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Association between triglyceride-glucose (TyG) related indices and cardiovascular diseases and mortality among individuals with metabolic dysfunction-associated steatotic liver disease: a cohort study of UK Biobank

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Abstract

Background Triglyceride-glucose (TyG) related indices, which serve as simple markers for insulin resistance, have been closely linked to metabolic dysfunction-associated steatotic liver disease (MASLD), cardiovascular disease (CVD), and mortality. However, the prognostic utility of TyG-related indices in predicting the risk of CVD and mortality among patients with MASLD remains unclear.

Methods Data of 97,331 MASLD patients, with a median age of 58.0 years and free of CVD at baseline, were obtained from the UK Biobank. The TyG index, along with its combination with adiposity parameters (i.e. body mass index [BMI], waist circumference [WC], and waist-to-height ratio [WHtR]), were calculated. Cox proportional hazards models and restricted cubic spline (RCS) were performed to evaluate the associations between TyG-related indices and the risk of overall CVD, coronary heart disease (CHD), stroke, all-cause mortality, and cardiovascular mortality. Additionally, Harrell's C-index, net reclassification index (NRI), and integrated discrimination improvement index (IDI) were used to assess the predictive performance of these indices.

Results Over a median follow-up of 13.56 years, we identified 13,256 cases of overall CVD, 10,980 CHD, 2,926 stroke, 8,809 all-cause mortality, and 1,796 cardiovascular mortality. Compared with the lowest quartile of TyG-related indices, participants with MASLD in the high quartile of TyG-related indices had a significantly increased risk of incident overall CVD, CHD, stroke, and mortality. Specifically, the hazard ratios of occurring overall CVD in the fourth versus the first quartiles were 1.19 (95% confidence interval: 1.13–1.25) for TyG, 1.35 (1.28–1.42) for TyG-BMI, 1.33 (1.26–1.40) for TyG-WC, and 1.39 (1.32–1.46) for TyG-WHtR. RCS analyses indicated a nonlinear association of TyG with CVD outcomes

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(all *P* values for nonlinearity < 0.05), whereas there exhibited linear trends in TyG-BMI, TyG-WC, and TyG-WHtR with CVD outcomes (all *P* values for nonlinearity > 0.05, except for TyG-WC with stroke). Furthermore, TyG-WC and TyG-WHtR demonstrated the significantly higher C-index, NRI, and IDI in predicting risk of CVD and mortality in MASLD patients.

Conclusion TyG-related indices, especially TyG-WC and TyG-WHtR, had significant predictive values for the risk of incident CVD and mortality in individuals with MASLD. TyG-related indices may serve as effective surrogate predictors of CVD and mortality in MASLD patients.

Keywords Triglyceride glucose index (TyG), MASLD, Cardiovascular disease, UK Biobank, Cohort study

Introduction

Non-alcoholic fatty liver disease (NAFLD), characterized by the excessive accumulation of triglycerides and free fatty acids in hepatocytes, has become a prominent global public health issue, affecting over 30% of adults worldwide [1, 2]. In 2023, an international expert panel proposed the new nomenclature "metabolic dysfunction-associated steatotic liver disease (MASLD)" to replace NAFLD, which addresses the limitations of exclusive features and removes stigma in the NAFLD definition [3]. More importantly, the MASLD terminology highlights the critical role of insulin resistance (IR) and metabolic dysfunction in the pathophysiology of liver disease [3]. MASLD is widely considered as a multisystemic condition, contributing to a series of adverse intrahepatic and extrahepatic outcomes [4–6]. Mounting evidence has demonstrated that patients with MASLD had a remarkably elevated risk of cardiovascular disease (CVD) and mortality [6–8]. Given that no approved pharmacotherapies currently exist for MASLD, it is crucial to identify reliable indicators that could predict CVD and mortality risk in MASLD patients and thereby formulate preventive strategies to avert adverse events.

IR refers to a reduced sensitivity and responsiveness of insulin in promoting glucose utilization, leading to metabolic abnormalities and CVD incidence [9]. Additionally, IR was considered the cornerstone pathological mechanism of MASLD [3, 10]. To date, the gold standard for detecting IR is the hyperinsulinemic-euglycemic clamp test, but such approach is invasive, costly, and thereby unsuitable for routine clinical practice [11]. An alternative approach is the homeostatic model assessment of IR (HOMA-IR), which was calculated using fasting blood glucose and insulin concentrations [12]. However, its predictive accuracy has been compromised in people receiving insulin treatment or those without functioning beta cells [12], and fasting insulin is rarely measured in primary care settings. Currently, the triglyceride-glucose (TyG) index and its combination with adiposity indices (such as body mass index [BMI], waist circumference [WC], and waist-to-height ratio [WHtR]) have been proposed as effective and easily accessible surrogate indicators for IR [13, 14]. These indices show comparable efficacy in evaluating IR compared to traditional indicators and are suitable for clinical settings and large-scale epidemiological research [15–17]. Previous studies have elucidated the significant associations between TyG-related indices and the higher risk of MASLD and severe liver disease [10, 18]. Meanwhile, other studies have found that TyG-related indices are associated with the hazard of incident CVD and mortality in the general population [19] or in people with hypertension [20], diabetes [21], or metabolic syndrome (MetS) [22]. To date, only a few studies investigated the associations between TyG index and mortality in patients with MASLD/NAFLD, showing that those with higher TyG levels were at an elevated risk of all-cause and cardiovascular mortality [23–25]. However, these studies were conducted exclusively within the US population. Moreover, only two cross-sectional studies reported the positive correlation of TyG index with CVD and coronary heart disease (CHD) in people with MASLD [23, 26]. There still lacks the prospective cohort study to evaluate the prognostic values of TyG-related indices in new-onset occurrence of CVD among MASLD patients. An in-depth understanding of the associations between TyG-related indices and CVD outcomes in MASLD population may provide the scientific evidence for the primary prevention of CVD and clinical management in MASLD patients.

To fill these knowledge gaps, the present study aimed to investigate the associations of TyG index and its combination of adiposity indices with the risk of CVD incidence, all-cause mortality, and cardiovascular mortality in individuals with MASLD, based on a large population-based cohort study of UK Biobank. Moreover, we compared the prognostic values of various TyG-related indices in the risk of CVD and mortality in MASLD population.

Methods

Data source

Between 2006 and 2010, the UK Biobank study recruited more than 500,000 adults aged 37–73 years from the community population, which was one of the large-scaled epidemiological cohort studies worldwide [27]. At the baseline visit, participants completed a touch-screen questionnaire, a face-to-face interview, and anthropometric measurements in one of 22 assessment centers

across England, Scotland, and Wales. Extensive information was collected on early-life experiences, demographic characteristics, lifestyle factors, and physical and mental health status, along with the biological sample collection. The North West Multi-Centre Research Ethics Committee (reference: 21/NW/0157) approved the ethical of UK Biobank study, and all participants wrote the informed consent before the baseline assessment.

Definitions of MASLD population

According to the international expert consensus [3], MASLD was defined as the hepatic steatosis in combination with at least one following metabolic dysfunction: excess adiposity (WC ≥ 88 cm for females or ≥ 102 cm for males, or BMI ≥ 25 kg/m^2), prediabetes (glycated haemoglobin [HbA1c] ≥ 39 mmol/L) or type 2 diabetes, hypertension (systolic/diastolic blood pressure ≥ 130/85 mmHg, or using antihypertensive drugs), hypertriglyceridemia (triglycerides [TG] ≥ 1.70 mmol/L, or using lipid-lowering drugs), and decreased high-density lipoprotein cholesterol (HDL-C) (HDL-C ≤ 1.0 mmol/L, or using lipid-lowering drugs). Due to the absence of ultrasonographic assessments of hepatic steatosis in the UK Biobank, fatty liver index (FLI) was calculated to determinate hepatic steatosis [28], which has been validated in evaluating the hepatic steatosis in previous studies [29]. The calculation of FLI incorporated BMI, WC, serum TG, and serum γ-glutamyltransferase and the equation was as following: FLI = $\frac{\left(e^{0.953*\mathrm{Ln(TG)}+0.139*\mathrm{BMI}+0.718*\mathrm{Ln(GGT)}+0.053*\mathrm{WC}-15.745}\right)}{\left(1+e^{0.953*\mathrm{Ln(TG)}+0.139*\mathrm{BMI}+0.718*\mathrm{Ln(GGT)}+0.053*\mathrm{WC}-15.745}\right)} * 100$. According to previous study [28], an FLI ≥ 60 was unitized to diagnose hepatic steatosis, representing a sensitivity of 87% and specificity of 86%.

