Cardiovascular Diabetology

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Association between cumulative changes of the triglyceride glucose index and incidence of stroke in a population with cardiovascular-kidney-metabolic syndrome stage 0–3: a nationwide prospective cohort study

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Abstract

Background The triglyceride-glucose (TyG) index was associated with higher risk of mortality in individuals with Cardiovascular-Kidney-Metabolic (CKM) syndrome stages 0–3. However, the relationship between cumulative of TyG (cumTyG) and incidence of stroke remains unclear in individuals with CKM syndrome stages 0–3.

Method Participants with CKM syndrome stage 0–3 were enrolled from the China Health and Retirement Longitudinal Study (CHARLS) from 2011 to 2015. TyG was calculated as ln [fasting triglyceride (mg/dL)×fasting glucose (mg/dL)/2], and the cumTyG, as an area-under-the-curve estimate (mean TyG × time span), was calculated as $(TyG_{2012} + TyG_{2015})/2 * time_{(2015–2012)}$. TyG control levels were classified using *k-mean* clustering analysis. Logistic regression was used to analyze the effect of cumTyG and TyG control levels on the incidence of stroke. Restricted cubic spline models (RCS) were performed to explore the potential non-linear relationship between cumTyG and stroke risk at different CKM syndrome stages 0–3.

Results A total of 4,700 CKM syndrome stages 0–3 participants were enrolled, among 280 patients had developed stroke during the 3-year follow-up period. After adjusting for confounders, compared to class 1 group, the odds ratio (OR) of incidents of stroke for class 2 was 1.39 [95% confidence interval (CI) 1.003, 1.92], $P = 0.046$; the OR of incidents of stroke for class 3 was 1.28 (95% CI 0.92–1.77), $P = 0.147$, the OR of incidents of stroke for class 4 was 1.28 (95% CI 0.84–1.94), $P = 0.238$. Elevated cumTyG was associated with an increase in incidence of stroke (OR 1.13, 95% CI 1.05, 1.22, $P = 0.002$). The relationship between the cumTyG index and stroke was linear in restricted cubic spline regression.

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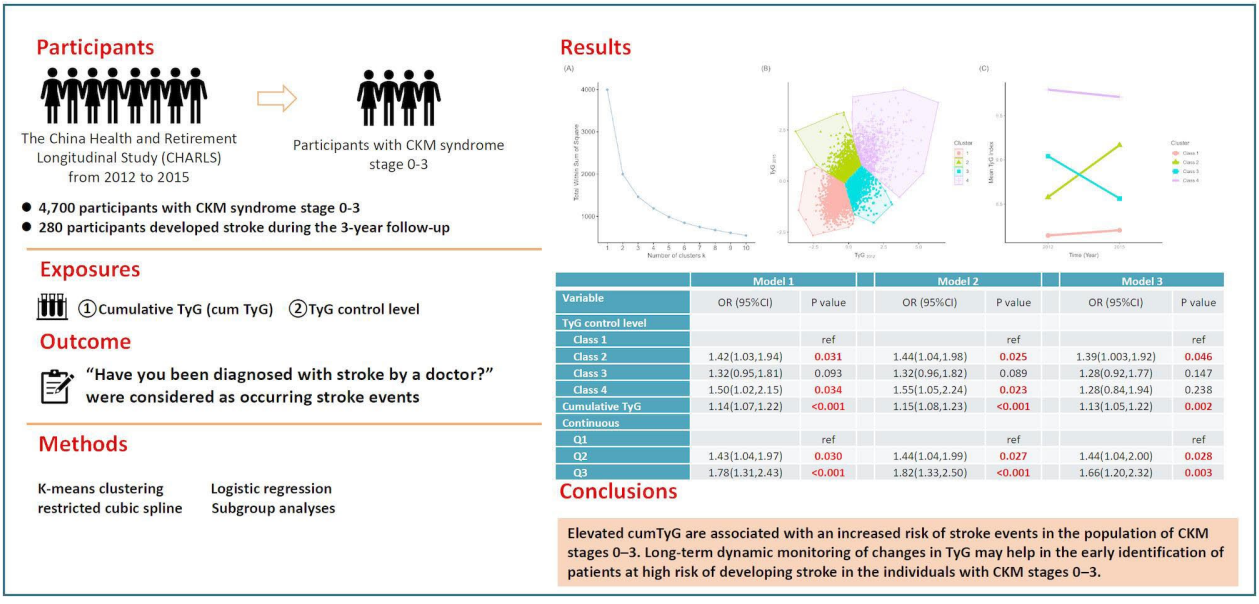
Conclusions Elevated cumTyG was associated with an increased risk of stroke events in the population of CKM syndrome stages 0–3. Long-term dynamic monitoring of changes of TyG may help in the early identification of patients at high risk of developing stroke in the individuals with CKM syndrome stages 0–3.

Keywords Triglyceride-glucose, Cumulative of Triglyceride-glucose, The China Health and Retirement Longitudinal Study, Stroke, Cardiovascular-kidney-metabolic syndrome

Graphical Abstract

Association between cumulative changes of the triglyceride glucose index and incidence of stroke in a population with Cardiovascular-Kidney-Metabolic syndrome stage 0–3: a nationwide prospective cohort study



	Model 1		Model 2		Model 3	
Variable	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
TyG control level						
Class 1		ref		ref		ref
Class 2	1.42(1.03,1.94)	0.031	1.44(1.04,1.98)	0.025	1.39(1.003,1.92)	0.046
Class 3	1.32(0.95,1.81)	0.093	1.32(0.96,1.82)	0.089	1.28(0.92,1.77)	0.147
Class 4	1.50(1.02,2.15)	0.034	1.55(1.05,2.24)	0.023	1.28(0.84,1.94)	0.238
Cumulative TyG	1.14(1.07,1.22)	<0.001	1.15(1.08,1.23)	<0.001	1.13(1.05,1.22)	0.002
Continuous						
Q1		ref		ref		ref
Q2	1.43(1.04,1.97)	0.030	1.44(1.04,1.99)	0.027	1.44(1.04,2.00)	0.028
Q3	1.78(1.31,2.43)	<0.001	1.82(1.33,2.50)	<0.001	1.66(1.20,2.32)	0.003

Research insights

What is currently known about this topic?

