kcal/day)	1893.11 ± 19.19	1977.48 ± 18.58	< 0.001
Carbohydrate (% of energy)	48.47 ± 0.23	46.97 ± 0.20	< 0.001
Protein (% of energy)	16.57 ± 0.12	16.74 ± 0.09	0.232
Fat (% of energy)	34.35 ± 0.19	36.03 ± 0.17	< 0.001
Physical activity (%)			0.065
< 500 (MET-min/week)	1884 (52.79)	2190 (50.95)	
≥ 500 (MET-min/week)	381 (10.68)	429 (9.98)	
Not recorded	1304 (36.53)	1679 (39.07)	
TyG index	9.27 ± 0.02	9.43 ± 0.02	< 0.001
BMI (kg/m^2)	26.07 ± 0.06	36.95 ± 0.14	< 0.001
Waist circumference (cm)	96.18 ± 0.22	119.30 ± 0.29	< 0.001
FPG (mmol/L)	8.52 ± 0.09	8.48 ± 0.07	0.764
HbA1c (%)	7.01 ± 0.04	7.18 ± 0.03	0.003
SBP (mmHg)	130.94 ± 0.50	130.06 ± 0.42	0.175
TC (mmol/L)	4.97 ± 0.03	4.92 ± 0.02	0.250
TG (mmol/L)	2.20 ± 0.06	2.39 ± 0.04	0.008
UA (umol/L)	322.26 ± 2.17	349.61 ± 2.24	< 0.001
Scr (umol/L)	87.47 ± 1.27	82.36 ± 0.74	< 0.001
eGFR (ml/min/1.73 m^2)	79.52 ± 0.66	82.36 ± 0.56	< 0.001
Diabetes duration ≥ 10 years (%)	1008 (28.24)	1174 (27.32)	< 0.001
Take insulin	566 (15.86%)	858 (19.96%)	< 0.001
Continued			

Characteristic	T2DM participants defined by BMI		p value
	Non-obese ($n = 3569$)	Obese ($n = 4298$)	
Hypertension (%)	1982 (55.53)	2923 (68.01)	< 0.001
Hypercholesterolemia (%)	1821 (51.02)	2271 (52.84)	0.109
CKD (%)	931 (26.09)	1021 (23.76)	0.017
CVD (%)	757 (21.21)	977 (22.73)	0.105
Cancer (%)	460 (12.89)	500 (11.63)	0.090

Table 1. Characteristics of the T2DM participants defined by BMI. Data were adjusted for survey weights of NHANES. Continuous variables are presented as means ± SEs. Categorical variables are presented as numbers (percentages). *T2DM* type 2 diabetes mellitus, *BMI* body mass index, *PIR* poverty-income ratio, *TyG index* triglyceride-glucose index, *FPG* fasting plasma glucose, *HbA1c* hemoglobin A1c, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglycerides, *UA* uric acid, *Scr* serum creatinine, *eGFR* estimate glomerular filtration rate, *CKD* chronic kidney disease, *CVD* cardiovascular disease.