Selection of study population

Of 502,366 participants in the UK Biobank study, we firstly excluded those without complete data on components of MASLD or TyG-related indices (n = 97,465), leaving a total of 404,901 participants. In addition, we further excluded those with a diagnosis of CVD at or before the baseline assessment (n = 30,775), those with missing data on covariates (n = 98,425), and those free of MASLD at baseline (n = 178,370). Finally, a total of 97,331 participants with MASLD and free of CVD were included in current study. Figure 1 illustrated the detailed procedure of selecting study population.

Assessment of TyG-related indices

A random peripheral venous blood sample was taken from each participant at the baseline assessment, and biochemical measurements, including glucose, TG, total cholesterol, HDL-C, low-density lipoprotein cholesterol, C-reactive protein, uric acid, and creatinine, were performed on a Beckman Coulter AU5800 chemistry analyzer. Detailed methods and quality control are available on the UK Biobank website (https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=1227). Besides, three indictors of BMI, WC, and WHtR were selected to measure general or central obesity in participants with MASLD. Thus, the final analyses included four TyG-related indices, namely TyG, TyG-BMI, TyG-WC, and TyG-WHtR [30]. The following equations were used to calculate four above indices:

(1) TyG = Ln[TG (mg/dL)*glucose (mg/dL)/2]
(2) TyG-BMI = Ln[TG (mg/dL)*glucose (mg/dL)/2]*[weight (kg) / height^2 (m^2)]
(3) TyG-WC = Ln[TG (mg/dL)*glucose (mg/dL)/2]*WC (cm).
(4) TyG-WHtR = Ln[TG (mg/dL)*glucose (mg/dL)/2]*[WC(cm)/height(cm)]

Assessment of outcomes

The primary outcome in present study was the incidence of overall CVD (including CHD and stroke) in individuals with MASLD. The secondary outcome was all-cause and cardiovascular mortality. Participants were followed from the date of competing baseline assessment to the date of incident first CHD or stroke, or death, or November 30, 2022, whichever came first. The date of new-onset incident cases was identified through linkage with hospital inpatient data and death register records. The occurrence of overall CVD and cardiovascular mortality was defined by the 10th revision of International Classification of Diseases (ICD-10) codes, including I20-I25 for CHD and I60-I64 for stroke.

Covariates

According to previous related studies, we also collected several potential covariates at the baseline visit. These factors included baseline age (years, continue variable), sex (female and male), ethnicity (white and non-white ethnicity), Townsend deprivation index (TDI) (continue variable, with a higher score indicating more deprived), education (college degree and above and others), employed status (employed and not), family income (less than £18,000, £18,000 to £51,999, and equal to or greater than £52,000), smoking (never, ever, and current smoking), physical activity (total amount of moderate-intensity activity ≥ 75 min/week or vigorous-intensity activity ≥ 150 min/week or equal combination and not), frequency of alcohol drinking (never drinking or special occasions, one to three times a month, once or twice a week, once or twice a week, three or four times a week, and daily or almost daily), total sleep duration (< 7 h/day, 7–8 h/day, and > 8 h/day), healthy diet score (continue

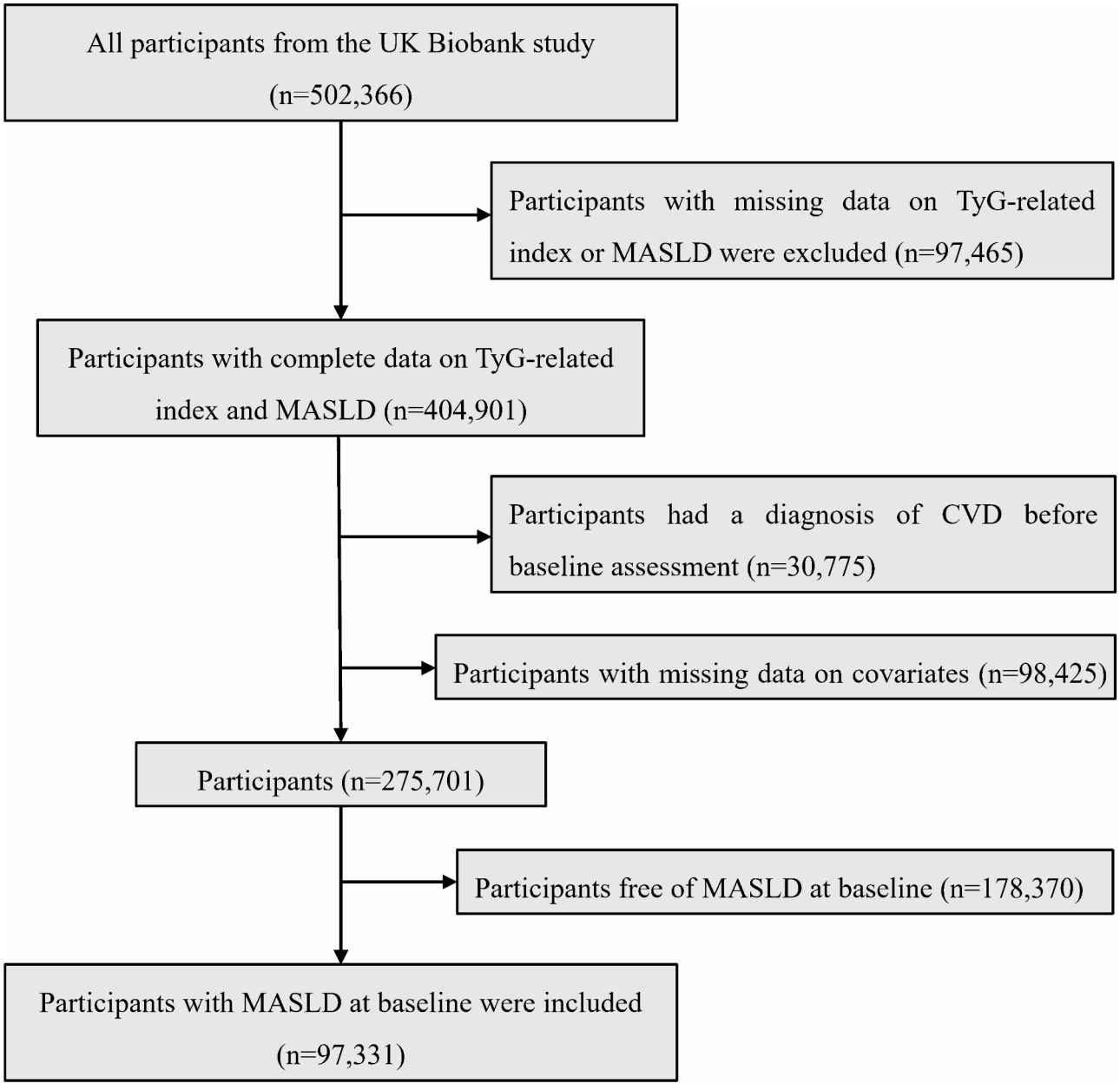

Fig. 1 Flowchart of participants selection

variable, a higher score indicating healthier diet, comprising of seven diet components) [31], family history of cardiometabolic diseases (yes and not, including hypertension, diabetes, and CVD).

Statistical analysis

Baseline characteristics of study population were summarized according the occurrence of new-onset overall CVD. Kolmogorov-Smirnov test was used to examine the normality of continue variables. Non-normally distributed continue variables were summarized as median (interquartile range, IQR), while normally distributed variables as mean (standard deviation, SD). Categorical variables were expressed as number (%). Then, Student's t tests (for continue variables with normal distribution) or Kruskal-Wallis ranks-sum tests (for continue variables with non-normal distribution) or Pearson Chi-square tests (for categorical variables) were performed to compare the between-group differences in baseline characteristics. In addition, we divided participants into four groups according to the quartiles of TyG index and compared the baseline characteristics in each group with the same statistical methods as above.

