Cardiovascular Diabetology

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Comparison of triglyceride glucose index and modified triglyceride glucose indices in predicting cardiovascular diseases incidence among populations with cardiovascular-kidney-metabolic syndrome stages 0–3: a nationwide prospective cohort study

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Abstract

Background Cardiovascular-kidney-metabolic (CKM) syndrome has been recently proposed by American Heart Association recently. The triglyceride glucose (TyG) index and TyG-related indices combined with obesity indicators have proven to be associated with the incidence of cardiovascular diseases (CVD). However, there are few studies to explore whether these associations exist among people with CKM syndrome stages 0–3.

Methods A total of 7,364 participants from the China Health and Retirement Longitudinal Study were included. Cox hazard regression and restricted cubic spline regression were used to analyze the associations of these indices with CVD incidence. To compare predictive performance, time-dependent Harrell's C-indices, net reclassification index and integrated discrimination improvement were conducted.

Results The CVD incidence was 20.55% over nine years. The TyG single index and all the modified TyG indices were capable of predicting CVD incidence. RCS regression analyses showed that all indicators had linear relationships with CVD incidence and these linear relationships of TyG combined with waist circumference (TyG-WC) or waist-to-height ratio (TyG-WHtR) still existed in CKM stage 1, stage 2 and stage 3. TyG-WC (C-index: 0.621, $p < 0.001$) and TyG-WHtR

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(C-index: 0.621, $p < 0.001$) almost had the highest C-indices in predicting CVD incidence, compared to single TyG index (C-index: 0.611, $p < 0.001$) and TyG combined with body mass index (C-index: 0.616, $p < 0.001$).

Conclusion The TyG index and all the modified TyG indices were independent predictors of CVD incidence among people with CKM syndrome stages 0–3. It was found that modified indices had better predictive performance, especially TyG combined with waist circumference or waist-to-height ratio.

Keywords Cardiovascular kidney metabolic syndrome, Cardiovascular disease, Triglyceride glucose index, Modified triglyceride glucose indices

Introduction

According to the Global Burden of Disease(GBD) Study 2019, cardiovascular disease(CVD) was the leading cause of death and disability worldwide, and modifiable risk factors of CVD burden still increased globally [1]. Cardiovascular-kidney-metabolic (CKM) syndrome contains those modifiable risk factors, and was proposed by the American Heart Association (AHA) in October 2023 [2]. CKM syndrome is a systemic disorder resulting from the pathophysiological interactions among metabolic risk factors, chronic kidney diseases (CKD) and CVD [2, 3]. The clinical burden of different stages of CKM syndrome is disproportionately related to CVD, and it is essential to consider metabolism, kidney and cardiovascular system as a unified system [4–6]. The AHA has focused identifying the preclinical stages and emphasized that studies among people with CKM stage 0–3 should focused more on preventing CVD incidence [3].

Insulin resistance (IR) is a metabolic syndrome, referring to reduced or impaired insulin sensitivity of target organs or tissues, which is manifested by an impairment in the absorption and oxidation of glucose [7–10]. It has been proven that people with chronically high levels of IR have higher risks of developing CVD, even if they are not affected by type 2 diabetes [9–10]. The triglyceride glucose (TyG) index, a marker of IR, was first proposed in 2008 [11] and proven to be associated with the incidence, adverse outcome and mortality of CVD, including acute coronary syndrome, coronary heart disease, stroke, heart failure or other heart problems [12–17]. IR is not only affected by metabolic biomarkers including triglycerides and glucose, but also closely related to the content and distribution of fat in the body [18, 19]. Hormones and cytokines in fat cells can enhance or inhibit blood glucose response and insulin signaling [18]. Given the strong link between IR and obesity, an increasing number of researchers have focused on modified TyG indices, which involve TyG and body mass index (BMI), waist circumference (WC) and waist-to-height ratio (WHtR) [19] combined. The modified TyG indices were confirmed to have better predictive ability, than the TyG index, for CVD [20–22]. A large prospective cohort study concluded that TyG-WC and TyG-WHtR were superior to TyG and TyG-BMI in predicting the occurrence of cardiovascular disease (C-index: TyG = 0.583, TyG-BMI = 0.584, TyG-WC = 0.612, TyG-WHTR = 0613) [20].

In the context of cardiometabolic medicine, TyG is proven to be a promising marker for prevention [23]. And in the background of CKM syndrome, TyG-BMI is also proven by Weipeng Li to be related to CVD incidence [24]. However, among the population at CKM stage 0–3, few studies have focused on TyG single index and other modified TyG indices, which were important on CVD incidence. Hence, this study based on the data from the China Health and Retirement Longitudinal Study (CHARLS) 2011–2020, is to explore the association between TyG and modified TyG indices with CVD incidence among the population at CKM stage 0–3 for early detection and intervention, including non-linear relationship, comparison of predictive performance and further investigation of each CKM syndrome stage.

Methods

Study population

CHARLS is a nationally representative longitudinal survey in China, covering 450 villages, 150 counties and 28 provinces. This study was carried out by the National School of Development at Peking University, setting survey in 2011–2022 as baseline (Wave 1) and completing four follow-up surveys to date (Wave 2 in 2013, Wave 3 in 2015, Wave 4 in 2018 and Wave 5 in 2020). The CHARLS was approved by the Institutional Review Board of Peking University (IRB00001052-11015) and all participants provided written informed consent before enrolling in the study. The study was conducted in accordance with Enhanced Observational Epidemiological Research Reports (STROBE) reporting guidelines [25]. Detailed information of the CHARLS has been described previously [26] and data is able to download online (https://charls.pku.edu.cn/) after completing registration and application.

Our study was a secondary analysis using data from all five waves of CHARLS waves. The exclusion criteria of our study were as follows: (1) age less than 45 years, (2) have a history of cardiovascular diseases at/before baseline (Wave 1), (3) lacking or having abnormal values of exposure indicators, (4) missing indicators necessary for CKM syndrome staging, (5) lacking of baseline

characteristics, and (6) following up less than two years. We included 17,708 samples from Wave 1 for screening and enrolled 7,364 participants in the final analysis. The detailed process of population selection is shown in Fig. 1.

Data assessment

Outcome ascertainment

The primary outcome was the incidence of cardiovascular diseases including heart problems and stroke, during the 9-year follow-up (from Wave2 to Wave 5). The follow-up duration was calculated from enrollment to either the occurrence of the outcome event or the last recorded contact. Outcome event occurrence was assessed by two standardized questions [12, 19]: "Have you been diagnosed by a doctor with a heart attack, coronary heart disease, angina, congestive heart failure or other heart problems?" and "Have you been diagnosed with stroke by a doctor?". Participants who had answered "yes" to one of these two questions were considered to have CVD.

Assessment of TyG and modified TyG indices

Fasting blood glucose (FBG) and triglyceride (TG) were collected after a night of fasting and analyzed using a Hitachi 7180 chemistry analyzer (Hitachi, Tokyo, Japan) through Enzymatic colormetric test. As for physical examination, height, weight and WC were all measured three times and the averages were recorded as the final measurements. A vertical altimeter and a weight scale were respectively used to measure height and weight. WC was measured by a soft ruler encircling the waist at the navel horizontal when participants stood. The formula of TyG index was " $\mathrm{TyG\ index} = \ln[\mathrm{TG(mg/dl)} \times \mathrm{FBG(mg/dl)}/2]$ " [27]. BMI was calculated as " $\mathrm{Weight\ (kg)}/\mathrm{Height\ (m)}^2$ " [28] and WHtR was defined as " $\mathrm{Waist\ (cm)}/\mathrm{Height\ (cm)}$ " [19]. Through multiplying TyG with BMI, WC and WHtR respectively, modified TyG indices were produced (TyG-BMI, TyG-WC and TyG-WHtR). TyG and modified TyG indices were all divided into four groups according to quartiles (Q):

TyG, Q1: TyG < 8.20, Q2: 8.20 ≤ TyG < 8.56, Q3: 8.56 ≤ TyG < 8.97; Q4: 8.97 ≤ TyG;
TyG-BMI, Q1: TyG-BMI < 174.74, Q2: 174.74 ≤ TyG-BMI < 196.62, Q3: 196.62 ≤ TyG-BMI < 223.35, Q4: 223.35 ≤ TyG-BMI;
TyG-WC, Q1: TyG-WC < 650.20, Q2: 650.20 ≤ TyG-WC < 720.82, Q3: 720.82 ≤ TyG-WC < 802.82, Q4: 802.82 ≤ TyG-WC;
TyG-WHtR, Q1: TyG-WHtR < 4.10, Q2: 4.10 ≤ TyG-WHtR < 4.58, Q3: 4.58 ≤ TyG-WHtR < 5.11, Q4: 5.11 ≤ TyG-WHtR.