- Cardiovascular-Kidney-Metabolic (CKM) syndrome was associated with an increase risk of mortality.
- Baseline Triglyceride glucose index was associated with an increase incidence of stroke in patients with CKM syndrome stages 0-3.

What is the key research question?

- Whether cumulative of TyG index also was associated with an increase incidence of stroke in patients with CKM syndrome stages 0-3.

What is new?

- Our study showed that high cumTyG was associated with an increased risk of stroke in the population of CKM syndrome stages 0–3.

How might this study influence clincal practice?

- Long-term dynamic monitoring of changes in TyG may help in the early identification of patients at high risk of developing stroke in the individuals with CKM syndrome stages 0–3.

Introduction

The American Heart Association (AHA) recently introduced the concept of Cardiovascular-Kidney-Metabolic (CKM) syndrome, a systemic disorder characterized by the interplay of obesity, metabolic risk factors, chronic kidney disease (CKD), diabetes, and cardiovascular dysfunction [1]. Approximately 90% of US adults fulfilled criteria for CKM syndrome (stage 1 or higher), while 15% qualified for advanced stages [2]. Stage 2 CKM syndrome exhibited the highest prevalence in South Korea [3]. A disproportionate burden of CKM syndrome exists across social determinants of health (SDOH) and sex, highlighting the urgent need to address these inequities [4, 5]. CKM syndrome exerts widespread effects on nearly all major organ systems, resulting in significant clinical complications, including kidney failure [6], early-onset cognitive deterioration [7], metabolic dysfunction–related steatotic liver disease [8], obstructive sleep apnea [9],

a graded risk for cardiovascular mortality [10, 11], and elevated risk of cancer [12]. The progression of CKM syndrome is driven by the convergence of multiple comorbidities, including hypertension, hypertriglyceridemia, metabolic syndrome (MetS), type 2 diabetes, and CKD [13]. Over time, these overlapping conditions contribute to the development of subclinical coronary atherosclerosis, as indicated by coronary artery calcification, as well as subtle abnormalities in myocardial structure and function. Concurrently, kidney function progressively declines, further exacerbating the risk of clinical cardiovascular disease (CVD), renal failure, disability, and mortality. Given the asymptomatic nature of CKM syndrome in its early stages, early identification and intervention are critical to mitigating its long-term consequences [14].

Insulin resistance (IR) is a metabolic condition characterized by diminished or impaired sensitivity of target organs or tissues to insulin, leading to disruptions in glucose uptake and utilization [15, 16]. Several methods are available to evaluate IR, with the hyperinsulinemic euglycemic clamp (HEC) considered the gold standard [17]. However, HEC requires intravenous administration of glucose and insulin, along with frequent blood sampling [18], making it a complex, expensive, and impractical option for routine clinical use. Meanwhile, the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is widely used to assess IR and has demonstrated effectiveness in predicting the risk of cardiovascular and cerebrovascular events [19–21]. Despite its utility, HOMA-IR requires fasting insulin measurements, which limits its clinical applicability. Unlike HOMA-IR, which depends on fasting insulin (a parameter not routinely measured in clinical practice), the triglyceride-glucose (TyG) index relies solely on universally available fasting glucose and triglycerides from standard laboratory results. Emerging evidence suggests that TyG index, which exhibits a higher area under the curve (AUC) than HOMA-IR, may be serve as a superior diagnostic tool for diagnosing metabolic syndrome [22]. Additionally, the TyG index demonstrates a stronger independent association with arterial stiffness compared with HOMA-IR in patients with type 2 diabetes [23]. Consequently, TyG index had been most widely used to report IR. Previous studies have demonstrated that elevated TyG levels are associated with an elevated risk of heart failure mortality [24–26], stroke and cardiovascular disease [27–32], developing carotid plaque incidence [33], acute kidney injury [34], cerebrovascular disease [35]. It also predicts coronary artery calcification, multivessel coronary disease [36], severe consciousness disturbances [37], and the severity of new-onset coronary artery disease [38], highlighting its utility as a marker for diverse cardiovascular and metabolic risks. In population with CKM syndrome stages 0–3, several studies have shown that TyG was associated with all-cause, cardiovascular mortality and future cardiovascular disease risk [39, 40]. The TyG index has typically been assessed at a single time point, with no exploration of its fluctuations over time or the long-term impact of these changes. Evaluating the TyG index dynamically, rather than relying on a one-time measurement, could provide more meaningful prognostic insights. However, fewer studies have examined the associations between longitudinal changes in the TyG index and stroke incidence.

Therefore, this study aimed to investigate the associations between longitudinal changes in the TyG index and the incidence of stroke in a large community-based prospective cohort with a 3-year follow-up.

Method

Study population

The China Health and Retirement Longitudinal Study (CHARLS) is a nationally representative survey targeting middle-aged and elderly individuals aged 45 and above, managed by the Chinese Academy of Social Sciences, Peking University's National School. The study employed a longitudinal design with data collection waves in 2011–2012 (baseline, wave 1), 2013 (wave 2), 2015 (wave 3), and 2018 (wave 4). Biological samples, including fasting blood, were collected during waves 1 (2011–2012) and 3 (2015). Further details on the study population have been described in prior publications [41]. Eligibility criteria included being 45 or older, having complete data on fasting blood glucose (FBG) and triglycerides (TG), no history of stroke prior to 2015 and completed information of CKM syndrome stages 0–3. 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.