We obtained the opposite conclusion regarding the correlation between TyG index and CVD-related mortality under different obesity diagnostic criterias. In BMI-defined non-obesity, TyG index was positively associated with CVD-related mortality, whereas in WC-defined obesity, TyG index was significantly associated with CVD-related mortality. An overview map of the results is presented in Fig. 2. Based on the findings from this study, the following points need to be considered. First, the limitations of BMI as the obesity classification index. BMI cannot scientifically represent obesity status. In fact, it cannot distinguish between body fat and lean mass, as well as central and peripheral fat[22]. That is the so-called obesity paradox we often discuss nowadays. For instance, athletes with increased muscle mass may be misclassified as obese when using BMI alone to diagnose obesity[22]. Similar with our results, a recent retrospective study showed the increased cardiometabolic risk in children and adolescents without obesity defined by BMI but with obesity defined by BF%[23]. Another study also demonstrated that BMI-classified obesity conferred a false mortality risk in people with CKD when compared with different indicators defining obesity[24]. Beside of this, we speculated that the non-obese participants defined by BMI might be metabolically obese but had normal weight (MONW). In the baseline characteristics of our study, BMI-defined non-obese T2DM participants were more likely to have a worse metabolic status such as higher prevalence of current smokers, CKD, and were older than obese T2DM participants. Second, WC might serve as a better indicator for diagnosing abdominal obesity in diabetes and predicting CVD risk[25,26]. It can detect individuals with lower body weight but increased ectopic fat accumulation[27,28]. Compared with non-obese T2DM participants, which includes a significant number of MONW individuals, non-obese T2DM participants classified based on WC should have less abdominal fat and mild IR. Numerous studies have proved that WC is an independent risk factor for obesity-related CVD in both European, American and Asian populations[29–32]. A recent meta-analysis from the British Medical Journal (BMJ) also confirmed the notion that central fatness index were positively associated with higher mortality risk, independent of overall adiposity defined by BMI[33]. And finally, TyG index is a more precise indicator of IR in people with central obesity than general obesity[34,35]. TyG index is proposed as an alternative to IR assessment and calculated from triglycerides and fasting glucose levels. In central obesity populations, the abnormalities in lipid and glucose metabolism may be more pronounced, potentially linked to exacerbated visceral fat inflammation, abnormal adipokine secretion, and hepatic fat accumulation[36,37]. Higher levels of IR are closely associated with an increased risk of CVD[38,39].

Therefore, in the centrally obese T2DM population, TyG index can be a powerful indicator to assess CVD risk due to its special fat distribution characteristics and metabolic abnormalities. Consistent with our findings, research has indicated that TyG index mediated the correlation between general and central obesity and CVD risk, with a stronger predictive value in central obesity populations[40]. Overall, our study suggested that in clinical practice, relying solely on the BMI definition without considering fat distribution patterns when using the simple TyG index to predict CVD risk related to obesity in T2DM individuals could lead to misleading outcomes.

Our results also showed a non-linear association between TyG index and CVD-related mortality in obese T2DM participants defined by WC. Only when TyG index ≥ 8.2, positive correlation can be observed. The results suggest us that for people with central obesity, controlling the level of TyG index within 8.2 may be valuable for reducing the risks of CVD-related mortality. Although we have also obtained the corresponding TyG index risk cut point in non-obese T2DM participants defined by BMI, considering the non-obese population and the defects of BMI itself, the clinical significance may be less significant .

Innovation points and limitations

In our conventional view, obese people with T2DM should have a greater CVD risk than non-obese people since pronounced IR. However, our study is the first to demonstrate that when the classification criteria of obesity were different, TyG index, an IR indicator, showed significant difference with CVD-related mortality in obese people. Again, this demonstrated that the limitations of BMI as a classification criterion for obesity in research and clinical practice. Further, finding of the threshold of TyG index for predicting the CVD-related death in obese T2DM patients by WC definition might provide guidance for clinical practice. Certainly, there were some limitations in our study. Firstly, obesity was not distinguished by BF%, which may be more accurate than BMI and WC. Secondly, we used the fasting TG level captured at one time to measure TyG index which could not objectively represent the IR status of participants and need further investigations in the future. Additionally, the