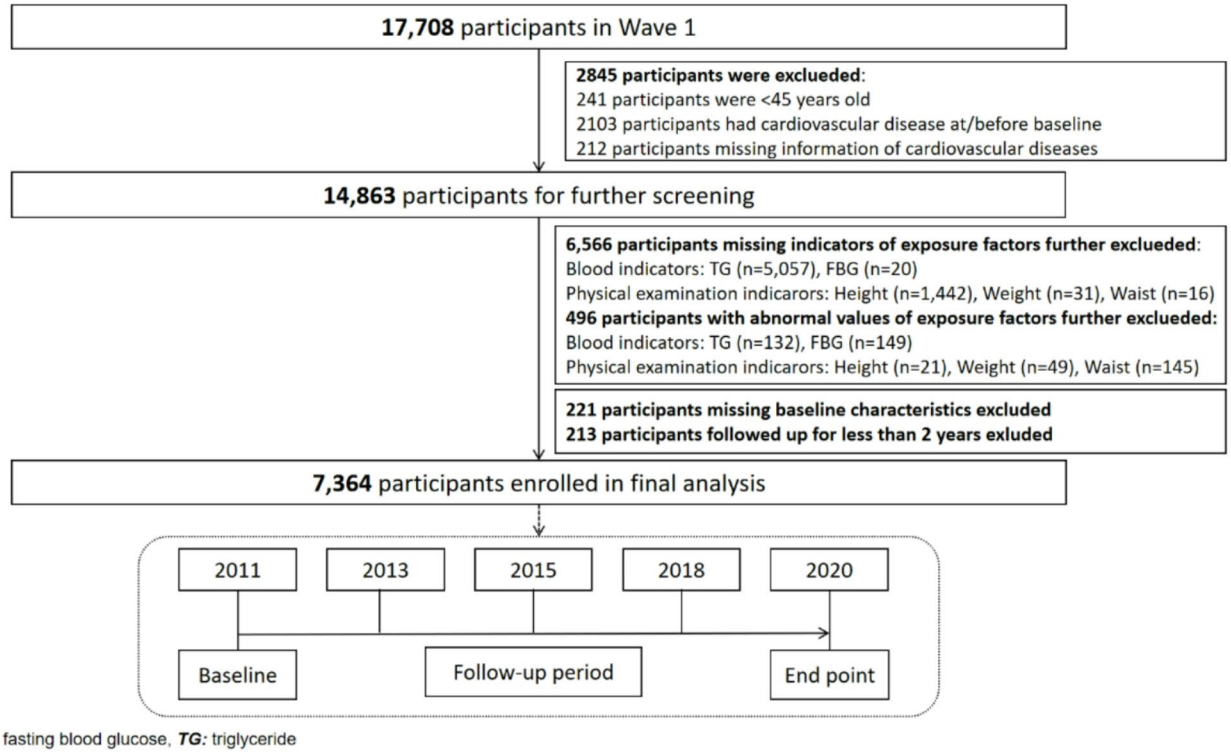

Fig. 1 Flowchart illustrating the selection of the study population

Definition of CKM syndrome stages 0–3

According to a presidential advisory from the AHA [3], the stages of CKM syndrome from 0 to 3 are as follows: Stage 0 includes individuals without CKM syndrome risk factors; Stage 1 involves overweight, abdominal obesity or dysfunctional adipose tissue without CKD; Stage 2 includes individuals with metabolic risk factors (such as hypertriglyceridemia, hypertension, metabolic syndrome, or type 2 diabetes), moderate-to-high-risk CKD, or both; Stage 3 includes people with high risks or presence of subclinical CVD.

Risk equivalents of subclinical CVD were assessed based on high predicted 10-year CVD risk and very high-risk CKD. The Framingham risk score was used to assess 10-year CVD risk, which when above 20% was considered to be high predicted risk [29]. The CKD stages were classified according to Kidney Disease Improving Global Outcomes (KDIGO) [3]. High-risk CKD was defined as having an estimated glomerular filtration rate (eGFR) below 30 (ml/min per 1.73m^2) based on a review issued in JAMA in 2019 [30]. The formula we used for calculating eGFR was "$\text{eGFR (ml/min per 1.73m}^2) = 175 \times \text{Scr}^{-1.234} \times \text{age}^{-0.179} \times 0.79\,(\text{if female})$" according to the Chinese Modification of Diet in Renal Disease (C-MDRD) [31].

Data collection

This study included the following data:

1. sociodemographic data: age, gender, education level (elementary school and below, secondary school, college and above), marital status (married, other status: separated, divorced, widowed, never married) and residency registration (rural, others: including non-agricultural residency registration, unified residency registration and people without residency registration);
2. health status data: self-reported smoking and drinking status, and self-reported history of hypertension and diabetes;
3. physical examination data: height, weight, WC and systolic blood pressure (SBP);
4. laboratory examination data: TG, FBG, glycated hemoglobin (HBA1c), total cholesterol (TC), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), blood urea nitrogen (BUN), uric acid (UA) and serum creatinine (Cr).

In Wave 1, the sociodemographic data and health status data were collected by trained investigators using a structured questionnaire [26].

Statistical analysis

Baseline characteristics were described according to the stages of CKM syndrome (Stages 0–3) and outcome status (yes or no). Before statistical analysis, normality of continuous variables was assessed using Kolmogorov-Smirnov test. Variables with $p < 0.05$ in the Kolmogorov-Smirnov test were following normal distributions, which were described using means and standard deviation (SD), and One-way ANOVA or t-test used to analyzed the differences among groups. When variables were not following normal distributions, median and interquartile range were used to describe the distribution, and the differences among groups were assessed via Kruskal-Wallis test or Mann-Whitney U test. For categorical variables, quantity and percentage were used for description, and differences among groups were analyzed by chi-square test or Fisher's exact test. The distribution of those indices were shown through histograms. We divided those indices into four groups (Q1-Q4) according to their quartiles. Kaplan-Meier curves were used to represent the cumulative incidence of CVD incidences. The potential non-liner associations between these indices and CVD incidence were analyzed through restricted cubic spline (RCS) regression. The number of knots was determined based on the convergence of the solution, with an empirical test showing that a set of four knots produced satisfactory results for the problem. The knots were placed at adaptive intervals within the [0, 1] interval, ensuring a sufficient coverage of the solution space. For assessing the associations between those indices and CVD incidences, Cox hazard regression models were conducted using crude models and three adjusted models. Schoenfeld residual test method was used to test proportional risk hypothesis and RCS was used to assess linear relationship. The selection principles of the covariates in the Cox hazard regression models were following: (1) clinical constraints and previous findings; (2) generalized variance inflation factor (GVIF) analysis used to identify multicollinearity; (3) p-value of variables less than 0.1 for univariate analysis. Model 1 adjusted gender and age. Model 2 further adjusted for marital status (married; other status: including separated, divorced, widowed, never married), education level (elementary school and below; secondary school; college and above), smoking status (yes: have ever or still smoked; no: never smoked), drinking status (yes: drunk in the past year; no: none of any alcoholic beverages in the past year) and history of hypertension and diabetes (yes: have been diagnosed by a doctor; no: never been diagnosed by a doctor) on the basis of model 1. Model 3 adjusted for factors in model 2 and BUN, UA, eGFR and LDL. In order to compare the predictive capacity of TyG, TyG-BMI, TyG-WC and TyG-WHtR in CVD incidence, we calculated the time-dependent Harrell's C-indices. Net reclassification index

(NRI) and integrated discrimination improvement (IDI) index were also used to further evaluate the incremental predictive value.

Furthermore, to explore the association between CVD incidence and these indices among different stages of CKM syndrome (Stage 0 to Stage 3), subgroup analysis, interaction analyses and RCS regression analyses were also employed in the CKM stage 0, CKM stage 1, CKM stage 2 and CKM stage 3 populations, respectively. Sensitivity analyses were conducted to assess the robustness of the model. All statistical analyses were performed using R software (version 4.4.0). A two-sided $P < 0.05$ was considered statistically significant.

Results

A total of 7,364 participants were included this study, with 53.1% female and an average age of 60.53 ± 9.33 years old. The follow-up period was from 2 years to 9 years, during which about 78.25% of the participants completed nearly 9 years following up, with a median follow-up time of 9.0 years. CKM Stage 2 had the greatest number of participants ($n = 2,474$). People in CKM stage 3 were mostly male (82.9%) and smokers (75.4%), had the highest SBP (142.70 ± 25.64mmHg), FBG (109.08 ± 23.44 mg/dL) and 10-year risk (27.46 ± 3.33%) (Table 1). The baseline characteristics according to CVD incidence is shown in Additional File 1; Table S1 with an incidence of 20.55%. Figure 2 shows the distribution of TyG, TyG-BMI, TyG-WC and TyG-WHtR among the individuals at CKM stage 0–3.

Relationship between TyG and modified TyG indices with CVD incidence among people with CKM stage 0–3

TyG and modified TyG indices (TyG-BMI, TyG-WC, TyG-WHtR) were divided in four groups based on their quartiles (Q1-Q4), which are displayed in Additional file 1; Table S2. Kaplan-Meier curves of the cumulative incidence of CVD are shown in Fig. 3. In order to ensure the accuracy of the RCS analysis, knots were adaptively distributed within the [0, 1] interval, with a total of 4 knots. RCS regression analysis indicated that the TyG and modified TyG indices had linear relationships with CVD occurrence (TyG, P for non-linear: 0.126; TyG-BMI, P for non-linear: 0.4456; TyG-WC, P for non-linear: 0.6691; TyG-WHtR, P for non-linear: 0.7286, cut-off: 4.5882; Fig. 4).