Kaplan-Meier curves stratified by the quartiles of TyG index with log-rank tests were applied to compare the cumulative hazard of each study outcome. Cox

proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the associations of TyG-related indices with CVD and mortality in participants with MASLD. Multivariate-adjusted HRs were estimated for higher quartiles of each TyG-related index versus the lowest quartiles and for each 1-standard deviation (SD) increment in TyG-related indices. Additionally, restrict cubic spline (RCS) based on the Cox proportional hazards models were applied to flexibly evaluate the shape of associations between TyG-related indices and all study outcomes with four knots (at the 5th, 35th, 65th, and 95th percentiles). If there existed nonlinear relationship, the threshold values were estimated by trying all possible values and chose with the highest likelihood. We further fitted the two-segmented Cox proportional hazard models on both sides of the threshold point to assess the associations between TyG-related indices and outcomes. All above models were adjusted for age, sex, ethnicity, education, TDI value, family incomes, employed status, smoking, drinking, physical activity, sleep duration, diet, and family of cardiometabolic diseases.

Additionally, we calculated Harrell's C index, net reclassification index (NRI), and integrated discrimination improvement index (IDI) to assess the incremental performance of TyG-related indices over conventional risk factors for CVD and mortality in MASLD patients [32]. C index is a discrimination index, while IDI and NRI assess whether the new model provides improved risk stratification compared to the basic model. A basic model was developed using variables from the Framingham Cardiovascular Risk Score [33], including age, sex, smoking status, BMI, SBP, anti-hypertensive medication, diabetes, total cholesterol, and HDL-C. We then compared the predictive value of the basic model with that obtained by incorporating TyG-related indices.

Several additional analyses were performed to confirm the robustness of our results. Firstly, to minimize the potential reverse causality, landmark sensitivity analyses were conducted by excluding MASLD patients who occurred corresponding study outcome within the first 2 years of follow-up. Secondly, we repeated all analyses with the multiple imputation of missing data on covariates using a chained equation method. Thirdly, to control the competing risk from other cause mortality, Fine-Gray competing risk models were conducted to analyze overall CVD, CHD, stroke, and cardiovascular mortality, when treating mortality from other causes as a competing risk. Fourthly, considered the effect of diabetes on CVD and mortality risk, we reanalyzed the associations between TyG-related indices and risk of CVD and mortality in those with diabetes at baseline. Fifthly, we additionally adjusted for HbA1c to reduce the potential influence of non-fasting blood glucose [19]. Finally, subgroup analyses were conducted according to baseline age (< 60 vs. ≥ 60 years), sex (female vs. male), and the frequency of drinking (less than twice a week vs. more than twice week a week) to evaluate the susceptible population.

Two-sided $P < 0.05$ was considered to be statistically significant. All statistical analyses were conducted using R software (version 4.4.0, R Foundation for Statistical Computing).

Results

Baseline characteristics of study population

Of 97,331 participants with MASLD in present study, the median age (IQR) was 58.0 years (50.0–63.0), 66.3% were males, and 91.8% were White ethnicity. Table 1 summarized the baseline characteristics of study participants stratified by the occurrence of overall CVD during follow-up. Compared with those free of overall CVD, participants developing overall CVD during follow-up were more likely to be older, male, less educated, unemployed, more deprived, smoker, daily drinking, have an unrecommended daily sleep duration, take an unhealthy diet, have a lower household income, hypertension, type 2 diabetes, and have a family history of cardiometabolic diseases. Moreover, they also had the higher levels of TyG-related indices at baseline.

We also compared the baseline characteristics of MASLD patients according to the quartiles of TyG index at baseline. As shown in Table S1, compared with those in lowest quartile of TyG index, those in high quartiles tended to be older, male, white ethnicity, college degree, current smoker, unhealthy diet, have a recommended daily sleep duration, have a diagnosis of hypertension and type 2 diabetes.

Association of TyG-related indices with CVD in participants with MASLD

During a median follow-up of 13.56 years (IQR: 12.63–14.37), we identified 13,256 cases of overall CVD, including 10,980 CHD and 2,926 stroke. Kaplan-Meier curves depicted the significantly higher cumulative hazard of incident CVD outcomes in participants with the fourth quartile level of TyG index (all P values for log-rank test < 0.05, Fig. 2A–C). After full adjustment of covariates, cox regression analyses showed that each 1-SD increment in the TyG index was associated with an 8% and 9% higher risk of incident overall CVD (HR = 1.08, 95% CI = 1.06–1.10) and CHD (1.09, 1.07–1.11), while the association with stroke was not statistically significant (1.03, 0.99–1.07) (Table 2). Compared with the lowest quartile, the multivariate-adjusted HRs (95% CIs) in the fourth quartile of TyG were 1.19 (1.13–1.25) for overall CVD, 1.23 (1.16–1.29) for CHD, and 1.03 (0.93–1.14) for stroke, respectively (Table 2). Similarly, there were positive and significant associations of TyG-BMI, TyG-WC,

Table 1 Baseline characteristics of study population stratified by the occurrence of overall CVD

Characteristics	Total population (*n* = 97,331)	Occurrence of overall CVD		*P* value
		No (*n* = 84,075)	Yes (*n* = 13,256)	
Age (years)	58.0 (50.0, 63.0)	57.0 (50.0, 62.0)	61.0 (55.0, 65.0)	< 0.001
Males	64,539 (66.3)	54,628 (65.0)	9911 (74.8)	< 0.001
White ethnicity	89,334 (91.8)	77,140 (91.8)	12,194 (92.0)	0.364
College degree	30,064 (30.9)	26,554 (31.6)	3510 (26.5)	< 0.001
Household income				< 0.001
Less than £18,000	22,081 (22.7)	18,111 (21.5)	3970 (29.9)	
£18,000 to £51,999	51,251 (52.7)	44,384 (52.8)	6867 (51.8)	
Greater than £52,000	23,999 (24.7)	21,580 (25.7)	2419 (18.2)	
Employed	90,765 (93.3)	78,545 (93.4)	12,220 (92.2)	< 0.001
Townsend deprivation index	− 2.1 (− 3.6, 0.6)	− 2.1 (− 3.6, 0.5)	− 2.0 (-3.6, 0.8)	< 0.001
Smoking status				< 0.001
Never smoking	48,373 (49.7)	42,750 (50.8)	5623 (42.4)	
Ever smoking	38,263 (39.3)	32,411 (38.6)	5852 (44.1)	
Current smoking	10,695 (11.0)	8914 (10.6)	1781 (13.4)	
Frequency of alcohol drinking				< 0.001
Never or special occasions only	16,848 (17.3)	14,296 (17.0)	2552 (19.3)	
One to three times a moth	10,820 (11.1)	9455 (11.2)	1365 (10.3)	
Once or twice a week	25,070 (25.8)	21,775 (25.9)	3295 (24.9)	
Three or four times a week	23,125 (23.8)	20,164 (24.0)	2961 (22.3)	
Daily or almost daily	21,468 (22.1)	18,385 (21.9)	3083 (23.3)	
Physical activity				0.145
< 150 min/week	21,424 (22.0)	18,441 (21.9)	2983 (22.5)	
≥ 150 min/week	75,907 (78.0)	65,634 (78.1)	10,273 (77.5)	
Sleeping duration per day				< 0.001
7–8 h	64,593 (66.4)	56,190 (66.8)	8403 (63.4)	
< 7 h	25,275 (26.0)	21,637 (25.7)	3638 (27.4)	
> 8 h	7463 (7.7)	6248 (7.4)	1215 (9.2)	
Healthy diet score	3.08 (1.34)	3.09 (1.34)	3.03 (1.36)	< 0.001
Hypertension	81,398 (83.6)	69,452 (82.6)	11,946 (90.1)	< 0.001
Type 2 diabetes	8714 (9.0)	6777 (8.1)	1937 (14.6)	< 0.001
Family history of cardiometabolic disease	75,775 (77.9)	65,099 (77.4)	10,676 (80.5)	< 0.001
TyG index	9.1 (8.8, 9.4)	9.1 (8.7, 9.4)	9.1 (8.8, 9.5)	< 0.001
Tyg-BMI index	275.3 (255.2, 301.8)	275.1 (255.1, 301.4)	276.4 (256.0, 304.4)	< 0.001
TyG-WC index	910.8 (858.8, 977.5)	908.3 (856.8, 973.9)	926.9 (871.5, 999.7)	< 0.001
TyG-WHtR index	5.3 (5.0, 5.7)	5.3 (5.0, 5.7)	5.4 (5.1, 5.8)	< 0.001

Data are expressed as median (interquartile range) or mean (standard deviation) for continue variables and n (%) for categorical variables. CVD: cardiovascular disease; MASLD: metabolic-associated steatotic liver disease; TyG: triglyceride glucose index; BMI: body mass index, WC:waist circumference; WHtR: waist-to-height ratio

and TyG-WHtR with all CVD outcomes (Table 2). In the fully-adjusted models, the HRs (95% CIs) of overall CVD in the fourth quartile versus the first quartile were 1.35 (1.28–1.42) for TyG-BMI, 1.33 (1.26–1.40) for TyG-WC, and 1.39 (1.32–1.46) for TyG-WHtR, respectively (Table 2). The corresponding HRs (95% CI) in the fourth quartiles of TyG-BMI, TyG-WC, and TyG-WHtR versus the first quartile were 1.40 (1.33–1.48), 1.38 (1.31–1.46), and 1.44 (1.36–1.52), respectively, for CHD, and 1.16 (1.04–1.29), 1.15 (1.03–1.28), and 1.20 (1.08–1.33), respectively, for stroke (Table 2).