Characteristic	T2DM participants defined by WC		*p* value
	Non-obese (*n* = 1833)	Obese (*n* = 6034)	
Age (years)	57.28 ± 0.52	58.54 ± 0.26	0.024
Male (%)	1428 (77.91)	2716 (45.01)	< 0.001
Race (%)			< 0.001
Mexican American	391 (21.33)	1215 (20.14)	
Other Hispanic	181 (9.87)	559 (9.26)	
Non-Hispanic White	525 (28.64)	2352 (38.98)	
Non-Hispanic Black	376 (20.51)	1513 (25.07)	
Other Race	360 (19.65)	395 (6.55)	
Education level (%)			0.011
Less than high school	717 (39.12)	2166 (35.90)	
High school	379 (20.68)	1396 (23.14)	
More than high school	732 (39.93)	2466 (40.86)	
Not recorded	5 (0.27)	6 (0.10)	
PIR (%)			0.180
≤ 1	367 (20.02)	1256 (20.82)	
> 1, <4	937 (51.12)	3080 (51.04)	
≥ 4	323 (17.62)	1119 (18.54)	
Not recorded	206 (11.24)	579 (9.60)	
Smoking status (%)			< 0.001
Current	371 (20.24)	871 (14.43)	
Past	634 (34.59)	2112 (35.01)	
Never	828 (45.17)	3051 (50.56)	
Alcohol consumption (%)			< 0.001
Yes	1112 (60.67)	3327 (55.14)	
No	571 (31.15)	2331 (38.63)	
Not recorded	150 (8.18)	376 (6.23)	
Nutritional intake			
Total energy (kcal/day)	2021.44 ± 26.40	1922.43 ± 16.50	0.002
Carbohydrate (% of energy)	48.26 ± 0.30	47.42 ± 0.18	0.020
Protein (% of energy)	16.78 ± 0.16	16.64 ± 0.08	0.403
Fat (% of energy)	33.91 ± 0.25	35.70 ± 0.15	< 0.001
Physical activity (%)			< 0.001
< 500 (MET-min/week)	1031 (56.25)	3043 (50.43)	
≥ 500 (MET-min/week)	226 (12.33)	584 (9.68)	
Not recorded	576 (31.42)	2407 (39.89)	
TyG index	9.20 ± 0.03	9.40 ± 0.02	< 0.001
BMI (kg/m^2)	24.72 ± 0.10	34.42 ± 0.13	< 0.001
Waist circumference (cm)	90.30 ± 0.27	114.70 ± 0.27	< 0.001
FPG (mmol/L)	8.64 ± 0.12	8.46 ± 0.06	0.152
HbA1c (%)	7.02 ± 0.06	7.13 ± 0.03	0.060
SBP (mmHg)	129.52 ± 0.62	130.65 ± 0.38	0.118
TC (mmol/L)	4.96 ± 0.05	4.94 ± 0.02	0.743
TG (mmol/L)	2.12 ± 0.10	2.36 ± 0.04	0.027
UA (umol/L)	318.28 ± 3.15	343.41 ± 1.88	< 0.001
Scr (umol/L)	89.17 ± 1.91	83.27 ± 0.70	0.003
eGFR (ml/min/1.73 m^2)	82.04 ± 1.12	80.96 ± 0.48	0.376
Diabetes duration ≥ 10 years (%)	489 (26.68)	1693 (28.06)	< 0.001
Take insulin	278 (14.76%)	1146 (18.99%)	< 0.001
Continued			

Characteristic	T2DM participants defined by WC		*p* value
	Non-obese ($n = 1833$)	Obese ($n = 6034$)	
Hypertension (%)	877 (47.85)	4028 (66.76)	< 0.001
Hypercholesterolemia (%)	863 (47.08)	3229 (53.51)	< 0.001
CKD (%)	434 (23.68)	1518 (25.16)	0.199
CVD (%)	355 (19.37)	1379 (22.85)	0.002
Cancer (%)	191 (10.42)	769 (12.74)	0.008

Table 2. Characteristics of the T2DM participants defined by WC. Data were adjusted for survey weights of NHANES. Continuous variables are presented as means ± SEs. Categorical variables are presented as numbers (percentages). *T2DM* type 2 diabetes mellitus, *BMI* body mass index, *PIR* poverty-income ratio, *TyG index* triglyceride-glucose index, *FPG* fasting plasma glucose, *HbA1c* hemoglobin A1c, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglycerides, *UA* uric acid, *Scr* serum creatinine, *eGFR* estimate glomerular filtration rate, *CKD* chronic kidney disease, *CVD* cardiovascular disease.