Table 2 displays the associations of TyG index and modified TyG indices with CVD incidence. The p-values of Schoenfeld residual test for all the cox regression models were all above 0.05. When setting TyG and modified indices as continuous dependent variables, the risk of CVD increased with each rise in standard deviation. In model 3, a 23.0% increase in risk of CVD incidence occurred for every standard deviation in TyG-WC, which had the most increase compared to TyG (HR: 1.11, 95%CI: 1.05–1.17), TyG-BMI (HR: 1.21, 95%CI: 1.15–1.28) and TyG-WHtR (HR: 1.20, 95%CI: 1.14–1.27). TyG and modified indices also were converted into categorical variables by quartile. In the complete adjusted model, setting the lowest quartile as reference, people in the highest quartile of these four indices were associated significantly with a higher risk of CVD incidence. The adjusted HRs (95% CI) were as follows: TyG: 1.27 (1.09–1.48), TyG-BMI: 1.70 (1.45–1.99), TyG-WC: 1.79 (1.54–2.10) and TyG-WHtR: 1.65 (1.40–1.94). The greatest increase in CVD risk of 79% was observed in the highest quartile of TyG-WC compared to their reference (Table 2).

Based on the adjusted cox regression model 3, C-index analysis, NRI and IDI anlysis were used to assess predictive performance. The overall C-index values were 0.621 ($p < 0.001$) for TyG-WC and TyG-WHtR ($p < 0.001$), followed by 0.616 ($p < 0.001$) for TyG-BMI and 0.611 ($p < 0.001$) for TyG. The time-dependent Harrell's C-indices of TyG and modified indices are shown in Fig. 5. Figure 6 shows the NRI and IDI indices comparing the models. The categorical NRI of 0.005 ($p = 0.898$) and IDI of 0.001 ($p = 0.754$) were not significant when comparing TyG-BMI to TyG, which was similar to comparing TyG-WHtR with TyG-WC (NRI: 0.016, $p = 0.475$; IDI: 0.001, $p = 0.603$). Against TyG alone, TyG-WC and TyG-WHtR yielded significant NRI indices (TyG-WC: 0.084, $p = 0.008$; TyG-WHtR: 0.102, $p = 0.004$) and IDI indices (TyG-WC: 0.006, $p = 0.012$; TyG-WHtR: 0.007, $p = 0.036$). Compared to TyG-BMI, both TyG-WC and TyG-WHtR had better discriminatory power and risk reclassification (TyG-WC: NRI = 0.060, $p = 0.048$, IDI = 0.006, $p = 0.004$; TyG-WHtR: NRI = 0.100, $p < 0.001$, IDI = 0.005, $p = 0.012$).

Relationship between TyG and modified TyG indices with CVD incidence in the CKM stage 0, CKM stage 1, CKM stage 2 and CKM stage 3 populations

Subgroup analysis was performed to explore the relationship between TyG and modified TyG indices with CVD incidence in different age, gender and CKM stage populations (Table 3). TyG and modified TyG indices had no interactions with age, gender and CKM stages (Additional file 1; Table S3). All the indices were predictive factors of CVD incidences in people younger than and greater than 60 years old. These relationships were also significant in male and female populations. TyG-BMI and TyG-WC still had predictive value of CVD incidence among people in CKM stage 1 (HR: TyG-BMI, 1.27; TyG-WC, 1.45), stage 2 (HR: TyG-BMI, 1.17; TyG-WC, 1.20) and stage 3 (HR: TyG-BMI, 1.17; TyG-WC, 1.18). TyG was a predictive factor among people in CKM stage 1 (HR: 1.32).

In CKM stage 1, 2 and 3, sensitivity analyses were conducted to address potential heterogeneity across CKM

Table 1 Baseline characteristic according to CKM stages

Characteristics	Total	CKM Stage				*P*-value
		Stage 0	Stage 1	Stage 2	Stage 3	
n	7364	652	1937	2474	2301	
Gender (%)						< 0.001
Male	3457 (46.9)	324 (49.7)	601 (31.0)	624 (25.2)	1908 (82.9)	
Female	3907 (53.1)	328 (50.3)	1336 (69.0)	1850 (74.8)	393 (17.1)	
Age, years (mean (SD))	60.53 (9.33)	57.68 (8.09)	57.05 (8.06)	58.43 (8.41)	66.52 (8.74)	< 0.001
Education.level (%)						0.007
Elementary school and below	450 (69.0)	1319 (68.1)	1714 (69.3)	1684 (73.2)	1806 (72.3)	
Secondary school	196 (30.1)	597 (30.8)	728 (29.4)	587 (25.5)	661 (26.5)	
College and above	6 (0.9)	21 (1.1)	32 (1.3)	30 (1.3)	32 (1.3)	
Marital.status (%)						< 0.001
Married	595 (91.3)	1754 (90.6)	2226 (90.0)	1954 (84.9)	2137 (85.5)	
Others	57 (8.7)	183 (9.4)	248 (10.0)	347 (15.1)	362 (14.5)	
Residency registration (%)						< 0.001
Rural	6227 (84.6)	591 (90.6)	1683 (86.9)	2069 (83.6)	1884 (81.9)	
Others	1137 (15.4)	61 (9.4)	254 (13.1)	405 (16.4)	417 (18.1)	
Smoke (%)						< 0.001
Yes	2865 (38.9)	252 (38.7)	442 (22.8)	437 (17.7)	1734 (75.4)	
No	4499 (61.1)	400 (61.3)	1495 (77.2)	2037 (82.3)	567 (24.6)	
Drink (%)						< 0.001
Yes	2465 (33.5)	249 (38.2)	550 (28.4)	569 (23.0)	1097 (47.7)	
No	4899 (66.5)	403 (61.8)	1387 (71.6)	1905 (77.0)	1204 (52.3)	
Hypertension (%)						< 0.001
Yes	1475 (20.0)	0 (0.0)	0 (0.0)	683 (27.6)	792 (34.4)	
No	5889 (80.0)	652 (100.0)	1937 (100.0)	1791 (72.4)	1509 (65.6)	
Diabetes (%)						< 0.001
Yes	267 (3.6)	0 (0.0)	0 (0.0)	121 (4.9)	146 (6.3)	
No	7097 (96.4)	652 (100.0)	1937 (100.0)	2353 (95.1)	2155 (93.7)	
Height, cm (mean (SD))	157.91 (8.46)	158.06 (8.89)	156.50 (8.17)	156.18 (8.01)	160.91 (8.23)	< 0.001
Weight, kg (mean (SD))	58.14 (10.56)	50.59 (7.39)	57.57 (9.63)	58.70 (10.76)	60.15 (10.86)	< 0.001
WC, cm (mean (SD))	84.70 (9.64)	75.36 (5.33)	84.50 (8.47)	85.97 (9.88)	86.15 (9.77)	< 0.001
BMI, kg/m^2 (mean (SD))	23.26 (3.49)	20.17 (1.68)	23.45 (3.16)	24.00 (3.65)	23.17 (3.49)	< 0.001
WHtR(mean(SD))	0.54 (0.06)	0.48 (0.03)	0.54 (0.06)	0.55 (0.07)	0.54 (0.06)	< 0.001
SBP, mmHg (mean (SD))	129.95 (23.92)	116.78 (20.36)	122.93 (18.39)	127.05 (21.77)	142.70 (25.64)	< 0.001
HbA1c, % (mean (SD))	5.18 (0.57)	4.98 (0.39)	5.16 (0.50)	5.21 (0.58)	5.23 (0.65)	< 0.001
FBG, mg/dL (mean (SD))	105.32 (20.61)	90.33 (8.16)	104.35 (17.56)	106.53 (20.51)	109.08 (23.44)	< 0.001
TC, mg/dL (mean (SD))	192.64 (37.30)	179.14 (31.58)	186.87 (34.58)	197.28 (37.82)	196.35 (38.87)	< 0.001
HDL, mg/dL (mean (SD))	52.06 (15.07)	59.20 (14.09)	56.56 (14.02)	49.44 (13.80)	49.07 (15.90)	< 0.001
LDL, mg/dL (mean (SD))	117.11 (33.84)	107.00 (28.21)	115.45 (30.71)	117.54 (35.15)	120.90 (35.68)	< 0.001
TG, mg/dL (mean (SD))	121.50 (69.38)	76.70 (25.13)	85.21 (25.45)	152.87 (75.99)	131.01 (75.17)	< 0.001
BUN, mg/dL (mean (SD))	15.72 (4.48)	15.33 (4.28)	15.18 (4.06)	15.54 (4.49)	16.48 (4.76)	< 0.001
Cr, mg/dL (mean (SD))	0.78 (0.22)	0.71 (0.12)	0.68 (0.12)	0.78 (0.18)	0.87 (0.30)	< 0.001
UA, mg/dL (mean (SD))	4.43 (1.23)	3.98 (1.01)	3.94 (0.97)	4.45 (1.19)	4.96 (1.29)	< 0.001
eGFR, ml/min per 1.73 m^2 (mean (SD))	108.21 (27.65)	119.25 (22.50)	120.39 (24.12)	102.66 (28.61)	100.78 (26.22)	< 0.001
Framingham, 10-year CVD risk% (mean (SD))	14.63 (9.82)	8.51 (5.40)	7.66 (4.96)	9.76 (5.01)	27.46 (3.33)	< 0.001
TyG (mean (SD))	8.61 (0.58)	8.09 (0.36)	8.34 (0.37)	8.87 (0.58)	8.71 (0.59)	< 0.001
TyG-BMI (mean (SD))	200.84 (36.57)	163.15 (15.45)	195.58 (28.16)	213.21 (37.86)	202.63 (37.56)	< 0.001
TyG-WC (mean (SD))	730.96 (108.88)	609.70 (52.05)	704.73 (79.27)	763.30 (109.01)	752.63 (113.02)	< 0.001
TyG-WHtR (mean (SD))	4.64 (0.71)	3.86 (0.34)	4.51 (0.54)	4.90 (0.71)	4.69 (0.74)	< 0.001