Data assessment

Assessment of TyG index, cum TyG, TyG control levels

Fasting blood samples were collected after an 8-h fast and analyzed for glucose and triglycerides using a Hitachi 7180 automated chemistry analyzer (Hitachi, Tokyo, Japan) via enzymatic colorimetric assays. TyG was calculated as ln [fasting triglyceride (mg/dL) × fasting glucose (mg/dL)/2], and the cumTyG, as an area-under-the-curve estimate (mean TyG × time span), was calculated as $(TyG_{2012} + TyG_{2015})$ /2* $time_{(2015-2012)}$[29, 42, 43]. Subsequently,the participants were divided into four TyG trajectory groups based on TyG control levels using k-mean analysis: Class 1 —Stable Low-Risk Group; Class 2 —Rapidly Increasing Group, Class 3 - Significant Improvement Group; Class 4 —Persistent High-Risk Group[44].

Assessment of CKM syndrome stages 0–3

According to the American Heart Association Presidential Advisory Statement [1], the stages of CKM syndrome from 0 to 3 were as follows at baseline (in 2012, wave 1): 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 [40, 45].

Outcome ascertainment

The primary outcome of our study was the incidence of stroke. In follow-up period (wave 4), participants who had answered "yes" to the question of "Have you been diagnosed with stroke by a doctor?" were considered as occurring stroke events according to the previous studies [46–48].

Data collection

At baseline (Wave 1, 2011–2012), trained interviewers collected sociodemographic and health data via standardized questionnaires. Sociodemographic details encompassed gender, age, educational attainment (Lower than high school, or High school or above), body mass index (BMI). Health-related information included self-reported smoking and drinking habits (yes/no) and physician-diagnosed conditions such as hypertension, diabetes, and dyslipidemia. Additionally, laboratory test results, including triglycerides (TG), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), Hemoglobin, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), Uric acid, estimated Glomerular Filtration Rate and total cholesterol (TC).

Statistical analysis

Continuous variables with normal distributions were presented as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median (interquartile range, IQR). Categorical variables were reported as frequencies and percentages. Group comparisons were performed using χ^2 tests for categorical variables, ANOVA for normally distributed continuous variables, and Kruskal-Wallis tests for non-parametric data.

Firstly, the participants were classified into four TyG control levels based on TyG values from 2012 to 2015 using *K-means* clustering. *K-means* clustering is a technique that has the goal of dividing N observations into K clusters, *K-means* clustering efficiently captures subtle variations in dynamic TyG index changes, providing a scientific basis for revealing its relationship with stroke risk. Its flexibility, data-driven nature, and support for multidimensional data analysis make it a powerful tool for exploring the relationship between complex metabolic data and clinical outcomes. In our study, we employed the elbow method-a well-established technique for optimizing cluster number selection in unsupervised learning—to evaluate the optimal partitioning of TyG trajectories. As illustrated in Fig. 2A, the marginal improvement in within-cluster variance (or distortion) substantially diminished beyond K = 4, reaching an inflection point where additional clusters provided negligible explanatory power (the 'elbow' criterion). This plateau indicated that four clusters optimally balanced model parsimony with explanatory accuracy while avoiding overfitting. Each observation is assigned to the cluster with the closest mean value, which serves as the prototype of the cluster (Fig. 2B). The four clustering was consistent with the findings in previous studies [44]. secondly, we also use continuous cumTyG and tertile of cumTyG group (low cumTyG group[Q1], medium cumTyG group[Q2], high cumTyG group[Q3]) to assess the associations between long-term change in TyG index and stroke incidence. Logistic regression analyses were conducted to evaluate the associations between continuous cumTyG, TyG control level and stroke incidents, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated across four models: Model 1 was unadjusted. Model 2 was adjusted for age, gender, BMI, education. Model 3 was adjusted for age, gender, BMI, education, smoking status, drinking status, diabetes, antidiabetic agents, antihyperlipidemic agents. Additionally, restricted cubic spline (RCS) regression analysis was employed to explore potential linear relationships between cumTyG and stroke incidence in participants with CKM syndrome. Subgroup analyses were performed adjusted for age, gender, BMI, education, smoking status, drinking status, diabetes, antidiabetic agents, antihyperlipidemic agents after stratification of the participants by age (< 60 years vs. ≥60 years), gender (male vs. female), education level (Lower than high school or High school or above), smoking status, drinking status, CKM stage (0–1, 2, 3), diabetes (yes or no), hypertension (yes or no), dyslipidemia (yes or no). To rigorously assess the robustness of our findings against potential confounding by pharmacological treatments and medium adherence, we conducted comprehensive sensitivity analyses by systematically excluding participants taking antidiabetic agents, antihyperlipidemic agents, antihypertensive medications, and medium adherence or persistence of the drug. Statistical analyses were performed using R 4.4.2 (Vienna, Austria). A two-sided P value of < 0.05 was considered to represent statistical significance.

Result

Demographic and clinical attributes of patients with CKM syndrome stages 0–3

Figure 1 illustrates the inclusion and exclusion criteria in this study. Specifically, we included 17,705 participants in wave 1 in CHARLS cohort. Of these, 9,777 participants were excluded for uncompleted CKM syndrome data, and 3,228 participants were excluded for uncompleted stroke data and TyG data from wave 1 and wave 3. A total of 4,700 participants were included in the final analysis. Table 1 summarizes the baseline characteristics of participants CKM syndrome stage 0–3 among four groups based on TyG control level (Class 1–4 groups): (1) Class 1 ($n=1884$), the TyG varied from 8.15 ± 0.31 in 2012 to 8.21 ± 0.31 in 2015, indicating Stable Low-Risk Group. (2) Class 2 ($n=1093$), the TyG varied from 8.58 ± 0.33 in 2012 to 9.17 ± 0.34 in 2015, indicating Stable Low-Risk Group. (3) Class 3 ($n=1106$), the TyG varied from 9.04 ± 0.34 in 2012 to 8.57 ± 0.29 in 2015, indicating Significant Improvement Group. (4) Class 4 ($n=617$), the TyG varied from 9.79 ± 0.59 in 2012 to 9.71 ± 0.48 in 2015, indicating Persistent High-Risk Group (Fig. 2C).