Figure 3 showed the dose-response associations of TyG-related indices with CVD incidence using the multivariate-adjusted RCS analyses. There existed an approximate J-shaped association between TyG index and overall CVD (*P* for non-linear < 0.001, Fig. 3A), CHD (*P* for non-linear = 0.002, Fig. 3E) and stroke (*P* for non-linear < 0.001, Fig. 3I). In contrast, except for the non-linear association of TyG-WC with stroke (*P* for non-linear = 0.030, Fig. 3K), multivariate-adjusted RCS models showed a linear dose-response association between TyG-BMI, TyG-WC, and TyG-WHtR and the incidence of overall CVD, CHD, and stroke (all *P* for non-linear > 0.5, Fig. 3B, C, D, F, G, H, J, L).

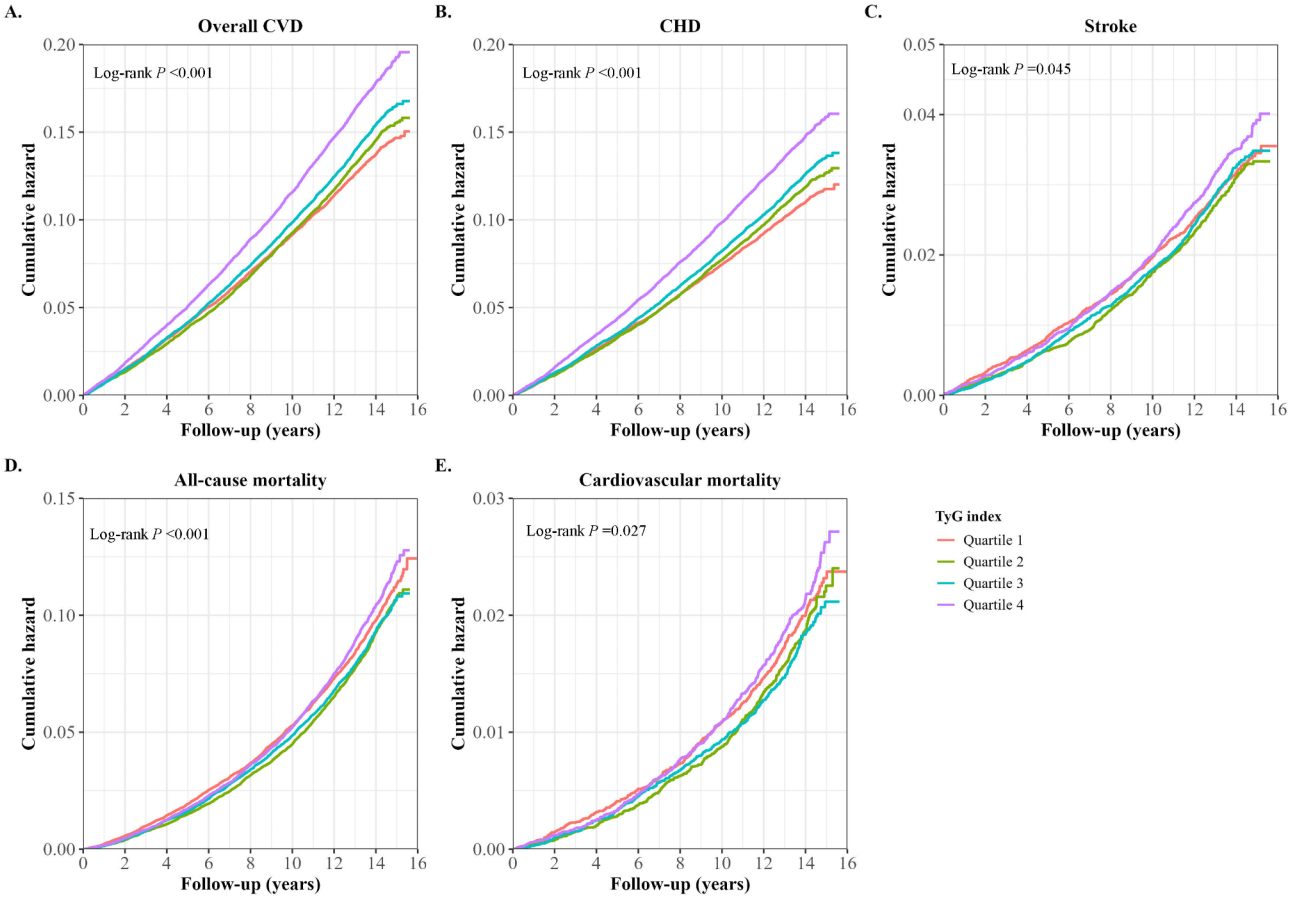

Fig. 2 Kaplan-Meier curves of cardiovascular disease and mortality according to the quartiles of the TyG index in participants with MASLD. Abbreviations: MASLD: metabolic dysfunction-associated steatotic liver disease; CVD: cardiovascular disease; CHD: coronary heart disease, TyG: triglyceride glucose index

Association of TyG-related indices with mortality in participants with MASLD

During the follow-up period, there were 8,809 cases of all-cause mortality and 1,796 cases of cardiovascular mortality. After fully adjusting for covariates, cox regression analyses showed the significant and positive associations of TyG-BMI, TyG-WC, and TyG-WHtR with all-cause and cardiovascular mortality, yet the associations with TyG index was not statistically significant (Fig. 2D–E; Table 3). Each 1-SD increment of TyG-BMI, TyG-WC, and TyG-WHtR was associated with a 13-17% higher risk of all-cause mortality and a 23-25% higher risk of cardiovascular mortality (Table 3). When compared with the lowest quartiles, the multivariate-adjusted HRs (95% CIs) of all-cause mortality in the highest quartiles were 1.26 (1.19–1.34) for TyG-BMI, 1.38 (1.30–1.47) for TyG-WC, and 1.37 (1.28–1.45) for TyG-WHtR, respectively (Table 3). For the cardiovascular mortality, the corresponding HRs (95% CIs) in the highest quartiles were 1.48 (1.29–1.68) for TyG-BMI, 1.63 (1.41–1.88) for TyG-WC, and 1.57 (1.37–1.80) for TyG-WHtR, respectively (Table 3).

After full covariate adjustment, RCS analyses showed a U-shaped association between TyG and all-cause and cardiovascular mortality (both *P* for non-linear < 0.001, Fig. 4A, E). Moreover, there were J-shaped non-linear associations of TyG-BMI, TyG-WC, and TyG-WHtR with all-cause and cardiovascular mortality (all *P* for non-linear < 0.001, Fig. 4B, C, D, F, H), except for the linear association of TyG-WC with cardiovascular mortality (*P* for non-linear = 0.060, Fig. 4G).