BMI: body mass index, BUN:blood urea nitrogen, Cr:serum creatinine, CKM: cardiovascular-kidney-metabolic syndrome, eGFR: estimated Glomerular Filtration Rate, FBG: fasting blood glucose, HbA1c: glycated hemoglobin, HDL: high density lipoprotein cholesterol, LDL: low density lipoprotein cholesterol, SBP: systolic blood pressure, TC: total cholesterol, TG: triglyceride, TyG: triglyceride glucose, TyG-BMI: TyG multiplied BMI, TyG-WC: TyG multiplied WC, TyG-WHtR: TyG multiplied WHtR, WC: waist circumference, WHtR: waist-to-height ratio, UA: uric acid

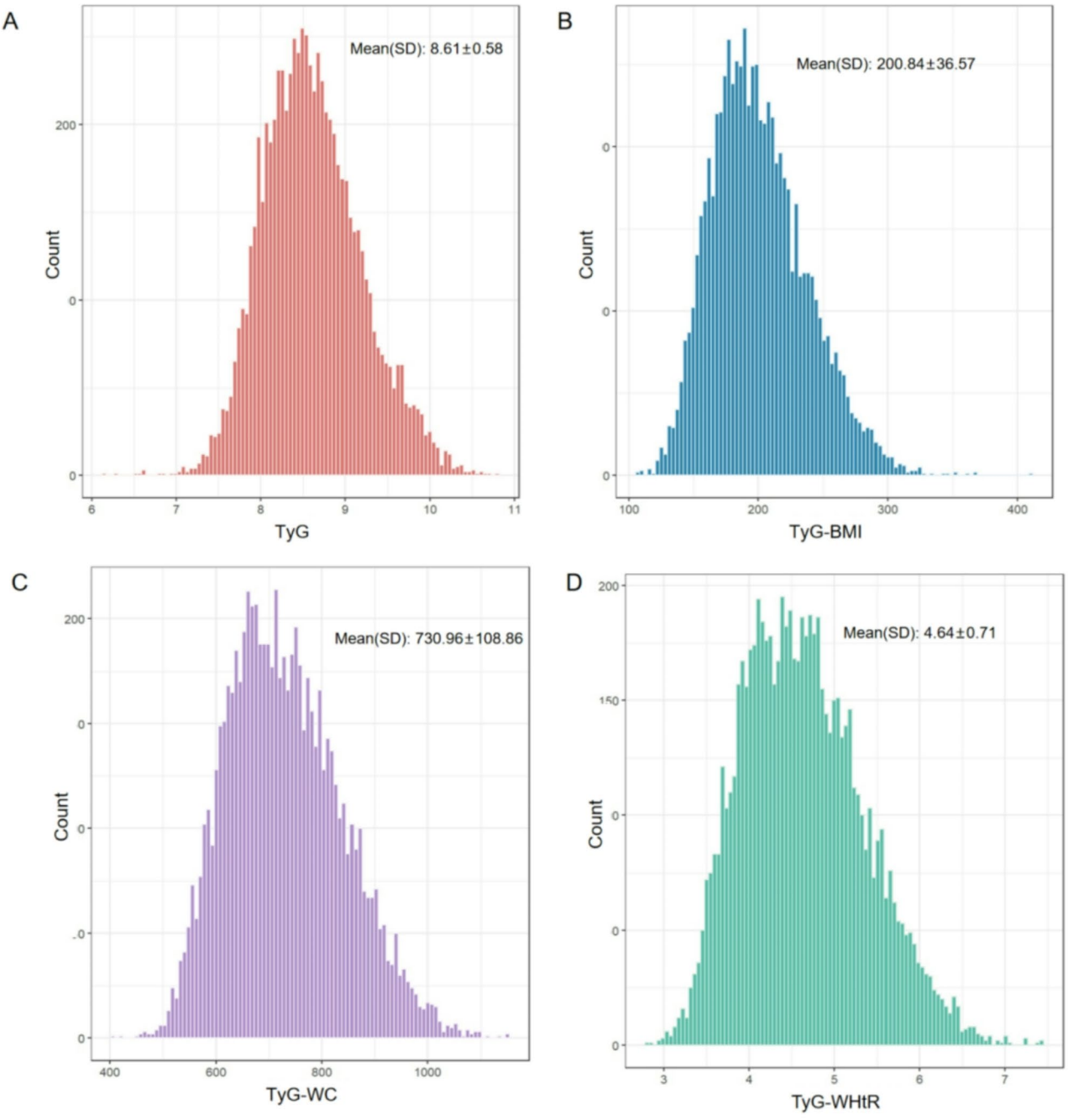

Fig. 2 Distribution of TyG and modified TyG indices

stages (Table 4). Cox regression model 2 was set as basic model (adjusted demographic and disease information, including age, gender, marital status, education level, smoking status, drinking status and history of hypertension and diabetes). Sensitivity 1 was adjusted stage-specific covariates: HbA1c and LDL-C for stage 1 because people in CKM stage 1 almost had metabolic factors, and eGFR for stages 2–3 because people in CKM 2 and 3 began with organ damage. Sensitivity 2 excluded participants who only follow up to Wave 1, and sensitivity 3 further excluded participants who follow up to Wave 2 based on sensitivity 2. After sensitivity analyses, the relationship of TyG and CVD incidence was only significant in people with CKM stage 1 and the sensitivity analyses also proved the robustness of the model. And the association between modified TyG indices and CVD incidence remained robust across CKM stage 1 to stage 3 (Table 4).