	Non-obese participants defined by BMI		Obese participants defined by BMI	
	HR (95%CI)[a]	*p* value	HR (95%CI)[a]	*p* value
CVD-related mortality				
Q1	1.00		1.00	
Q2	1.05 (0.77, 1.43)	0.751	0.91 (0.65, 1.26)	0.568
Q3	1.05 (0.77, 1.43)	0.755	0.99 (0.71, 1.37)	0.947
Q4	1.73 (1.26, 2.40)	< 0.001	1.18 (0.83, 1.67)	0.358
Per 1 unit increment	1.36 (1.17, 1.58)	< 0.001	1.13 (0.95, 1.34)	0.166

Table 3. Multivariate Cox regression analysis of TyG index with CVD-related mortality among 7867 T2DM participants defined by BMI. *BMI* body mass index, *HR* hazard ratio, *CI* confidence interval, *CVD* cardiovascular disease. [a]Adjusted for gender, age, race, PIR, educational level, smoking status, alcohol consumption, physical activity, diabetes duration, CVD, CKD, cancer, HDL-C, SBP and BMI.

	Non-obese participants defined by WC		Obese participants defined by WC	
	HR (95%CI)[a]	*p* value	HR (95%CI)[a]	*p* value
CVD-related mortality				
Q1	1.00		1.00	
Q2	0.83 (0.51, 1.32)	0.426	1.12 (0.86, 1.45)	0.408
Q3	0.71 (0.44, 1.13)	0.149	1.23 (0.95, 1.59)	0.110
Q4	1.40 (0.88, 2.22)	0.154	1.51 (1.14, 1.99)	0.004
Per 1 unit increment	1.22 (0.98, 1.52)	0.081	1.28 (1.12, 1.46)	< 0.001

Table 4. Multivariate Cox regression analysis of TyG index with CVD-related mortality among 7867 T2DM participants defined by WC. *WC* waist circumference, *HR* hazard ratio, *CI* confidence interval, *CVD* cardiovascular disease. [a]Adjusted for gender, age, race, PIR, educational level, smoking status, alcohol consumption, physical activity, diabetes duration, CVD, CKD, cancer, HDL-C, SBP and BMI.

study did not provide data on weight trajectory during the follow-up period, making it impossible to rule out the potential impact of weight loss due to uncontrolled diabetes on cardiovascular disease risk.

Conclusion

We found that under different obesity classification criterias for T2DM participants (systemic obesity defined by BMI and central obesity defined by WC), the relationship between TyG index and CVD-related mortality showed a completely opposite trend. BMI should be used cautionly when evaluating CVD risk in obese individuals.