Note: Data are presented as the mean (SD) or number (%). Significant P values <0.05 are in bold

Males accounted for 44.8%. The mean TyG of the study population was 8.68 ± 0.67 in 2012 and 8.71 ± 0.63 in 2015, and the cumTyG was 26.08 ± 1.73. Significant differences were observed across four classes for age, gender, BMI, education, smoking, drinking, CKM syndrome stages, comorbidities (hypertension, diabetes, dyslipidemia), and biochemical markers (TG, glucose, HbA1c, cholesterol). In detail, Class 4 group represented the most metabolically dysregulated group, with higher BMI, greater prevalence of comorbidities, and more severe abnormalities in biochemical markers (TG, glucose, HbA1c, cholesterol) compared to the other classes. Class 2 had higher LDL-cholesterol than other classes group (Table 1).

CumTyG, TyG control levels and stroke incidence among individuals with CKM syndrome stages 0–3

Table 2 displays the logistic regression results analyzing the association between cumTyG, TyG control levels and stroke incidence among individuals with CKM syndrome stages 0–3. In adjusted model (model 3), Class 2 group showed a significantly higher stroke risk compared to Class 1 group (OR 1.39, 95% CI 1.003–1.92, $P=0.046$), but no differences of stroke incidence were observed among Class 1 group, Class 3 group, and Class 4 group (all $P>0.05$). High cumTyG (OR 1.13, 95% CI 1.05–1.22, $P=0.002$) was significantly associated with increased stroke risk, we further divided the participants into three group based on tertile of cumTyG. Compared to Q1 (lower cumTyG), Q2 group (OR 1.44, 95% CI 1.04–2.00, $P=0.028$) and Q3 group(OR 1.66, 95% CI 1.20–2.32, $P=0.003$) had higher risk of stroke incidents. Multivariable-adjusted spline regression models showed linear associations between cumTyG index levels and the risk of stroke among CKM stages 0–3 (Fig. 3).

Subgroup analyses and sensitivity analyses

Table 3 presents subgroup analyses of the association between TyG control levels and stroke incidence in

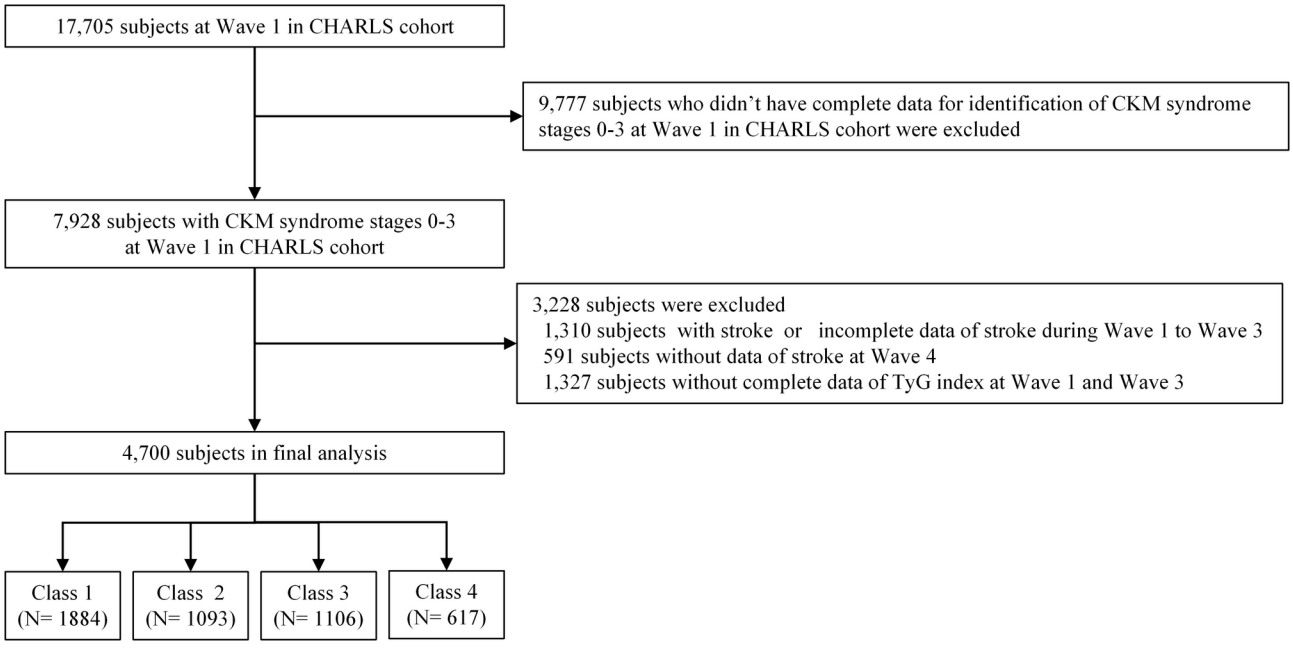


Fig. 1 Flowchart of the study population

Table 1 Baseline characteristics according to TyG control level classes.