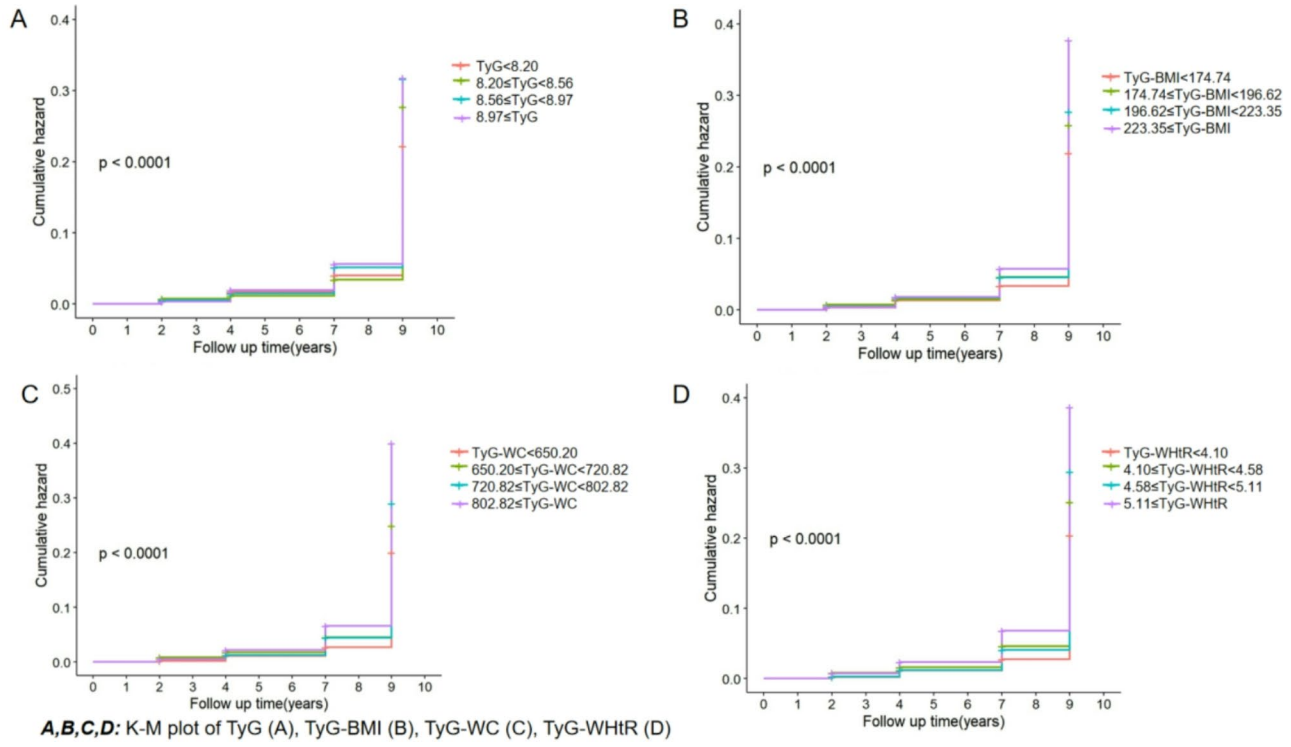

Fig. 3 K-M plot of CVD incidence by TyG and modified TyG indices

The RCS analysis between TyG index and modified indices with CVD incidence in a population with different CKM syndrome stages also shown in Fig. 7. Knots are adaptively distributed along [0, 1], with a total of 4 knots selected. In the CKM stage 0 population, the relationship between TyG and modified indices with CVD incidence was insignificant (P for overall > 0.05). TyG only had a relationship with CVD incidence in CKM stage 1, and this relationship was linear (P for overall: 0.007, P for non-linear: 0.496). Among people with CKM stage 1, the relationship between TyG-BMI and CVD incidence was non-linear (P for overall < 0.001, P for non-linear: 0.048, cut-off: 194.06), while TyG-WC and TyG-WHtR had linear relationships (TyG-WC, P for overall < 0.001, P for non-linear: 0.881; TyG-WHtR, P for overall < 0.001, P for non-linear: 0.299). All of the modified indices had a linear relationship with CKM stage 2 and CKM stage 3 (P for overall < 0.001, P for non-linear > 0.05).

Discussion

This study comprehensively explored the association between TyG single index and modified TyG indices with CVD incidence in the context of CKM syndrome. CKM syndrome proposed by the AHA [3] covers key factors of CVD incidences [2], and there exists interaction among heart, kidney and metabolism [2, 32]. Previous studies have proven that TyG single index and TyG-related indices combined with obesity indicators have significant relationships with CVD incidences in general population [19, 33–37]. In consequence, investigating the relationship between TyG and modified TyG indices with CVD in the background of CKM syndrome is essential.

IR is defined as the inability of insulin to optimally stimulate the transport of glucose into the body's cell, including hyperinsulinemia or impaired glucose tolerance [38], which plays an important role in cardiovascular diseases incidence [39]. One mechanism by which IR leads to CVD is through increases in vascular stiffness [40], and deficiency of insulin signaling in atherosclerotic lesion cells also contributes to CVD incidence [7]. The components of CKM syndrome are clearly associated with the risk of atherosclerosis, and one mechanism by which CKM progresses to CVD is the acceleration of atherosclerosis through IR [2]. TyG index and TyG-related indices combined with obesity indicators are important predictors for IR [41–43].

We have found that single TyG index and TyG-related indices combined with obesity indicators all had positive relationship with CVD incidences among people at CKM stages 0–3, and these relationships were linear. Xia X et al. also found TyG index and its related parameters were significantly positively correlated with CVD onset based on Chinese Kailuan database among general population [20]. For TyG-BMI, the risk of CVD increased by about 70% in the highest quartile compared with the lowest quartile. It is consistent with the results of Weipeng Li's

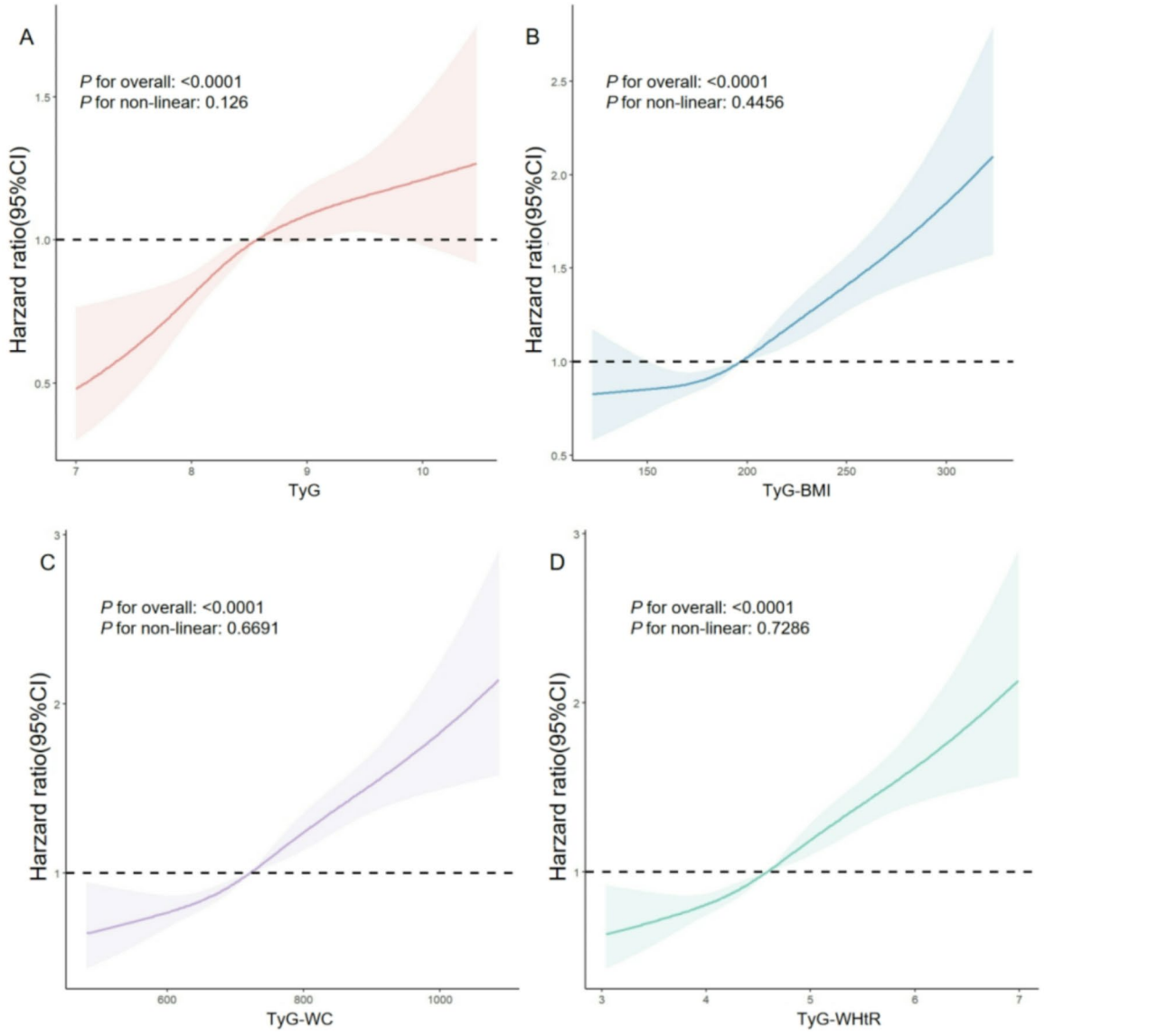

Fig. 4 RCS analysis of the relationship between TyG index and modified TyG indices with the incidence of CVD among individuals with CKM syndrome stages 0–3

study, which found that the highest quartile for TyG-BMI increased cardiovascular risk by 79.8% compared to the lowest quartile [24]. Our study used TyG single index and other modified TyG indices as continuous variables to analyze the relationship with CVD incidence in the context of CKM syndrome. As each standard deviation was increased, the CVD risk of all the modified TyG indices increased more than that of TyG single index (11%, $p < 0.001$), and TyG-WC index increased the cardiovascular risk the most (23%, $p < 0.001$).

CKM syndrome most commonly results from excess or dysfunctional adipose tissue or both [2]. When adipose tissue, especially visceral adipose tissue, is dysfunctional, pro-inflammatory and pro-oxidative factors will increase, leading to the damage of arteries, heart and kidney tissue, which promotes CVD incidence [44]. This inflammatory procedure also will lower the sensitivity to the action of insulin, resulting in IR [44]. More and more researchers have combined TyG and obesity index, because modified TyG indices can provide more relevant information to predict on-set CVD. A review proposed in Lancet al.so stated that it is essential of the addition of the measurement of triglyceride concentrations to the measurement of visceral adipose tissue like WC [45]. WC and WHtR