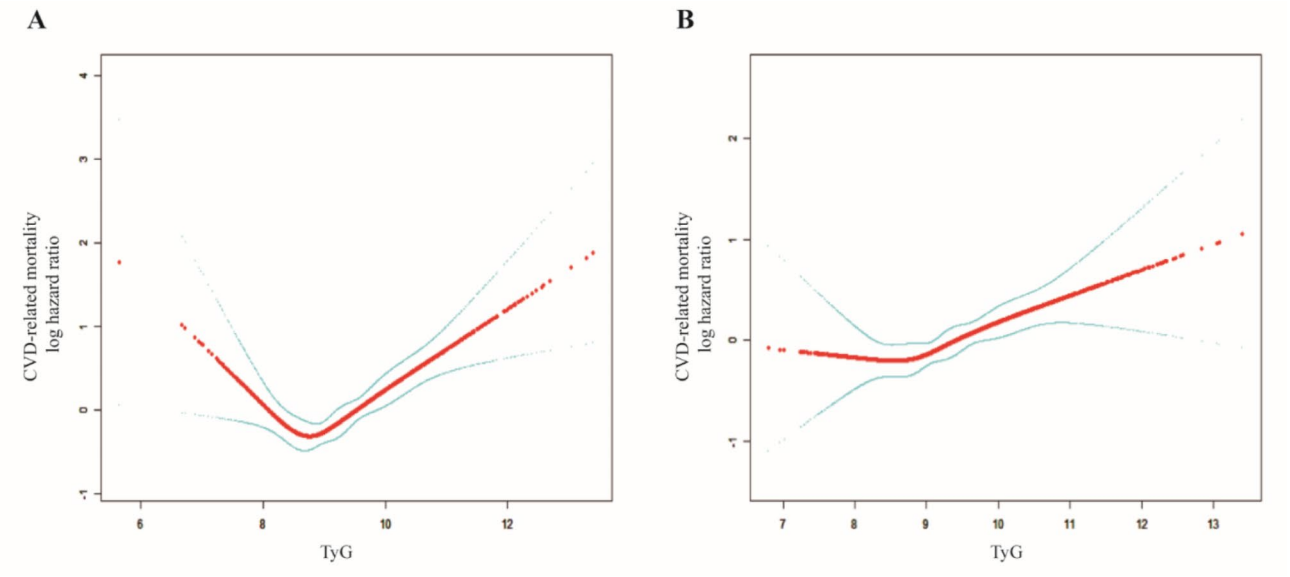

Fig. 1. The restricted cubic regression between TyG index with CVD-related mortality among the non-obese T2DM participants defined by BMI (**A**) or among the obese T2DM participants defined by WC (**B**). Models are adjusted for gender, age, race, PIR, educational level, smoking status, alcohol consumption, physical activity, diabetes duration, CVD, CKD, cancer, HDL-C, SBP and BMI.

	The non-obese paticipants defined by BMI	The obese participants defined by WC
CVD-related mortality		
Fitting by the two-piecewise linear model		
Inflection point	8.5	8.2
TyG index < 8.5/8.2	0.41 (0.24, 0.71) 0.002	0.37 (0.13, 1.07) 0.067
TyG index ≥ 8.5/8.2	1.58 (1.34, 1.85) <0.001	1.32 (1.15, 1.51) <0.001
p value for Log-likelihood ratio	< 0.001	0.04

Table 5. Threshold effect analysis of TyG index on CVD-related mortality in non-obese T2DM participants defined by BMI and obese T2DM participants defined by WC. Adjusted for gender, age, race, PIR, educational level, smoking status, alcohol consumption, physical activity, diabetes duration, CVD, CKD, cancer, HDL-C, SBP and BMI. *BMI* body mass index, *WC* waist circumference, *CVD* cardiovascular disease, *TyG index* triglyceride-glucose index.

Groups	*N*	HR (95%CI)	*p* value
Obese T2DM patients defined by BMI			
Without CVD	3321	1.11 (0.87, 1.41)	0.405
With CVD	977	1.16 (0.91, 1.49)	0.239
Non-obese T2DM patients defined by BMI			
Without CVD	2812	1.31 (1.08, 1.60)	0.007
With CVD	757	1.39 (1.11, 1.75)	0.004
Obese T2DM patients defined by WC			
Without CVD	4655	1.26 (1.06, 1.50)	0.010
With CVD	1379	1.28 (1.04, 1.56)	0.018
Non-obese T2DM patients defined by WC			
Without CVD	1478	1.25 (0.91, 1.72)	0.166
With CVD	355	1.25 (0.91, 1.72)	0.162

Table 6. TyG index and risk for CVD-related mortality among 7867 T2DM participants, stratified by obesity and CVD. *HR* hazard ratio, *CI* confidence interval, *T2DM* Type 2 diabetes mellitus, *BMI* body mass index, *CVD* cardiovascular disease, *WC* waist circumference. [a]Adjusted for gender, age, race, PIR, educational level, smoking status, alcohol consumption, physical activity, diabetes duration, CKD, cancer, HDL-C and SBP.