	Overall (*N* = 4700)	Class 1 (*N* = 1884)	Class 2 (*N* = 1093)	Class 3 (*N* = 1106)	Class 4 (*N* = 617)	*P* value
Age, n (%)						**0.008**
< 60	2827 (60.1)	1092 (58.0)	682 (62.4)	654 (59.1)	399 (64.7)	
≥ 60	1873 (39.9)	792 (42.0)	411 (37.6)	452 (40.9)	218 (35.3)	
Gender, n (%)						**< 0.001**
Female	2596 (55.2)	922 (48.9)	665 (60.8)	636 (57.5)	373 (60.5)	
Male	2104 (44.8)	962 (51.1)	428 (39.2)	470 (42.5)	244 (39.5)	
BMI, kg/m^2 (mean (SD))	23.65 (7.69)	22.37 (3.69)	24.68 (14.26)	23.75 (3.65)	25.54 (3.80)	**< 0.001**
Education, n (%)						0.870
Lower than high school	4278 (91.0)	1711 (90.8)	993 (90.9)	1007 (91.0)	567 (91.9)	
High school or above	422 (9.0)	173 (9.2)	100 (9.1)	99 (9.0)	50 (8.1)	
Smoking status, n (%)						**0.001**
Non-smokers	2947 (62.7)	1117 (59.3)	711 (65.1)	705 (63.7)	414 (67.1)	
Smokers	1753 (37.3)	767 (40.7)	382 (34.9)	401 (36.3)	203 (32.9)	
Drinking status, n (%)						0.082
Never	2897 (61.7)	1121 (59.6)	698 (63.9)	696 (63.0)	382 (61.9)	
Ever	1799 (38.3)	761 (40.4)	394 (36.1)	409 (37.0)	235 (38.1)	
CKM syndrome stages, n (%)						**< 0.001**
0	199 (4.2)	162 (8.6)	28 (2.6)	9 (0.8)	0 (0.0)	
1	578 (12.3)	355 (18.8)	166 (15.2)	57 (5.2)	0 (0.0)	
2	1390 (29.6)	362 (19.2)	361 (33.0)	445 (40.2)	222 (36.0)	
3	2533 (53.9)	1005 (53.3)	538 (49.2)	595 (53.8)	395 (64.0)	
Hypertension, n (%)						**< 0.001**
No	2026 (61.9)	890 (70.2)	452 (59.7)	466 (59.4)	218 (47.2)	
Yes	1246 (38.1)	378 (29.8)	305 (40.3)	319 (40.6)	244 (52.8)	
Diabetes, n (%)						**< 0.001**
No	3962 (84.3)	1774 (94.2)	983 (89.9)	884 (79.9)	321 (52.0)	
Yes	738 (15.7)	110 (5.8)	110 (10.1)	222 (20.1)	296 (48.0)	
Dyslipidemia,n (%)						**< 0.001**
No	4263 (91.9)	1774 (95.2)	976 (90.4)	1002 (92.4)	511 (83.8)	
Yes	375 (8.1)	89 (4.8)	104 (9.6)	83 (7.6)	99 (16.2)	
Antidiabetic agents, n (%)						**< 0.001**
No	4552 (97.0)	1864 (98.9)	1068 (97.8)	1075 (97.5)	545 (88.5)	
Yes	143 (3.0)	20 (1.1)	24 (2.2)	28 (2.5)	71 (11.5)	
Antihyperlipidemic agents, n (%)						**< 0.001**
No	4457 (96.1)	1823 (97.9)	1037 (96.0)	1046 (96.5)	551 (90.3)	
Yes	180 (3.9)	40 (2.1)	43 (4.0)	38 (3.5)	59 (9.7)	
Antihypertension agents, n (%)						**< 0.001**
No	4021 (85.7)	1705 (90.6)	917 (84.0)	939 (85.0)	460 (74.8)	
Yes	673 (14.3)	177 (9.4)	175 (16.0)	166 (15.0)	155 (25.2)	
TG, mg/dl (mean (SD))	132.80 (108.05)	74.16 (21.56)	110.03 (34.27)	162.65 (62.50)	298.66 (194.81)	**< 0.001**
Glucose, mg/dl (mean (SD))	109.44 (35.48)	98.35 (14.77)	102.96 (16.06)	112.68 (26.92)	148.93 (71.74)	**< 0.001**
HbA1c, % (mean (SD))	5.25 (0.79)	5.09 (0.46)	5.20 (0.55)	5.23 (0.66)	5.89 (1.50)	**< 0.001**
Hemoglobin, g/dl (mean (SD))	14.35 (2.20)	14.21 (2.22)	14.32 (2.15)	14.46 (2.23)	14.61 (2.12)	**< 0.001**
LDL-cholesterol, mg/dl (mean (SD))	115.91 (34.44)	111.23 (29.43)	126.04 (33.63)	118.14 (35.62)	108.21 (42.54)	**< 0.001**
HDL-cholesterol, mg/dl (mean (SD))	51.21 (15.23)	57.88 (15.02)	51.20 (13.25)	47.51 (13.02)	37.50 (10.72)	**< 0.001**
TC, mg/dl (mean (SD))	193.13 (37.92)	181.89 (33.29)	197.81 (36.87)	197.88 (37.70)	210.62 (43.04)	**< 0.001**
Uric acid, mg/dl (mean (SD))	4.34 (1.21)	4.18 (1.14)	4.34 (1.13)	4.43 (1.25)	4.66 (1.38)	**< 0.001**
eGFR, mL/min/1.73 m^2 (mean (SD))	93.98 (13.90)	95.05 (13.18)	93.82 (14.27)	92.69 (13.99)	93.32 (14.92)	**< 0.001**
TyG_{2012} (mean (SD))	8.68 (0.67)	8.15 (0.31)	8.58 (0.33)	9.04 (0.34)	9.79 (0.59)	**< 0.001**
TyG_{2015} (mean (SD))	8.71 (0.63)	8.21 (0.31)	9.17 (0.34)	8.57 (0.29)	9.71 (0.48)	**< 0.001**
Cumulative TyG (mean (SD))	26.08 (1.73)	24.53 (0.68)	26.62 (0.76)	26.41 (0.71)	29.26 (1.16)	**< 0.001**
Outcome						
Incidence of stroke	280 (6.0)	92 (4.9)	74 (6.8)	70 (6.3)	44 (7.1)	0.073