Table 2 Associations of TyG index and modified indices with CVD onset

	Crude		Model 1		Model 2		Model 3	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
TyG (per 1 SD)	1.15 (1.09–1.21)	< 0.001	1.15 (1.09–1.21)	< 0.001	1.10 (1.05–1.16)	< 0.001	1.11 (1.05–1.17)	< 0.001
TyG quartile								
Q1	ref	ref	ref	ref	ref	ref	ref	ref
Q2	1.23 (1.06–1.43)	0.007	1.23 (1.05–1.43)	0.008	1.20 (1.03–1.39)	0.021	1.17 (1.01–1.36)	0.043
Q3	1.41 (1.22–1.64)	< 0.001	1.37 (1.18–1.59)	< 0.001	1.30 (1.12–1.50)	0.001	1.26 (1.08–1.47)	0.003
Q4	1.43 (1.23–1.66)	< 0.001	1.42 (1.22–1.65)	< 0.001	1.28 (1.10–1.49)	0.001	1.27 (1.09–1.48)	0.003
TyG-BMI (per 1 SD)	1.22 (1.16–1.28)	< 0.001	1.27 (1.21–1.33)	< 0.001	1.20 (1.14–1.27)	< 0.001	1.21 (1.15–1.28)	< 0.001
TyG-BMI quartile								
Q1	ref	ref	ref	ref	ref	ref	ref	ref
Q2	1.18 (1.01–1.38)	0.034	1.27 (1.09–1.48)	0.003	1.25 (1.07–1.46)	0.0049	1.24 (1.06–1.45)	0.007
Q3	1.27 (1.09–1.47)	0.003	1.39 (1.19–1.63)	< 0.001	1.30 (1.11–1.52)	0.0010	1.29 (1.10–1.51)	0.002
Q4	1.71 (1.48–1.98)	< 0.001	1.94 (1.67–2.25)	< 0.001	1.70 (1.45–1.98)	< 0.001	1.70 (1.45–1.99)	< 0.001
TyG-WC (per 1 SD)	1.28 (1.22–1.35)	< 0.001	1.28 (1.22–1.34)	< 0.001	1.22 (1.16–1.28)	< 0.001	1.23 (1.16–1.29)	< 0.001
TyG-WC quartile								
Q1	ref	ref	ref	ref	ref	ref	ref	ref
Q2	1.26 (1.07–1.47)	0.005	1.28 (1.09–1.50)	0.003	1.24 (1.06–1.46)	0.007	1.24 (1.05–1.45)	0.010
Q3	1.45 (1.24–1.69)	< 0.001	1.45 (1.25–1.70)	< 0.001	1.38 (1.18–1.61)	< 0.001	1.37 (1.17–1.60)	< 0.001
Q4	2.00 (1.73–2.32)	< 0.001	2.02 (1.74–2.34)	< 0.001	1.78 (1.53–2.07)	< 0.001	1.79 (1.54–2.10)	< 0.001
TyG-WHtR (per 1 SD)	1.28 (1.22–1.34)	< 0.001	1.26 (1.20–1.32)	< 0.001	1.19 (1.13–1.26)	< 0.001	1.20 (1.14–1.27)	< 0.001
TyG-WHtR quartile								
Q1	ref	ref	ref	ref	ref	ref	ref	ref
Q2	1.24 (1.06–1.46)	0.007	1.27 (1.09–1.50)	0.003	1.25 (1.07–1.47)	0.005	1.24 (1.06–1.46)	0.007
Q3	1.44 (1.23–1.67)	< 0.001	1.44 (1.23–1.68)	< 0.001	1.34 (1.15–1.57)	< 0.001	1.33 (1.14–1.56)	< 0.001
Q4	1.90 (1.64–2.21)	< 0.001	1.87 (1.60–2.18)	< 0.001	1.65 (1.41–1.93)	< 0.001	1.65 (1.40–1.94)	< 0.001

Model 1: adjusted for age and gender; Model 2: adjusted for age, gender, education levels, marital status, smoking and drinking status and history of hypertension and diabetes; Model 3: adjusted for factors in model 2 and BUN, UA, eGFR and LDL.Predictive performance comparison

are useful parameter for evaluating abdominal obesity [46, 47], which are better than BMI in predicting CVD incidence [48, 49].

As for the predictive performance, our study found that TyG-WC and TyG-WHtR have the highest overall C-index, which are also proven to be better than single TyG index and TyG-BMI through IDI and NRI analysis. It was also found in a large cohort population without diabetes in South Korea that the C-index of TyG-WC and TyG-WHtR were significantly higher than that of TyG and TyG-BMI [50]. Based on the database of national health and nutrition examination surveys (NHANES), Zheng D et al. and Dang K et al. also found that TyG-WC and TyG-WHtR were superior to TyG-BMI and TyG in the diagnosis of CVD in the general population of the United States [21, 51]. Xia X et al. also had the consistent findings through the Chinese Kailuan database [50]. However, the C-indices are around 0.6, having low precision of predicting performance. The possible reason of this result is the small number of people having CVD incidence. Future research could combine TyG-WC or TyG-WHtR and use other methods such as machine learning to explore predicting models having better predictive performance.

A presidential advisory from the AHA stated that CKM syndrome is a progressive disease [3]. Excess and dysfunction of adipose tissue often develop as metabolic risk factors and CKD [52], which further promotes the development of sub-clinical coronary atherosclerosis and sub-clinical abnormalities in myocardial structure and function over time, as well as progressive decline in renal function [3]. This easily leads to a high risk of clinical CVD, kidney failure, disability and death [3]. Intervention in the early stages of CKM syndrome is important, and early detection and intervention are often associated with greater clinical benefit [2, 3]. Therefore, our study further explored the relationship between TyG and modified TyG with the occurrence of CVD in people with different stages of CKM syndrome.

In our study, the relationship between TyG and CVD incidences is only significant in CKM stage 1, which may because TyG could identify cardiovascular risk earlier, but its ability to predict patients with target organ damage is weak. However, TyG has been proven to be a valuable indicator in different stages of the cardiometabolic syndrome [23]. Future studies could conduct large-scale cohort studies or use other analytical methods to further explore the changes and predictive value of TyG in different stages of CKM syndrome. Our findings showed that

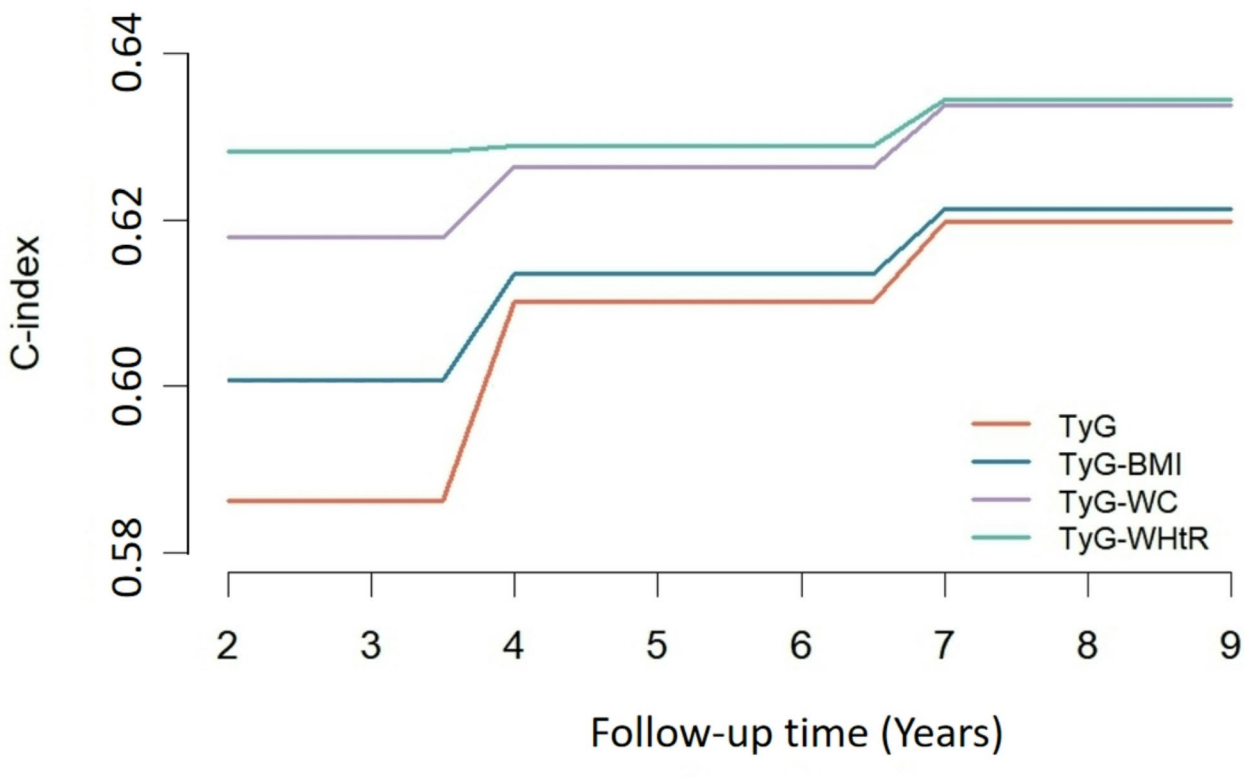

Fig. 5 Time-dependent predictive capacity of TyG and modified indices for CVD incidence

the relationship between TyG and modified TyG indices with the CVD incidence did not exist in people with CKM stage 0, which is similar to the study of Weipeng Li et al. about TyG-BMI and on-set CVD in the context of CKM syndrome [24]. One reason of these findings is that our study included fewer people with CKM stage 0 ($n = 652$), the other one is that people in CKM stage 0 were without any metabolic or cardiovascular risk factors and their risk factors had not reached an impact threshold. Among the population at stage 1 of CKM syndrome, TyG-BMI had non-linear relationship with CVD incidence (P for non-linear: 0.048, cut-off: 194.06), while TyG-WC and TyG-WHtR had linear relationship. All the modified TyG indices had a linear relationship with CKM stage 2 and CKM stage 3. It indicated that modified TyG indices, especially TyG-WC and TyG-WHtR, are still risk factors of CVD in early stages of CKM population, which could be monitored in the intervention. Large prospective studies are needed to explore the relationship of TyG index combined with obesity indicators in all stages of CKM syndrome.