Threshold effects of TyG-related indices on CVD and mortality in participants with MASLD

As there existed the non-linear associations of TyG with CVD and mortality outcomes, TyG-WC with stroke and all-cause mortality, and TyG-BMI and TyG-WHtR with mortality, we further fitted two-segmented cox proportional hazard models on both sides of inflection point to estimate the associations between TyG-related indices and corresponding outcomes. When TyG was less than the inflection point, there was no statistically significant relationship between TyG and overall CVD and CHD, yet the risks of stroke and mortality decreased with the increases in the TyG index (Table 4). On the contrary, the

Table 2 Association between TyG-related indices and cardiovascular disease in participants with MASLD

Exposure	Overall CVD		CHD		Stroke	
	No. of cases/person-years	HR (95% CI)	No. of cases/person-years	HR (95% CI)	No. of cases/person-years	HR (95% CI)
TyG index						
Per 1-SD increment		1.08 (1.06–1.10)		1.09 (1.07–1.11)		1.03 (0.99–1.07)
Quartile 1	2,994/308,723	1.00 (Reference)	2,431/311,694	1.00 (Reference)	718/321,815	1.00 (Reference)
Quartile 2	3,144/309,969	1.00 (0.95–1.05)	2,603/312,531	1.02 (0.97–1.08)	695/323,767	0.91 (0.82–1.01)
Quartile 3	3,312/307,928	1.04 (0.99–1.10)	2,750/310,558	1.07 (1.01–1.13)	718/322,904	0.94 (0.86–1.04)
Quartile 4	3,806/304,593	1.19 (1.13–1.25)	3,196/307,479	1.23 (1.16–1.29)	795/322,214	1.03 (0.93–1.14)
TyG-BMI index						
Per 1-SD increment		1.13 (1.11–1.15)		1.14 (1.12–1.16)		1.07 (1.03–1.11)
Quartile 1	3,199/308,043	1.00 (Reference)	2,615/310,930	1.00 (Reference)	746/321,960	1.00 (Reference)
Quartile 2	3,236/308,287	1.08 (1.03–1.13)	2,655/311,298	1.08 (1.03–1.14)	736/322,938	1.04 (0.94–1.16)
Quartile 3	3,281/308,601	1.17 (1.11–1.23)	2,713/311,145	1.19 (1.13–1.26)	718/323,657	1.07 (0.96–1.19)
Quartile 4	3,540/306,281	1.35 (1.28–1.42)	2,997/308,891	1.40 (1.33–1.48)	726/322,144	1.16 (1.04–1.29)
TyG-WC index						
Per 1-SD increment		1.13 (1.11–1.15)		1.15 (1.13–1.17)		1.08 (1.04–1.12)
Quartile 1	2,612/314,474	1.00 (Reference)	2,092/317,039	1.00 (Reference)	638/326,034	1.00 (Reference)
Quartile 2	3,077/310,060	1.04 (0.99–1.10)	2,533/312,717	1.06 (1.00-1.13)	706/323,767	0.99 (0.89–1.10)
Quartile 3	3,406/306,499	1.11 (1.05–1.17)	2,835/309,321	1.14 (1.08–1.21)	721/321,988	0.97 (0.87–1.08)
Quartile 4	4,161/300,179	1.33 (1.26–1.40)	3,520/303,187	1.38 (1.31–1.46)	861/318,909	1.15 (1.03–1.28)
TyG-WHtR index						
Per 1-SD increment		1.15 (1.13–1.17)		1.16 (1.14–1.18)		1.09 (1.05–1.13)

Table 2 (continued)

Exposure	Overall CVD		CHD		Stroke	
	No. of cases/person-years	HR (95% CI)	No. of cases/person-years	HR (95% CI)	No. of cases/person-years	HR (95% CI)
Quartile 1	2,688/313,635	1.00 (Reference)	2,200/316,069	1.00 (Reference)	619/325,659	1.00 (Reference)
Quartile 2	3,148/309,447	1.10 (1.04–1.15)	2,594/312,226	1.11 (1.05–1.17)	706/323,167	1.03 (0.92–1.15)
Quartile 3	3,399/306,708	1.16 (1.11–1.23)	2,794/309,567	1.18 (1.12–1.25)	747/322,447	1.04 (0.93–1.16)
Quartile 4	4,021/301,423	1.39 (1.32–1.46)	3,392/304,401	1.44 (1.36–1.52)	854/319,426	1.20 (1.08–1.33)

Models were adjusted for age, sex, ethnicity, employed status, Townsend deprivation index, education, family income, smoking status, alcohol drinking, sleep duration, physical activity, diet, and family history of cardiometabolic diseases

MASLD metabolic-associated steatotic liver disease, *CVD* cardiovascular disease, *CHD* coronary heart disease, *TyG* triglyceride glucose index, *BMI* body mass index, *WC* waist circumference, *WHtR* waist-to-height ratio, *HR* hazard ratio, *CI* confidence interval

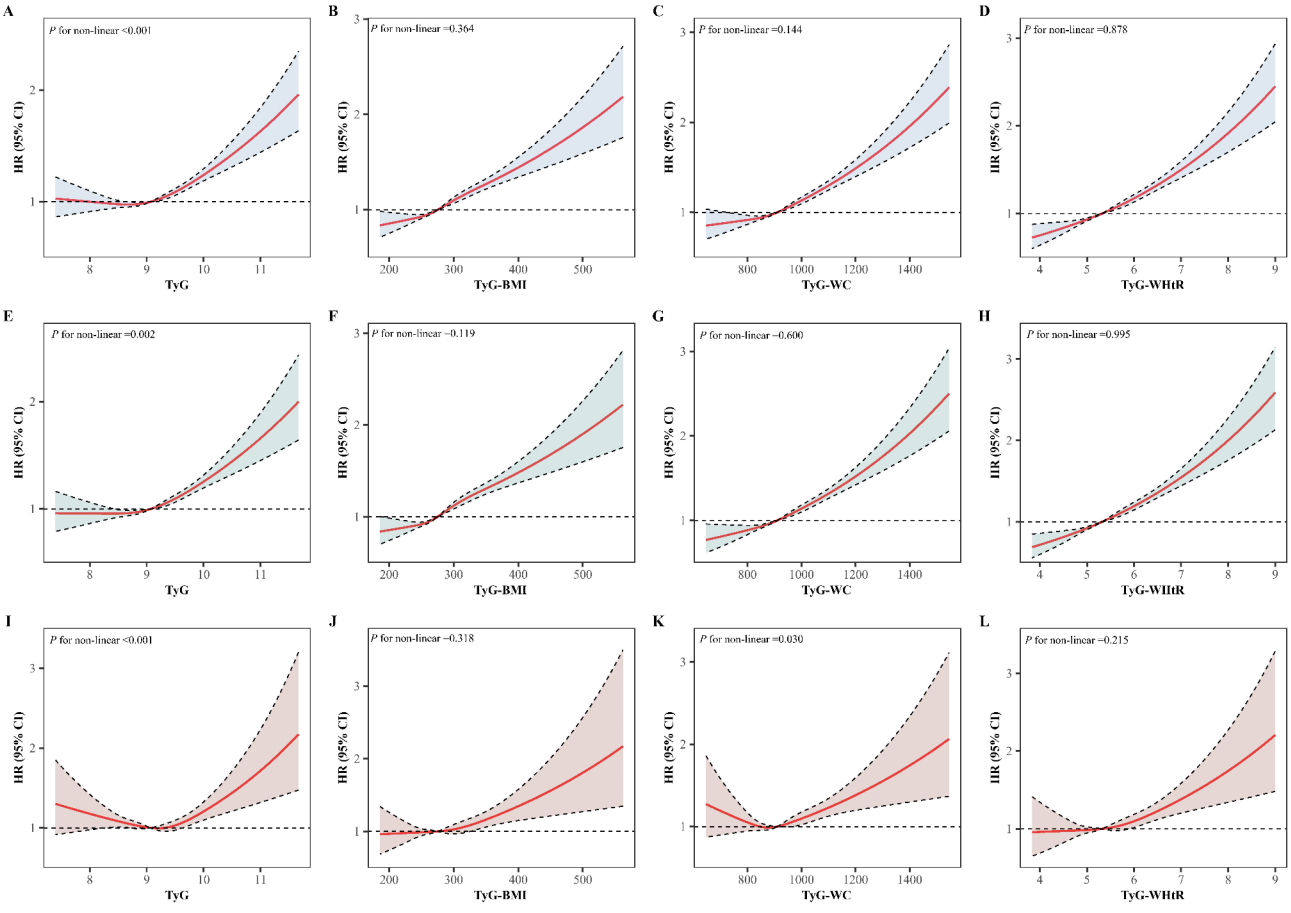

Fig. 3 Does-response relationship of TyG-related indices with cardiovascular diseases in participants with MASLD. Models were adjusted for age, sex, ethnicity, employed status, Townsend deprivation index, education, family income, smoking status, alcohol drinking, sleep duration, physical activity, diet, and family history of cardiometabolic diseases. Abbreviations: MASLD: metabolic-associated steatotic liver disease; CVD: cardiovascular disease; CHD: coronary heart disease; TyG: triglyceride glucose index; BMI: body mass index; WC: waist circumference; WHtR: waistto- height ratio; HR: hazard ratio; CI: confidence interval

Table 3 Association between TyG-related indices and all-cause and cardiovascular mortality in participants with MASLD