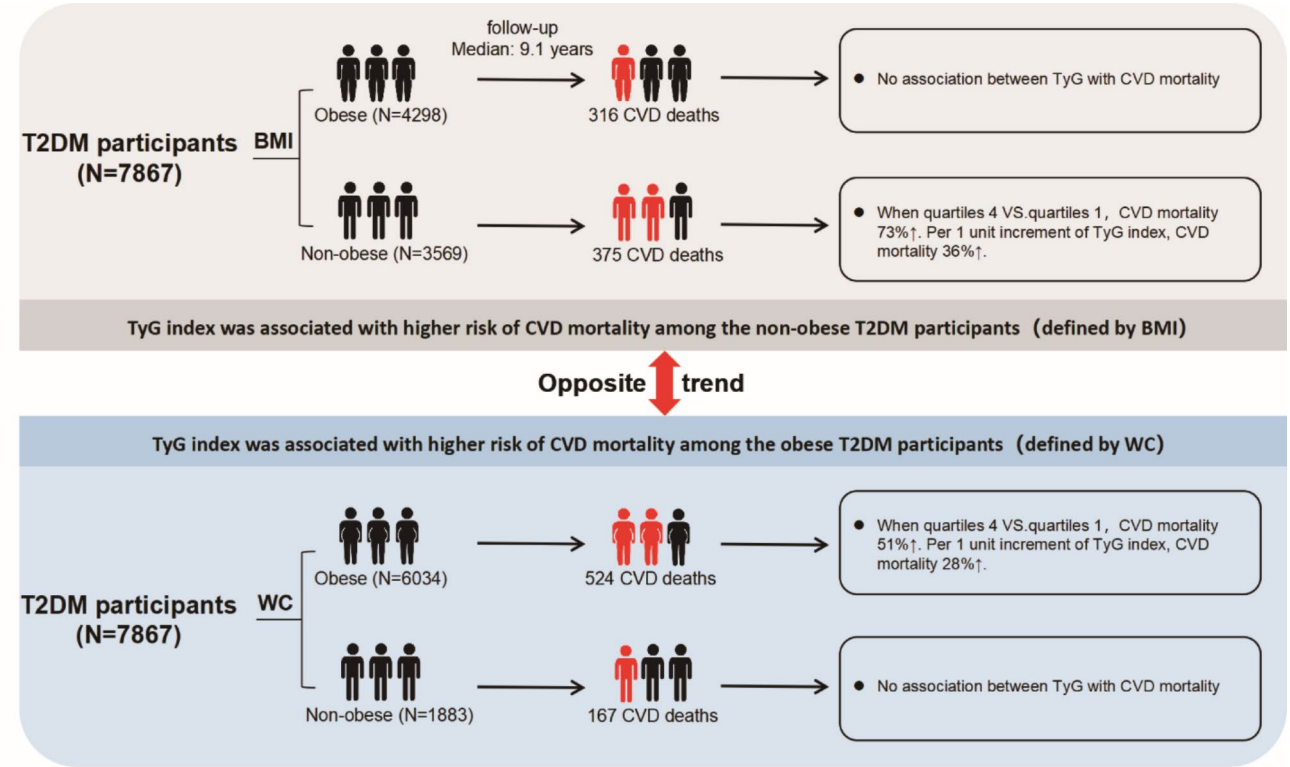

Fig. 2. Overview map of our research.

Data availability

The data that support the findings of this study are openly available in NHANES at http://www.cdc.gov/nchs/nhanes/index.htm.

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References

1. Taylor, K. S. et al. All-cause and cardiovascular mortality in middle-aged people with type 2 diabetes compared with people without diabetes in a large U.K. primary care database. *Diabetes Care* **36**(8), 2366–2371 (2013).