Highlights of this study are as follows: firstly, our study is a nationwide cohort study following up to nine years to focus on the specific population at CKM syndrome stage 0–3, whereas previous studies [19–22] primarily addressed the general population; secondly, while prior studies by Weipeng Li only focused on TyG-BMI [24], we specifically investigated TyG index, TyG-WC and TyG-WHtR, and revealing TyG combined with WC or WHtR had better predictive performance than TyG-BMI; thirdly, unlike using simple C-indices to compare the predictive performance [19], our approach incorporated NRI and IDI analyses to make the comparison more reliable; fourthly, we analyzed all indices as both categorical and continuous (per 10 units) variables, which is able to identify the association between various levels of indices and CVD risks and to align with clinical application; and especially, our research explored each stage of CKM syndrome across the board about the association between TyG index and modified indices with CVD incidence, which were not comprehensively covered in earlier work [19–22, 24], and which is consistent with the presidential advisory from the AHA [3] about early detection and intervention in the context of CKM syndrome.

However, there are several limitations of our study to be considered. Firstly, due to the limitation of CHARLS about long follow-up interval and few repeated measurements, our study preferred to conduct robust estimation of long-term associations, and future studies could conduct more frequent measurements to employ lagged framework for the assessment of the distinguish short-term and cumulative effects; secondly, we used the Famingham 10-year CVD risk score [18], but not the latest PREVENT Eqs. [6, 53], to define subclinical

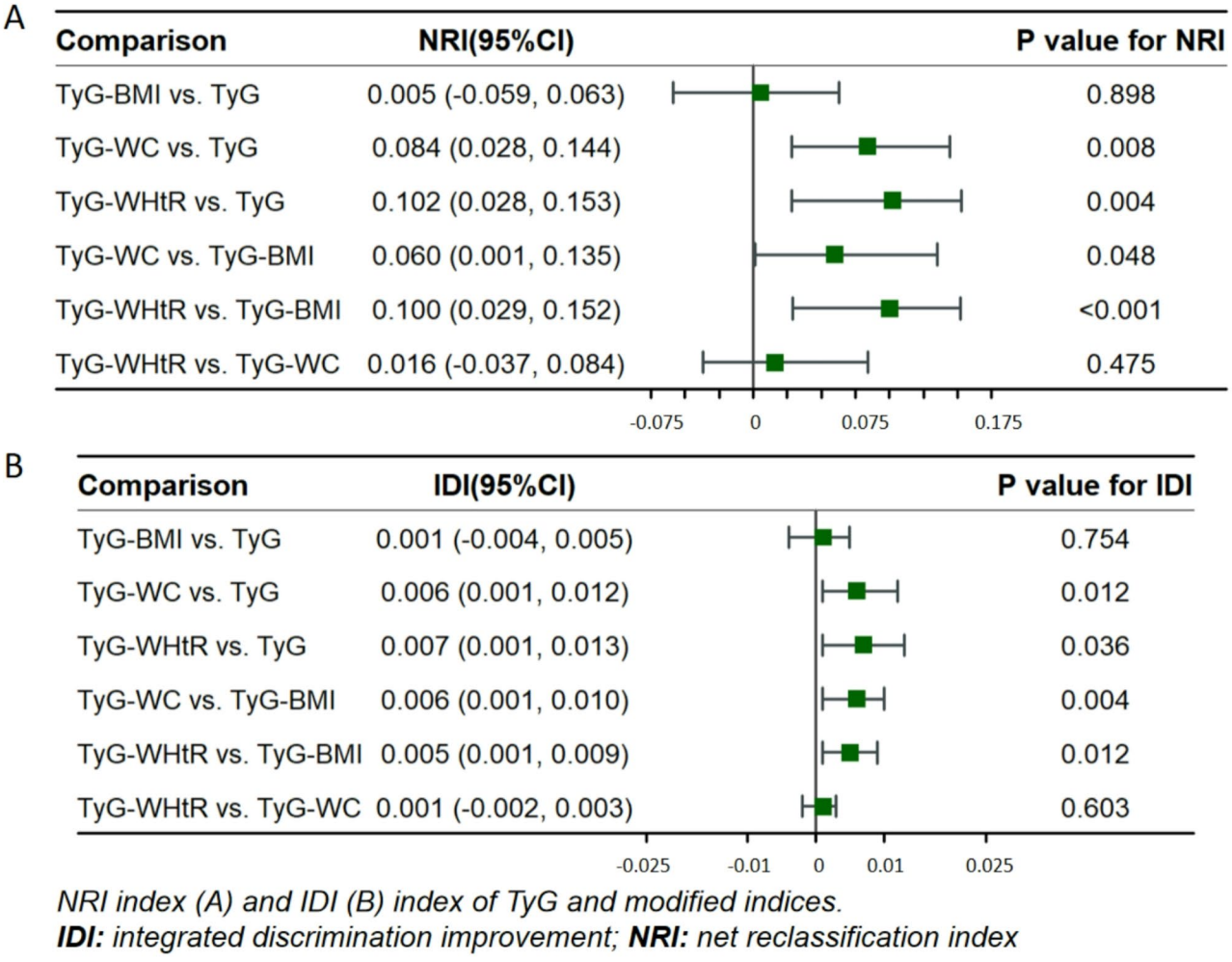

Fig. 6 NRI and IDI index of TyG and modified indices

Table 3 Subgroup analyses of the relationship between TyG index and modified indices with CVD incidence in a population with CKM syndrome stages 0–3

Characteristics	Number of participants	TyG		TyG-BMI		TyG-WC		TyG-WHtR	
		HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Age(years)									
< 60	3721	1.15 (1.06–1.24)	< 0.001	1.32 (1.22–1.42)	< 0.001	1.32 (1.22–1.43)	< 0.001	1.30 (1.20–1.41)	< 0.001
≥ 60	3643	1.14 (1.07–1.22)	< 0.001	1.21 (1.14–1.29)	< 0.001	1.25 (1.17–1.33)	< 0.001	1.23 (1.16–1.31)	< 0.001
Gender									
Male	3457	1.13 (1.05–1.22)	0.001	1.25 (1.16–1.35)	< 0.001	1.28 (1.19–1.38)	< 0.001	1.29 (1.19–1.40)	< 0.001
Female	3907	1.16 (1.08–1.23)	< 0.001	1.20 (1.13–1.28)	< 0.001	1.28 (1.20–1.37)	< 0.001	1.29 (1.21–1.38)	< 0.001
CKM stages									
Srage 0	652	0.89 (0.63–1.27)	0.534	0.88 (0.53–1.46)	0.612	1.02 (0.65–1.61)	0.932	0.99 (0.63–1.57)	0.965
Stage 1	1937	1.32 (1.11–1.57)	0.002	1.27 (1.11–1.45)	< 0.001	1.45 (1.26–1.66)	< 0.001	1.49 (1.31–1.71)	< 0.001
Stage 2	2474	1.03 (0.94–1.12)	0.515	1.17 (1.07–1.26)	< 0.001	1.20 (1.10–1.31)	< 0.001	1.23 (1.13–1.34)	< 0.001
Stage 3	2301	1.09 (1-1.18)	0.041	1.17 (1.08–1.27)	< 0.001	1.18 (1.09–2.18)	< 0.001	1.18 (1.09–1.28)	< 0.001

Note: TyG and modified TyG indices (TyG-BMI, Tyg-WC and TyG-WHtR) were analyzed as continuous variable (per 1 SD)

CVD because of limitations in the information collected from the CHARLS; thirdly, there was some bias because we excluded the individuals without relevant information (including outcome indicators, exposure factors and baseline characteristics), and the confounding and residual confounding due to measurement error were not assessed; and fourthly, this was a single center study only focused on Chinese adults 45 years old and above,

Table 4 Sensitivity analyses of the relationship between TyG index and modified indices with CVD incidence stratified by CKM stages