Exposure	All-cause mortality		Cardiovascular mortality	
	No. of cases/person-years	HR (95% CI)	No. of cases/person-years	HR (95% CI)
TyG index				
Per 1-SD increment		1.01 (0.99–1.03)		1.00 (0.95–1.05)
Quartile 1	2,240/325,339	1.00 (Reference)	460/325,339	1.00 (Reference)
Quartile 2	2,088/326,847	0.88 (0.83–0.93)	432/326,847	0.88 (0.78–1.01)
Quartile 3	2,118/326,017	0.88 (0.83–0.93)	410/326,017	0.82 (0.72–0.94)
Quartile 4	2,363/325,727	0.97 (0.91–1.03)	494/325,727	0.96 (0.84–1.09)
TyG-BMI index				
Per 1-SD increment		1.13 (1.11–1.15)		1.23 (1.18–1.29)
Quartile 1	2,274/325,406	1.00 (Reference)	455/325,406	1.00 (Reference)
Quartile 2	2,082/326,439	0.98 (0.92–1.04)	417/326,439	1.01 (0.88–1.15)
Quartile 3	2,044/326,727	1.01 (0.95–1.07)	399/326,727	1.04 (0.91–1.20)
Quartile 4	2,409/325,358	1.26 (1.19–1.34)	525/325,358	1.48 (1.29–1.68)
TyG-WC index				
Per 1-SD increment		1.17 (1.15–1.19)		1.25 (1.20–1.31)
Quartile 1	1,700/328,952	1.00 (Reference)	298/328,952	1.00 (Reference)
Quartile 2	1,994/326,996	1.03 (0.97–1.10)	399/326,996	1.13 (0.97–1.32)
Quartile 3	2,246/325,410	1.11 (1.04–1.18)	460/325,410	1.22 (1.05–1.42)
Quartile 4	2,869/322,573	1.38 (1.30–1.47)	639/322,573	1.63 (1.41–1.88)
TyG-WHtR index				
Per 1-SD increment		1.16 (1.14–1.18)		1.24 (1.19–1.30)
Quartile 1	1,702/328,517	1.00 (Reference)	327/328,517	1.00 (Reference)
Quartile 2	2,041/326,457	1.05 (0.98–1.12)	419/326,457	1.13 (0.98–1.31)
Quartile 3	2,179/325,824	1.05 (0.98–1.12)	429/325,824	1.10 (0.95–1.28)
Quartile 4	2,887/323,132	1.37 (1.28–1.45)	621/323,132	1.57 (1.37–1.80)

MASLD metabolic-associated steatotic liver disease, *TyG* triglyceride glucose index, *BMI* body mass index, *WC* waist circumference, *WHtR* waist-to-height ratio, *HR* hazard ratio, *CI* confidence interval

Models were adjusted for age, sex, ethnicity, employed status, Townsend deprivation index, education, family income, smoking status, alcohol drinking, sleep duration, physical activity, diet, and family history of cardiometabolic diseases

hazards of all study outcomes significantly increased after the inflection point of TyG, with adjusted HRs being 1.26 to 1.42 (Table 4). Similarly, when values were less than the inflection points, there were negative associations of TyG-BMI, TyG-WC, and TyG-WHtR with all-cause mortality, and TyG-BMI with cardiovascular mortality, yet TyG-WHtR was positively associated with cardiovascular mortality (Table 4). Conversely, when the values were greater than the inflection points, TyG-BMI, TyG-WC, and TyG-WHtR were significantly and positively associated with corresponding outcomes (Table 4).

Incremental predictive values of TyG-related indices in participants with MASLD

We further examined whether adding TyG-related indices to the basic model could improve the predicative power for CVD and mortality in patients with MASLD. As summarized in Table 5, adding TyG-related indices to the basic model significantly improved the Harrell's C index, IDI, and NRI for all study outcomes (all P values < 0.001, except for adding TyG index in CVD outcomes P value > 0.05). For overall CVD and CHD, TyG-WHtR index had the highest increment in Harrell's C index (0.664 for overall CVD and 0.663 for CHD), continue NRI (5.008 for overall CVD and 5.177 for CHD), and IDI (0.144 for overall CVD and 0.141 for CHD), followed by TyG-WC, TyG-BMI, and TyG. For stroke, adding TyG-WHtR index had the significant increases in continue NRI (3.040, 95% CI: 0.728–4.803) and IDI (0.014, 95% CI: 0.002–0.043). For all-cause and cardiovascular mortality, TyG-WC (continue NRI: 3.539 for stroke, 6.539 for all-cause mortality, and 8.233 for cardiovascular mortality) and TyG-WHtR (continue NRI: 3.096 for stroke, 6.248 for all-cause mortality, and 6.814 for cardiovascular mortality) had the higher increment in predictive values.

Sensitivity and subgroup analyses

Additional sensitivity and subgroup analyses were conducted to confirm the robustness of our results. In the sensitivity analyses, similar results were found after excluding those occurred outcomes within the first two years of follow-up (Figs. S1–S2), imputing missing data on covariates using multiple chain imputation method (Figs. S3–S4), considering the competing risk of other-cause mortality for CVD and cardiovascular mortality

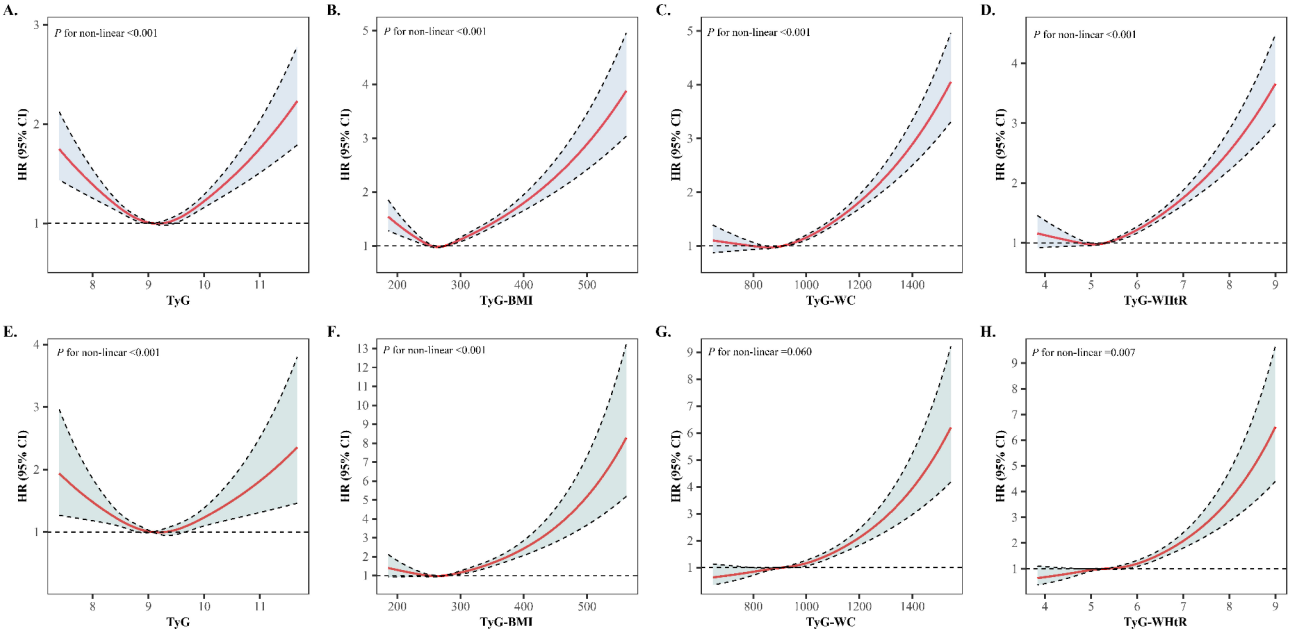

Fig. 4 Does-response relationship of TyG-related indices with all-cause and cardiovascular mortality in participants with MASLD. Models were adjusted for age, sex, ethnicity, employed status, Townsend deprivation index, education, family income, smoking status, alcohol drinking, sleep duration, physical activity, diet, and family history of cardiometabolic diseases. Abbreviations: MASLD: metabolicassociated steatotic liver disease; CVD: cardiovascular disease; CHD: coronary heart disease; TyG: triglyceride glucose index; BMI: body mass index; WC: waist circumference; WHtR: waist-to-height ratio; HR: hazard ratio; CI: confidence interval

(Fig. S5), only including those with diabetes at baseline (Figs. S6–S7), and additionally adjusting for HbA1c to reduce the potential influence of non-fasting blood glucose (Figs. S8–S9). Additionally, subgroup analyses stratified by age (< 60 vs. ≥ 60 years, Fig. S10), sex (female vs. male, Fig. S11), drinking frequency (less than twice a week vs. more than twice a week, Fig. S12) showed the consistent results with primary analyses.