2. Mancusi, C. et al. Myocardial mechano-energetic efficiency and insulin resistance in non-diabetic members of the strong heart study cohort. *Cardiovasc. Diabetol.* **18**(1), 56 (2019).
3. Guerrero-Romero, F. et al. Fasting triglycerides and glucose index as a diagnostic test for insulin resistance in young adults. *Arch. Med. Res.* **47**(5), 382–387 (2016).
4. Guo, W. et al. Triglyceride glucose index is Associated with arterial stiffness and 10-Year Cardiovascular Disease Risk in a Chinese Population. *Front. Cardiovasc. Med.* **8**, 585776 (2021).
5. Lee, M. J. et al. Triglyceride-glucose index predicts type 2 diabetes mellitus more effectively than oral glucose tolerance test-derived insulin sensitivity and secretion markers. *Diabetes Res. Clin. Pract.* **210**, 111640 (2024).
6. da Silva, A. et al. Triglyceride-glucose index is associated with symptomatic coronary artery disease in patients in secondary care. *Cardiovasc. Diabetol.* **18**(1), 89 (2019).
7. Mann, J. P. & Savage, D. B. What lipodystrophies teach us about the metabolic syndrome. *J. Clin. Invest.* **129**(10), 4009–4021 (2019).
8. Fabbrini, E. et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. *Proc. Natl. Acad. Sci. U S A.* **106**(36), 15430–15435 (2009).
9. Krssak, M. et al. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: A 1H NMR spectroscopy study. *Diabetologia* **42**(1), 113–116 (1999).
10. Chen, W. et al. Association between the insulin resistance marker TyG index and subsequent adverse long-term cardiovascular events in young and middle-aged US adults based on obesity status. *Lipids Health Dis.* **22**(1), 65 (2023).
11. Zhao, Y. et al. Association of BMI with cardiovascular disease incidence and mortality in patients with type 2 diabetes mellitus: A systematic review and dose-response meta-analysis of cohort studies. *Nutr. Metab. Cardiovasc. Dis.* **31**(7), 1976–1984 (2021).
12. Xing, Z. et al. Waist circumference is associated with major adverse cardiovascular events in male but not female patients with type-2 diabetes mellitus. *Cardiovasc. Diabetol.* **19**(1), 39 (2020).
13. Li, C. I. et al. Association of body indices and risk of mortality in patients with type 2 diabetes. *BMJ Open. Diabetes Res. Care* **11**(4), e003474 (2023).
14. ElSayed, N. A. et al. 2. Classification and diagnosis of diabetes: Standards of Care in Diabetes-2023. *Diabetes Care* **46**(Suppl 1), S19–S40 (2023).
15. Wang, S. et al. Cobalamin Intake and related biomarkers: Examining associations with mortality risk among adults with type 2 diabetes in NHANES. *Diabetes Care* **45**(2), 276–284 (2022).
16. Wei, J., Liu, X., Xue, H., Wang, Y. & Shi, Z. Comparisons of visceral adiposity index, body shape index, body mass index and waist circumference and their associations with diabetes mellitus in adults. *Nutrients* **11**(7), 1580 (2019).
17. Wang, Y. Stage 1 hypertension and risk of cardiovascular disease mortality in United States adults with or without diabetes. *J. Hypertens.* **40**(4), 794–803 (2022).
18. Wang, D., Jia, S., Yan, S. & Jia, Y. Development and validation using NHANES data of a predictive model for depression risk in myocardial infarction survivors. *Heliyon* **8**(1), e08853 (2022).
19. Xu, J. et al. Identifying distinct risk thresholds of Glycated Hemoglobin and systolic blood pressure for Rapid Albuminuria Progression in type 2 diabetes from NHANES (1999–2018). *Front. Med. (Lausanne)* **9**, 928825 (2022).
20. Casagrande, S. S., Lee, C., Stoeckel, L. E., Menke, A. & Cowie, C. C. Cognitive function among older adults with diabetes and prediabetes, NHANES 2011–2014. *Diabetes Res. Clin. Pract.* **178**, 108939 (2021).
21. Levey, A. S. et al. A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* **150**(9), 604–612 (2009).
22. Oliveros, E., Somers, V. K., Sochor, O., Goel, K. & Lopez-Jimenez, F. The concept of normal weight obesity. *Prog Cardiovasc. Dis.* **56**(4), 426–433 (2014).
23. Zapata, J. K. et al. BMI-based obesity classification misses children and adolescents with raised cardiometabolic risk due to increased adiposity. *Cardiovasc. Diabetol.* **22**(1), 240 (2023).