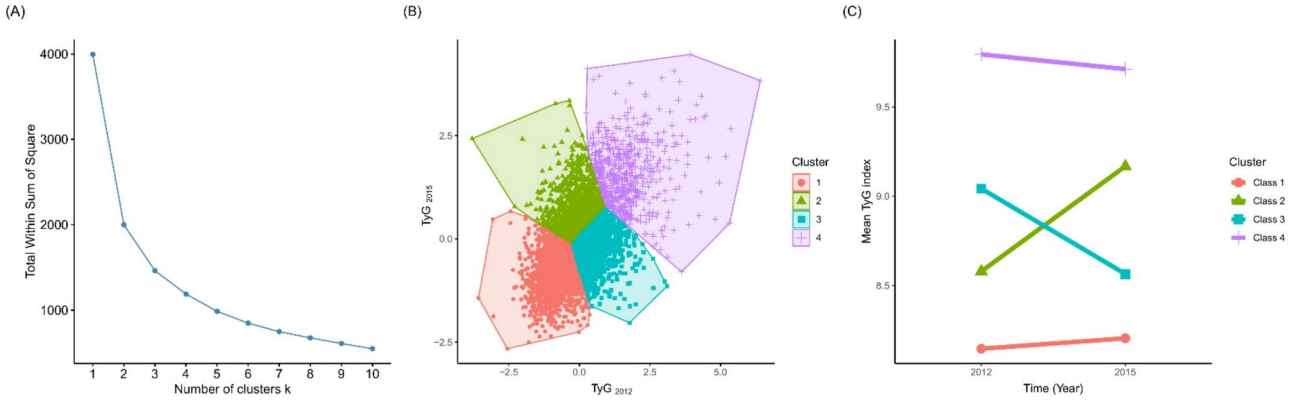


Fig. 2 Clustering of changes of TyG from Wave 1 to Wave 3. Changes in TyG classified into four classes using the K-means algorithm (**A**, **B**); Mean TyG for the four classes in 2012 and 2015 (**C**); Class 1 (Red)—Stable Low-Risk Group; Class 2 (Green)—Rapidly Increasing Group, Class 3 (Cyan)- Significant Improvement Group; Class 4 (Purple)—Persistent High-Risk Group

Table 2 Logistic regression results for the association of TyG control level and cumulative TyG with stroke among individuals with CKM syndrome stage 0–3.

	Model 1		Model 2		Model 3	
Variable	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
TyG control levels						
Class 1	Reference		Reference		Reference	
Class 2	1.42 (1.03, 1.94)	**0.031**	1.44 (1.04, 1.98)	**0.025**	1.39 (1.003, 1.92)	**0.046**
Class 3	1.32 (0.95, 1.81)	0.093	1.32 (0.96, 1.82)	0.089	1.28 (0.92, 1.77)	0.147
Class 4	1.50 (1.02, 2.15)	**0.034**	1.55 (1.05, 2.24)	**0.023**	1.28 (0.84, 1.94)	0.238
Cumulative TyG	1.14 (1.07, 1.22)	**< 0.001**	1.15 (1.08, 1.23)	**< 0.001**	1.13 (1.05, 1.22)	**0.002**
Tertiles of cumulative TyG						
Q1	Reference		Reference		Reference	
Q2	1.43 (1.04, 1.97)	**0.030**	1.44 (1.04, 1.99)	**0.027**	1.44 (1.04, 2.00)	**0.028**
Q3	1.78 (1.31, 2.43)	**< 0.001**	1.82 (1.33, 2.50)	**< 0.001**	1.66 (1.20, 2.32)	**0.003**

Low cumTyG group[Q1], medium cumTyG group[Q2], high cumTyG group [Q3]; Significant P values <0.05 are in bold

Model 1 was unadjusted

Model 2 was adjusted for age, gender, BMI and education

Model 3 was adjusted for age, gender, BMI, education, smoking status, drinking status, diabetes, antidiabetic agents and antihyperlipidemic agents

patients with CKM syndrome stages 0–3, stratified by age, gender, education, smoking, drinking, CKM 0–3 stages, diabetes, hypertension, and dyslipidemia. We found a significant interaction between TyG control level and age, gender, smoking (all $P < 0.05$). For cumTyG, a significant interaction was observed between three cumTyG group and CKM syndrome stages 0-3 stage (all $P < 0.05$) (Table S1–S2). Sensitivity analyses were performed using the complete dataset without antidiabetic agents, antihyperlipidemic agents, and antihypertension agents. CumTyG consistently showed the strongest association with the incidence of stroke (Tables S3–S7).

Discussion

Our study provided valuable insights into the relationship between cumulative TyG, the TyG control levels and stroke incidence among individuals with varying stages of CKM syndrome. Our findings revealed that individuals with moderate increases in the TyG index (Class 2) exhibited a significantly higher stroke risk compared to those with persistently low TyG levels (Class 1). Furthermore, cumTyG was independently associated with an increase in stroke risk, with participants in the higher tertiles of cumTyG demonstrating progressively increased stroke risk. These results highlighted the prognostic significance of longitudinal TyG index assessments and underscore the importance of metabolic dysregulation in developing stroke in participants with CKM syndrome stages 0–3.

The AHA recommends individuals with CKM syndrome stages 0–3 as a key target for early intervention, emphasizing the critical role of the TyG index in predicting their prognosis. Studies by Li et al. and Hong et al. have demonstrated a positive linear association between the TyG-related index and increased CVD incidence in populations with CKM syndrome stages 0–3 populations [39, 49]. Furthermore, Zhang et al. used data from the National Health and Nutrition Examination Survey