	TyG		TyG-BMI		TyG-WC		TyG-WHtR	
	HR (95%CI)	***P*-value**	**HR (95%CI)**	***P*-value**	**HR (95%CI)**	***P*-value**	**HR (95%CI)**	***P*-value**
CKM stage1								
Basic model	1.14 (1.02–1.27)	0.019	1.27 (1.14–1.41)	< 0.001	1.29 (1.17–1.43)	< 0.001	1.28 (1.14–1.42)	< 0.001
Sensitivity analysis 1*	1.14 (1.02–1.27)	0.025	1.27 (1.14–1.41)	< 0.001	1.29 (1.17–1.43)	< 0.001	1.27 (1.14–1.42)	< 0.001
Sensitivity analysis 2	1.14 (1.02–1.27)	0.020	1.28 (1.15–1.42)	< 0.001	1.30 (1.17–1.44)	< 0.001	1.28 (1.15–1.43)	< 0.001
Sensitivity analysis 3	1.13 (1.02–1.27)	0.026	1.27 (1.14–1.41)	< 0.001	1.30 (1.17–1.44)	< 0.001	1.27 (1.14–1.43)	< 0.001
CKM stage2								
Basic model	1.09 (1-1.19)	0.060	1.17 (1.07–1.27)	0.006	1.19 (1.09–1.3)	0.001	1.17 (1.07–1.27)	0.008
Sensitivity analysis 1**	1.10 (1-1.2)	0.044	1.17 (1.07–1.28)	0.004	1.20 (1.1–1.31)	< 0.001	1.17 (1.07–1.29)	0.004
Sensitivity analysis 2	1.10 (1-1.2)	0.042	1.17 (1.07–1.28)	< 0.001	1.20 (1.1–1.3)	< 0.001	1.17 (1.07–1.28)	< 0.001
Sensitivity analysis 3	1.09 (1-1.2)	0.051	1.18 (1.08–1.29)	< 0.001	1.21 (1.11–1.32)	< 0.001	1.18 (1.08–1.3)	< 0.001
CKM stage3								
Basic model	1.07 (0.98–1.17)	0.125	1.16 (1.05–1.27)	0.002	1.17 (1.07–1.28)	0.001	1.15 (1.04–1.26)	0.005
Sensitivity analysis 1**	1.07 (0.98–1.17)	0.113	1.16 (1.06–1.28)	0.001	1.17 (1.07–1.28)	0.001	1.15 (1.04–1.26)	0.004
Sensitivity analysis 2	1.08 (0.99–1.18)	0.091	1.16 (1.06–1.28)	0.001	1.17 (1.07–1.29)	0.001	1.14 (1.04–1.26)	0.007
Sensitivity analysis 3	1.07 (0.98–1.17)	0.143	1.15 (1.04–1.27)	0.006	1.15 (1.04–1.26)	0.005	1.12 (1.01–1.24)	0.027

Note: Basic model: adjusted for age, gender, marital status, education level, smoking status, drinking status and history of hypertension and diabetes; Sensitivity analysis 1*: further adjusted LDL and HbA1c on the basis of basic model; Sensitivity analysis 1**: further adjusted eGFR on the the baisis of basic model; Sensitivity analysis 2: excluded participants who followed up only to the first wave, remaining participants with 1,874 cases in CKM stage1, 2,400 cases in CKM stage2 and 2,158 cases in CKM stage 3; Sensitivity analysis 3: excluded participants who followed up only to the first and the second wave, remaining participants with 1,712 cases in CKM stage1, 2,157 cases in CKM stage2 and 1,842 cases in CKM stage 3

and extrapolation of results to other population or other countries might be limited, so other database could be used to assess our conclusion in the future. Finally, because CHARLS is a database using questionnaire to collect information of health status, the CVD incidence was self-reported and not verified by a professional interviewer or the chronic diseases platform, which would potentially compromise the accuracy of the reported information. Future research should consider incorporating more rigorous validation methods to enhance the reliability of the findings.

Conclusion

This study demonstrates that TyG index, and all the TyG-related indices combining TyG with obesity indicators, are valuable tools for predicting CVD incidence among people with CKM stages 0–3. Modified TyG indices have better predictive ability than the TyG index alone. In particular, TyG-WC and TyG-WHtR had greater performance. Monitoring and managing modified TyG indices may be important in the early detection and intervention in the context of CKM syndrome.

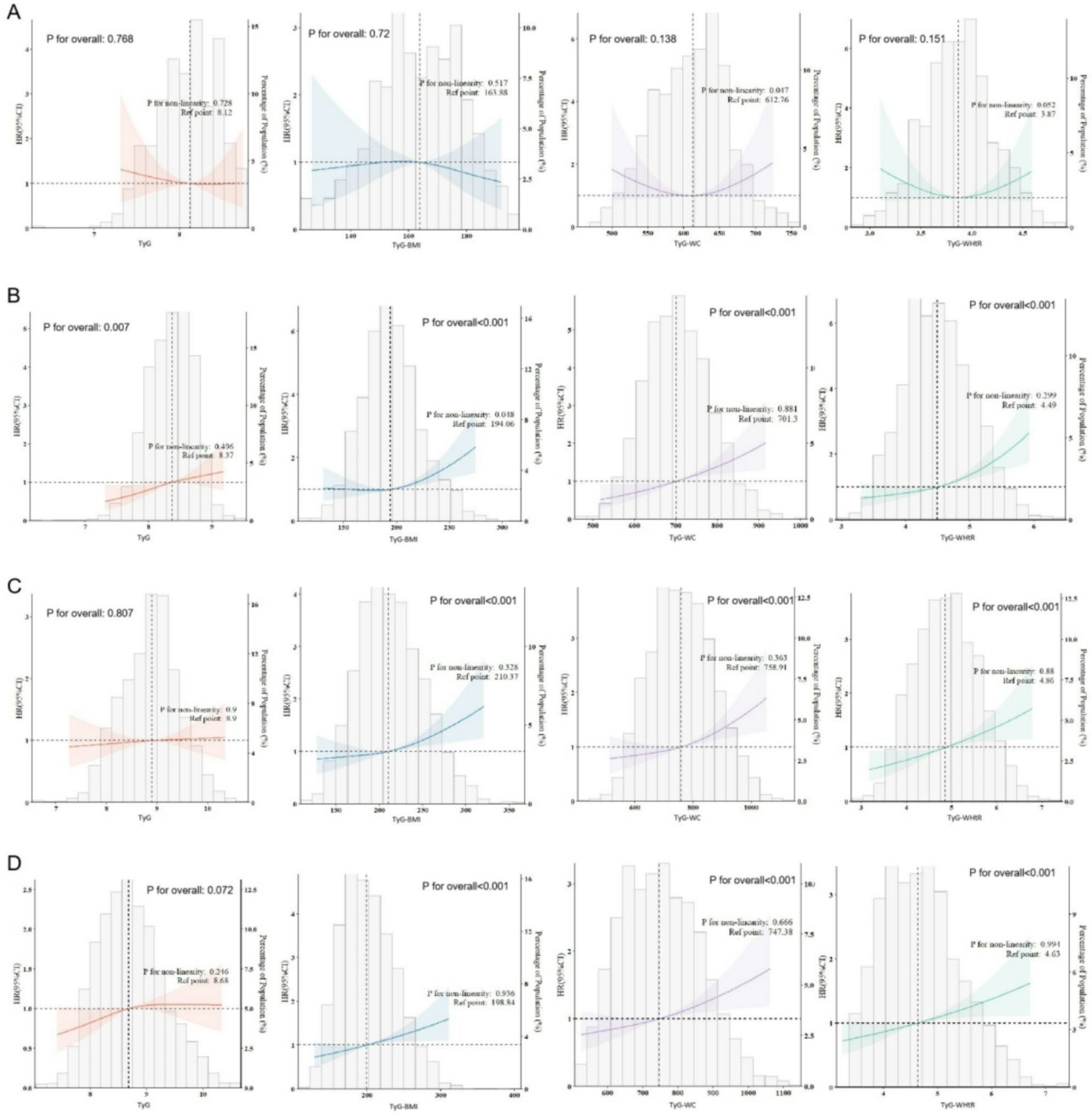

Fig. 7 RCS analysis between TyG index and modified indices with CVD incidence in a population with different CKM syndrome stages

Abbreviations

AHA	American Heart Association
AUC	area under the curve
BMI	body mass index
BUN	blood urea nitrogen
CHARLS	China Health and Retirement Longitudinal Study
CKD	chronic kidney diseases
CKM	Cardiovascular-Kidney-Metabolic syndrome
Cr	serum creatinine
CVD	cardiovascular diseases
eGFR	estimated glomerular hiltration rate
FBG	fasting blood glucose
HBA1c	glycated hemoglobin
HDL	high-density lipoprotein cholesterol
HR	hazard ratio
IR	insulin resistance
LDL	low-density lipoprotein cholesterol
RCS	restricted cubic spline
ROC	receiver operating characteristic
SBP	systolic blood pressure
SD	standard deviation
TC	total cholesterol
TG	triglyceride
TyG	triglyceride glucose

UA	uric acid
WC	waist circumference
WHtR	waist-to-height ratio
95% CI	95% confidence intervals

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02662-3 .

Supplementary Material 1

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Author contributions
Jianan Hong and Ruiying Zhang wrote the main manuscript text and designed the study and analyzed the data. Haoxian Tang and Shiwan Wu carried out literature search. Yequn Chen and Xuerui Tan performed the manuscript review. All authors reviewed the manuscript.

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Data availability
Online website(https://charls.pku.edu.cn/) contains the datasets used in this investigation. When registration is reviewed and approved, the data set could be downloaded following the provided instructions.

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by the Ethics Review Committee of Peking University. The patients/participants provided their written informed consent to participate in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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