24. Lin, T. Y., Lim, P. S. & Hung, S. C. Impact of misclassification of obesity by body mass index on mortality in patients with CKD. *Kidney Int. Rep.* **3**(2), 447–455 (2017).
25. Neeland, I. J. et al. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. *JAMA* **308**(11), 1150–1159 (2012).
26. Shen, S. et al. Waist-to-height ratio is an effective indicator for comprehensive cardiovascular health. *Sci. Rep.* **7**, 43046 (2017).
27. Smith, U. Abdominal obesity: A marker of ectopic fat accumulation. *J. Clin. Invest.* **125**(5), 1790–1792 (2015).
28. Corrêa, M. M., Thumé, E., De Oliveira, E. R. & Tomasi, E. Performance of the waist-to-height ratio in identifying obesity and predicting non-communicable diseases in the elderly population: A systematic literature review. *Arch. Gerontol. Geriatr.* **65**, 174–182 (2016).
29. Katzmarzyk, P. T., Hu, G., Cefalu, W. T., Mire, E. & Bouchard, C. The importance of waist circumference and BMI for mortality risk in diabetic adults. *Diabetes Care* **36**(10), 3128–3130 (2013).
30. Li, M., Zhu, P. & Wang, S. X. Risk for cardiovascular death associated with waist circumference and diabetes: A 9-Year prospective study in the Wan Shou Lu Cohort. *Front. Cardiovasc. Med.* **9**, 856517 (2022).
31. Wu, J. et al. Association between obesity indicators and cardiometabolic disease in Chinese adults. *PLoS ONE* **18**(1), e0273235 (2023).
32. Zhu, S. et al. Race-ethnicity-specific waist circumference cutoffs for identifying cardiovascular disease risk factors. *Am. J. Clin. Nutr.* **81**(2), 409–415 (2005).
33. Jayedi, A., Soltani, S., Zargar, M. S., Khan, T. A. & Shab-Bidar, S. Central fatness and risk of all cause mortality: Systematic review and dose-response meta-analysis of 72 prospective cohort studies. *BMJ* **370**, m3324 (2020).
34. Wolfgram, P. M. et al. In nonobese girls, Waist circumference as a predictor of insulin resistance is comparable to MRI Fat measures and Superior to BMI. *Horm. Res. Paediatr.* **84**(4), 258–265 (2015).
35. Després, J. P., Lemieux, I. & Prud'homme, D. Treatment of obesity: Need to focus on high risk abdominally obese patients. *BMJ* **322** (7288), 716–720 (2001).
36. Lee, S. H., Park, S. Y. & Choi, C. S. Insulin resistance: From mechanisms to therapeutic strategies. *Diabetes Metab. J.* **46**(1), 15–37 (2022).
37. Tchernof, A. & Després, J. P. Pathophysiology of human visceral obesity: An update. *Physiol. Rev.* **93**(1), 359–404 (2013).
38. Dang, K. et al. The association between triglyceride-glucose index and its combination with obesity indicators and cardiovascular disease: NHANES 2003–2018. *Cardiovasc. Diabetol.* **23**(1), 8 (2024).
39. Ramdas Nayak, V. K., Satheesh, P., Shenoy, M. T. & Kalra, S. Triglyceride glucose (TyG) index: A surrogate biomarker of insulin resistance. *J. Pak Med. Assoc.* **72**(5), 986–988 (2022).
40. Tian, X. et al. Insulin resistance mediates obesity-related risk of cardiovascular disease: A prospective cohort study. *Cardiovasc. Diabetol.* **21**(1), 289 (2022).

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Author contributions

HL and FG, design and revising it critically for important intellectual content; HH, analysis, interpretation of the data and drafting the work; JT, acquisition and drafting the work; JX, acquisition and revising it critically for important intellectual content; QC and MC, interpretation and revising it critically for important intellectual content. All authors approved the submitted version and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

The NCHS Ethics Review Board has approved the implementation of NHANES, and all participants have provided written informed consent.

Informed consent

The written informed consent of all subjects was obtained following the Declaration of Helsinki. Registry and the registration no. of the stydy/trial: Data: Protocol #2011-17.

Additional information

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