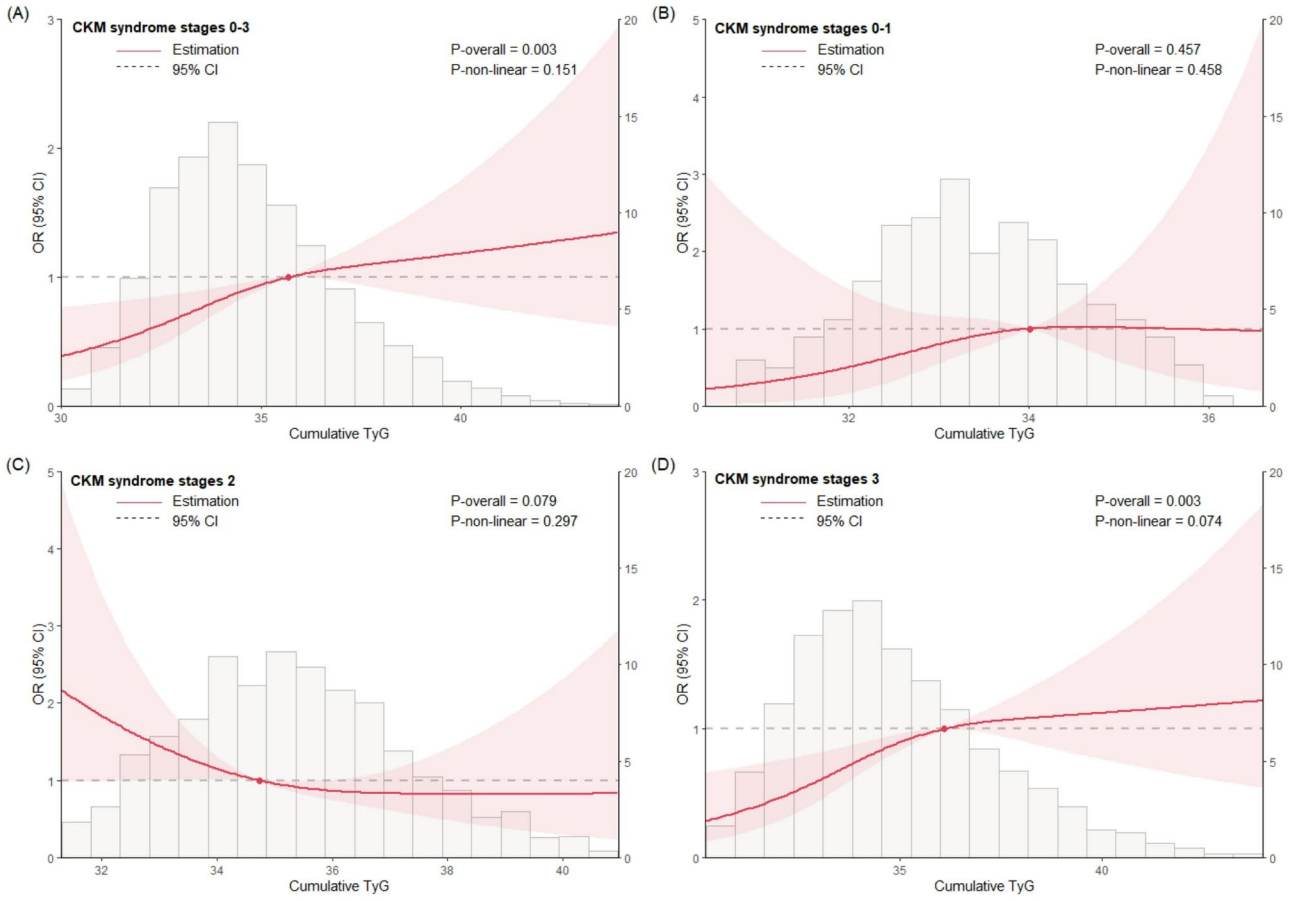


Fig. 3 The RCS analysis between the cumTyG index and stroke incidence in population with CKM syndrome stages 0–3. Model 3 was adjusted for age, gender, BMI, education, smoking status, drinking status, diabetes, antidiabetic agents, antihyperlipidemic agents

(NHANES) 2009–2018, revealed that TyG-related indices were significantly associated with higher risks of all-cause and cardiovascular mortality in this population [40]. These findings underscore the importance of monitoring and managing TyG and its derived indices in the early detection and intervention of CKM syndrome. However, due to the inherent variability of single-point measurements, continuous monitoring of TyG index changes may better reflect disease progression in CKM syndrome stages 0–3 populations. Building on these insights, we further investigated the prognostic value of cumTyG index in CKM syndrome populations. Our results revealed that high cumTyG level were significantly associated with an increased risk of stroke in individuals with CKM syndrome stages 0–3. This finding highlights the potential of long-term monitoring of TyG index trends, particularly cumTyG levels, to identify individuals at heightened stroke risk. Such an approach provides a robust foundation for early intervention and personalized management strategies in CKM syndrome patients.

We implemented *k-means* clustering analysis to examine the associations between TyG control levels and stroke incidence. The results showed that after adjusting for confounding factors, the logistic analysis indicated that only the rising phase of the TyG index in Class 2 was significantly associated with a higher risk of stroke, while other groups showed no significant associations with stroke risk. Based on the chart analysis, the Class 2 group showed a significant increase in the TyG index, indicating a rising metabolic state. This rapid upward trend is significantly associated with a higher risk of stroke, suggesting that insulin resistance and metabolic dysfunction in this group are rapidly worsening. In contrast, Class 4, inherently a high-risk group, maintained a relatively stable TyG index, with no significant increase stroke risk. Further comparison of differences between groups revealed that the Class 2 group had significantly higher LDL-C levels compared to other groups. This finding supports the high-risk characteristics of Class 2, as elevated LDL-C was a significant risk factor for atherosclerosis and stroke [50]. Lipid metabolism disorders, especially elevated LDL-C, are the most important independent risk factor for atherosclerotic CVD (ASCVD). Increased LDL-C was directly and causally associated with coronary heart

Table 3 Subgroup analysis of the association between TyG control levels and stroke incidents in patients with CKM syndrome stages 0–3.