Discussion

In this large-scale and prospective cohort study of middle-aged participants, our analyses demonstrated that except for no associations of TyG index with stroke and mortality, all TyG-related indices (e.g., TyG, TyG-BMI, TyG-WC, and TyG-WHtR) were positively with the risk of incident overall CVD, CHD, stroke, all-cause mortality, and cardiovascular mortality in MASLD patients. Specifically, persons with MASLD in the highest quartile of TyG, TyG-BMI, TyG-WC, and TyG-WHtR had a 1.19–1.39 times increased risk of incident overall CVD. RCS analyses depicted the dose-response relationship of TyG-related indices with CVD outcomes and mortality in MASLD patients. Moreover, TyG-WHtR and TyG-WC had the optimal predictive performance for the risk of CVD and mortality than other indicators in participants with MASLD.

Due to the similar risk factors and pathogenesis between MASLD and CVD, MASLD have been demonstrated to significantly heighten risk of occurring CVD in previous studies [6, 8]. However, there have been no effective MASLD treatment, and the early CVD prevention are superior issue in patients with MASLD [34]. Currently, TyG-related indices, as the simple and reliable surrogate indicators for IR, have been strongly associated with CVD in different population [30, 35]. For instance, using data of 403,335 middle-aged adults, Che et al. found that higher TyG levels were related with increased risk of developing CVD in general population [19]. Other research reported the elevated risks of CVD and mortality related with high TyG level in those with hypertension, diabetes, MetS, and CVD [20, 21, 24]. To date, only two past studies investigated the association between TyG-related indices and CVD outcomes in people with NAFLD [23, 26]. Based on the National Health and Nutrition Examination Survey (NHANES) datasets, Zhang and colleagues found the positive correlations of TyG and TyG-WHtR with CVD in NAFLD population, including chronic heart failure, CHD, and angina pectoris [23]. Another study reported that NAFLD patients with elevated levels of TyG were at increased likelihood of CHD [26]. However, two above studies were limited by the cross-sectional designs and the smaller sample sizes ($n = 424$ and $n = 6{,}627$), and whether TyG was associated with the risk of new-onset CVD remains unclear. Furthermore, limited studies demonstrated the prognostic effects of TyG on all-cause and cardiovascular mortality in MASLD population [23–25], yet the study participants in these studies were all U.S. population. In current study,

Table 4 Threshold effect analyses of TyG-related indices with cardiovascular disease and mortality in participants with MASLD

	Before inflection point	After inflection point	*P* for Log-likelihood ratio	Standard regression
TyG index				
Overall CVD				
Inflection point	8.933			
HR (95% CI)	0.960 (0.877–1.051)	1.262 (1.202–1.324)	< 0.001	1.164 (1.126–1.204)
CHD				
Inflection point	8.912			
HR (95% CI)	1.000 (0.902–1.109)	1.275 (1.210–1.343)	< 0.001	1.192 (1.149–1.237)
Stroke				
Inflection point	9.329			
HR (95% CI)	0.880 (0.784–0.998)	1.386 (1.191–1.612)	< 0.001	1.054 (0.981–1.134)
All-cause mortality				
Inflection point	9.217			
HR (95% CI)	0.769 (0.715–0.827)	1.374 (1.273–1.484)	< 0.001	1.014 (0.972–1.057)
Cardiovascular mortality				
Inflection point	9.236			
HR (95% CI)	0.733 (0.626–0.857)	1.422 (1.199–1.686)	< 0.001	0.996 (0.908–1.092)
TyG-BMI index				
All-cause mortality				
Inflection point	239.444			
HR (95% CI)	0.979 (0.974–0.983)	1.004 (1.003–1.004)	< 0.001	1.003 (1.003–1.004)
Cardiovascular mortality				
Inflection point	242.709			
HR (95% CI)	0.981 (0.973–0.990)	1.006 (1.005–1.007)	< 0.001	1.005 (1.004–1.006)
TyG-WC index				
Stroke				
Inflection point	912.946			
HR (95% CI)	0.999 (0.998-1.000)	1.001 (1.001–1.002)	0.004	1.001 (1.000-1.001)
All-cause mortality				
Inflection point	830.234			
HR (95% CI)	0.997 (0.995–0.998)	1.002 (1.002–1.002)	< 0.001	1.002 (1.001–1.002)
TyG-WHtR index				
All-cause mortality				
Inflection point	4.726			
HR (95% CI)	0.331 (0.224–0.490)	1.332 (1.285–1.381)	< 0.001	1.289 (1.245–1.335)
Cardiovascular mortality				
Inflection point	5.696			
HR (95% CI)	1.169 (1.002–1.364)	1.690 (1.501–1.902)	0.002	1.449 (1.345–1.561)

Models were adjusted for age, sex, ethnicity, employed status, Townsend deprivation index, education, family income, smoking status, alcohol drinking, sleep duration, physical activity, diet, and family history of cardiometabolic diseases

MASLD metabolic-associated steatotic liver disease, *CVD* cardiovascular disease, *CHD* coronary heart disease, *TyG* triglyceride glucose index, *BMI* body mass index, *WC* waist circumference, *WHtR* waist-to-height ratio, *HR* hazard ratio, *CI* confidence interval

we utilized data of over 90,000 adults with MASLD from the UK Biobank to assess the prospective associations of TyG-related indices with CVD risks. Our results showed that MASLD patients with high levels of TyG-related indices were at a significantly hazard of CVD and mortality, which undoubtedly address the existed knowledge gaps and expand the findings in previous studies. Notably, consistent with previous studies [19], we did not find a statistically significant association between the TyG index and stroke, which may be explained by two following reasons. First, the relatively small number of new-onset stroke cases ($n = 2{,}926$) may result in insufficient statistical power to detect such an association. Second, previous observational studies and Mendelian Randomization Study reported a significant association between TyG index and ischemic stroke, but did not find the association with hemorrhagic stroke [36, 37]. In our study, we combined two stroke subtypes as a composite outcome to increase the number of new-onset cases. However, the combination of two opposite effects may cause the non-significant association.

Obesity was commonly considered the leading risk factor for CVD and the key component in diagnosing MASLD [3]. Thus, the combination of TyG and adiposity

Table 5 Incremental predictive value of TyG-related indices for cardiovascular disease and mortality in participants with MASLD

Outcomes	Harrell's C index	*P* value	Continuous NRI, %	*P* value	IDI, %	*P* value
Overall CVD						
Basic model	0.662 (0.658–0.667)	-	–	–	–	–
Basic model + TyG	0.662 (0.658–0.667)	0.051	0.285 (– 0.841–1.150)	0.733	0.005 (– 0.000–0.021)	0.059
Basic model + TyG-BMI	0.663 (0.658–0.667)	0.003	4.213 (3.151–5.142)	< 0.001	0.078 (0.049–0.132)	< 0.001
Basic model + TyG-WC	0.663 (0.658–0.667)	< 0.001	3.927 (3.050–5.183)	< 0.001	0.096 (0.059–0.153)	< 0.001
Basic model + TyG-WHtR	0.664 (0.659–0.668)	< 0.001	5.008 (3.981–5.942)	< 0.001	0.144 (0.085–0.202)	< 0.001
CHD						
Basic model	0.661 (0.656–0.665)	–	–	–	–	–
Basic model + TyG	0.661 (0.656–0.666)	0.053	– 0.294 (-2.566–0.876)	0.574	0.003 (– 0.001–0.020)	0.218
Basic model + TyG-BMI	0.662 (0.657–0.666)	< 0.001	4.610 (3.564–5.789)	< 0.001	0.081 (0.052–0.141)	< 0.001
Basic model + TyG-WC	0.662 (0.657–0.667)	< 0.001	4.116 (3.205–5.332)	< 0.001	0.096 (0.058–0.160)	< 0.001
Basic model + TyG-WHtR	0.663 (0.658–0.667)	< 0.001	5.177 (4.220–6.331)	< 0.001	0.141 (0.089–0.201)	< 0.001
Stroke						
Basic model	0.684 (0.674–0.693)	–	–	–	–	–
Basic model + TyG	0.684 (0.675–0.693)	0.225	1.710 (– 1.968–3.410)	0.257	0.001 (– 0.002–0.020)	0.396
Basic model + TyG-BMI	0.684 (0.674–0.693)	0.575	2.228 (– 1.867–4.310)	0.238	0.004 (– 0.002–0.021)	0.198
Basic model + TyG-WC	0.684 (0.675–0.693)	0.391	2.485 (– 0.508–4.798)	0.099	0.008 (– 0.000–0.031)	0.059
Basic model + TyG-WHtR	0.684 (0.675–0.693)	0.262	3.040 (0.728–4.803)	0.040	0.014 (0.002–0.043)	< 0.001
All-cause mortality						
Basic model	0.711 (0.706–0.717)	–	–	–	–	–
Basic model + TyG	0.712 (0.707–0.717)	< 0.001	2.161 (0.734–3.078)	< 0.001	0.054 (0.021–0.085)	< 0.001
Basic model + TyG-BMI	0.712 (0.707–0.718)	< 0.001	5.377 (4.011–6.594)	< 0.001	0.130 (0.088–0.205)	< 0.001
Basic model + TyG-WC	0.714 (0.709–0.720)	< 0.001	6.855 (5.419–8.232)	< 0.001	0.312 (0.200–0.413)	< 0.001
Basic model + TyG-WHtR	0.714 (0.709–0.720)	< 0.001	6.924 (5.647–7.929)	< 0.001	0.300 (0.214–0.393)	< 0.001
Cardiovascular mortality						
Basic model	0.733 (0.722–0.744)	–	–	–	–	–
Basic model + TyG	0.734 (0.723–0.745)	0.042	1.808 (– 0.541-4.305)	0.218	0.025 (0.002–0.065)	0.02
Basic model + TyG-BMI	0.736 (0.725–0.748)	< 0.001	7.400 (4.695–10.512)	< 0.001	0.115 (0.054–0.265)	< 0.001
Basic model + TyG-WC	0.739 (0.727–0.750)	< 0.001	7.571 (5.104–9.910)	< 0.001	0.197 (0.117–0.309)	< 0.001
Basic model + TyG-WHtR	0.738 (0.727–0.749)	< 0.001	8.268 (5.508–10.689)	< 0.001	0.183 (0.097–0.300)	< 0.001

Basic models were adjusted for age, sex, smoking status, body mass index (BMI), systolic blood pressure (SBP), hypertension medication, diabetes, total cholesterol, high-density lipoprotein cholesterol (HDL-C).

MASLD metabolic-associated steatotic liver disease, *CVD* cardiovascular disease, *CHD* coronary heart disease, *TyG* triglyceride glucose inde, *BMI* body mass index, *WC* waist circumference, *WHtR* waist-to-height ratio, *NRI* net reclassification index, *IDI* integrated discrimination improvement index.

indicators (e.g., TyG-BMI, TyG-WC, and TyG-WHtR) had been proposed and determined the better performance than TyG index alone. Indeed, although BMI has typically served as a primary measure of obesity, it fails to distinguish fat from muscle and doesn't account for variations in body-fat distribution. In contrast, WC and WHtR are two valuable indices for central obesity, which showed the better performance for distinguishing metabolic dysfunction and CVD. Thence, TyG-WC and TyG-WHtR were reported to have higher predictive performance than other TyG-related parameters [23, 24]. In consistent with previous results, current study further found that TyG-WC and TyG-WHtR also had optimal predictive effect on CVD occurrence in individuals with MASLD, with the Harrell's C index being 0.661 to 0.739. Meanwhile, we found that both TyG-WC and TyG-WHtR had a linear association with the risk of developing overall CVD, CHD, and stroke (all *P* values for non-linearity > 0.05, except for TyG-WC with stroke), indicating that these two indices should be carefully controlled at a lower level in MASLD population. Taken together, our findings along with previous studies suggested that TyG-related indices, especially TyG-WC and TyG-WHtR, could survive as the simple and effective indicators to identifying high-risk CVD population in MASLD.

Although the explicit biological mechanisms underlying the association of TyG-related indices with CVD in MASLD remain unclear, the TyG index is a reliable surrogate indicator of IR and several potential reasons may be explained. First, the normal levels of insulin could exert nitric oxide-dependent vasodilation and endothelin-1 (ET-1)-dependent vasoconstriction, through phosphatidylinositol 3-kinase (PI3K)- and mitogen-activated protein kinase (MAPK)-dependent signaling pathways, to maintain the contractile and diastolic function in

vascular endothelial cells [9, 23, 38]. But this balance was disrupted under the IR condition, leading to endothelial abnormalities. Second, hyperglycaemia is commonly accompanied in patients with IR, which in turn triggers systolic inflammatory response and oxidative stress [14]. Besides, previous studies have demonstrated that hyperglycaemia-related excessive glycosylation can promote smooth muscle cell proliferation, collagen crosslinking, and collagen deposition, which further aggravate CVD progression [9]. Additionally, systemic lipid abnormalities have also been reported in IR, such as elevated TG and reduced HDL-C levels, which may cause the atherosclerosis [39].

To our knowledge, this study is the first to investigate the prognostic value of TyG-related indices for the risk of new-onset occurrence of CVD in MASLD patients. The primary strengths of our study included the larger sample size, the prospective cohort study design, the longer follow-up period, the comprehensive measurement of potential covariates, and the reliable assessment -up of outcomes. However, several limitations should be considered when interpreting our findings. First, due to the data availability of ultrasonographic measurements in the UK Biobank, hepatic steatosis was only defined based on the FLI ≥ 60. However, the sensitivity and specificity of FLI have been validated in previous studies [28, 29]. Second, the UK Biobank is not a nationally representative cohort study and majority individuals are White ethnicity, which limits the generality of our finding. Future studies in other population with different genetic background or sociodemographic characteristics are encouraged to confirm our results. Third, although several potential covariates were adjusted in our analyses, there may exist residual confounding factors due to the observational study design. Fourth, due to the unavailability of data on the age at which CVD was diagnosed in participants' parents and siblings, we cannot distinguish the family history of early-onset CVD, which is a well-established risk factor for CVD incidence and mortality. Fifth, TyG-related indices were measured only at baseline, which prevent us to further investigate the dynamic changes of TyG indices with CVD risks. Finally, non-fasting blood glucose was used to calculate the TyG-related indices, which could influence the TyG levels. According to previous study [19], we conducted a sensitivity analysis with the additional adjustment for the HbA1c in the fully adjusted models, and found the similar results with main results.

Conclusion

In conclusion, our study showed that high levels of TyG-related indices (e.g., TyG, TyG-BMI, TyG-WC, and TyG-WHtR) were independently and significantly associated with increased risk of developing CVD and mortality in MASLD patients. Moreover, TyG-WHtR and TyG-WC have the more pronounced prognostic values than other indices for the risk of occurring CVD in MASLD population. These findings indicate that TyG-related indices, especially TyG-WHtR and TyG-WC, should be measured and monitored in the clinical management of MASLD patients for the early prevention of CVD and mortality.

Abbreviations

BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence intervals
CVD	Cardiovascular disease
ET-1	Endothelin-1
FLI	Fatty liver index
HbA1c	Glycated haemoglobin
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic model assessment of insulin resistance
HR	Hazard ratio
ICD-10	The 10th revision of International Classification of Diseases
IDI	Integrated discrimination improvement index
IQR	Interquartile range
IR	Insulin resistance
MAPK	Mitogen-activated protein kinase
MASLD	Metabolic dysfunction-associated steatotic liver disease
MetS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
NHANES	National Health and Nutrition Examination Survey
NRI	Net reclassification index
PI3K	Phosphatidylinositol 3-kinase
RCS	Restrict cubic spline
SD	Standard deviation
TDI	Townsend deprivation index
TG	Triglycerides
TyG	Triglyceride-glucose
WC	Waist circumference
WHtR	Waist-to-height ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02572-w.

Supplementary Material 1

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Author contributions

YQH, CHZ, and YNQ conceived and designed the research, YQH performed the data analysis, WY and CC wrote the manuscript, YNQ and YQH interpreted the analyzed results, YQH, CHZ, and YNQ revised the manuscript critically for important intellectual content. All authors contributed to the interpretations of the findings and reviewed the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All participants gave written informed consent, and ethical approval of the UK Biobank was received from the North West Multicenter Research Ethics Committee (reference number: 21/NW/0157).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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