Variable	Class 1	Class 2	Class 3	Class 4	*P* for trend	*P* for interaction
Age						**0.014**
< 60	Ref	1.14 (0.69, 1.89)	1.60 (0.999, 2.56)	1.24 (0.68, 2.26)	0.108	
≥ 60	Ref	1.52 (0.99, 2.33)	0.95 (0.59, 1.53)	1.14 (0.63, 2.08)	0.154	
Gender						**0.018**
Female	Ref	1.02 (0.66, 1.58)	0.94 (0.60, 1.48)	1.02 (0.59, 1.75)	0.890	
Male	Ref	1.93 (1.19, 3.14)	1.74 (1.07, 2.84)	1.45 (0.74, 2.82)	0.711	
Education						0.408
Lower than high school	Ref	1.40 (0.998, 1.95)	1.26 (0.90, 1.78)	1.18 (0.76, 1.83)	0.637	
High school or above	Ref	1.41 (0.42, 4.73)	1.44 (0.43, 4.82)	2.54 (0.64, 10.06)	0.419	
Smoking status						**0.009**
Non-smokers	Ref	1.08 (0.71, 1.63)	0.84 (0.54, 1.30)	0.94 (0.56, 1.60)	0.406	
Smokers	Ref	1.94 (1.15, 3.28)	2.21 (1.33, 3.69)	1.92 (0.97, 3.80)	0.438	
Drinking status						0.056
Never	Ref	1.12 (0.73, 1.72)	1.01 (0.65, 1.58)	1.16 (0.68, 1.99)	0.990	
Ever	Ref	1.77 (1.07, 2.93)	1.69 (1.02, 2.81)	1.39 (0.71, 2.72)	0.804	
CKM						–
0–1	Ref	1.60 (0.63, 4.05)	1.17 (0.26, 5.38)	–	0.505	
2	Ref	0.68 (0.37, 1.23)	0.49 (0.26, 0.91)	0.41 (0.18, 0.94)	0.107	
3	Ref	1.60 (1.04, 2.45)	1.60(1.06, 2.44)	1.53 (0.94, 2.47)	0.614	
Diabetes						0.184
No	Ref	1.44 (1.03, 2.01)	1.23 (0.86, 1.76)	1.13 (0.66, 1.95)	0.410	
Yes	Ref	1.11 (0.34, 3.66)	1.62 (0.60, 4.33)	1.56 (0.61, 4.00)	0.857	
Hypertension						0.294
Yes	Ref	1.25 (0.75, 2.10)	0.97 (0.57, 1.67)	1.16 (0.64, 2.13)	0.964	
No	Ref	1.20 (0.69, 2.10)	1.30 (0.76, 2.24)	1.28 (0.60, 2.73)	0.333	
Dyslipidemia						0.820
No	Ref	1.34 (0.94, 1.90)	1.28 (0.90, 1.82)	1.23 (0.77, 1.98)	0.951	
Yes	Ref	1.52 (0.61, 3.76)	1.28 (0.48, 3.38)	1.27 (0.48, 3.38)	0.806	

Data was adjusted for age, gender, BMI, education, smoking status, drinking status, diabetes, antidiabetic agents and antihyperlipidemic agents. Significant P values <0.05 are in bold

disease, myocardial infarction, and ischemic stroke [51]. One key finding is that participants in Class 2 exhibited the highest risk for stroke, particularly among males, smokers, and those in CKM stage 3. However, it was notable that Class 4, which represented individuals with persistently high TyG levels, did not show a statistically significant association with stroke risk, despite numerically elevated hazard ratios. Possible explanations include limited statistical power in this subgroup, adaptive physiological responses in long-term high-risk individuals, or more intensive medical management. It may also suggest that dynamic metabolic worsening—rather than chronic elevation alone—carries greater short-term vascular consequences. In summary, the rising phase of the TyG index in the Class 2 group is associated with a higher risk of stroke, and its elevated LDL-C levels further exacerbate this risk. This finding emphasizes the importance of dynamically monitoring the TyG index and LDL-C levels to identify high-risk populations early and implement targeted interventions.

Our study showed that cumTyG was associated with stroke incidence in individuals with CKM syndrome stages 0-3. From a mechanistic perspective, the TyG index, as a surrogate marker of IR, reflects not only reduced insulin sensitivity but also multifaceted dysregulation in glucose and lipid metabolism, chronic inflammation, endothelial dysfunction, and oxidative stress [52]. These interconnected factors collectively contribute to the development and progression of stroke in CKM syndrome patients. First, IR, a core feature of CKM syndrome, leads to elevated blood glucose and triglyceride levels [1]. The TyG index provides a robust measure of IR that outperforms either parameter alone. This metabolic dysfunction elevates stroke risk through three principal mechanisms: (1) impaired vascular endothelial function promoting atherosclerosis [53–55] (2) chronic low-grade inflammation accelerating vascular damage [56, 57] and (3) enhanced platelet activation increasing thrombosis risk [58]. Second, the TyG index is also linked with stress hyperglycemia. The association between hyperglycemia and stroke is mediated through three core

mechanisms: (1) Oxidative stress pathway: Activation of the PKC/NADPH oxidase system increases reactive oxygen species (ROS) production while reducing nitric oxide synthase activity, leading to vascular endothelial dysfunction; [59, 60] (2) the Inflammatory-atherosclerotic pathway: In hyperglycemic conditions, macrophages engulf glycated LDL-C to form foam cells, accelerating atherosclerotic plaque formation; [61] (3) Direct neurotoxic effects: The hyperglycemic environment in the ischemic penumbra exacerbates neuronal damage and expands the infarction zone [62]. These interconnected mechanisms collectively contribute to worse clinical outcomes, with recent studies further confirming this multipathway injury mechanism. Our findings suggested that dynamic glucose monitoring can comprehensively reflect these interrelated pathophysiological processes [63]. In patients with CKM syndrome, the cumulative effects of these pathophysiological processes are reflected in the cumTyG index. High cumTyG levels indicated prolonged exposure to metabolic dysregulation, chronic inflammation, and oxidative stress, all of which synergistically increase stroke risk. Thus, dynamic monitoring of TyG index changes, particularly cumTyG levels, provides a comprehensive assessment of metabolic status and offers mechanistic insights into its association with stroke risk.

Moreover, high cumTyG levels may interact with other CKM syndrome-related complications, such as CKD and heart failure, further exacerbating the burden on the cardiovascular system. For example, CKD patients often exhibit calcium-phosphate metabolism disorders and vascular calcification, which, in combination with high TyG index levels, further amplify stroke risk [64].In summary, the association between cumulative TyG index and stroke risk can be explained through multiple mechanisms, including IR, metabolic dysregulation, chronic inflammation, oxidative stress, and multisystem interactions. These findings provide a robust pathophysiological basis for stroke risk prediction in CKM syndrome patients and highlight the importance of early intervention and comprehensive management. By targeting TyG index and its associated metabolic abnormalities, it may be possible to effectively reduce stroke risk and improve long-term outcomes in this vulnerable population.

Study strengths and limitations

Our study has several strengths, including the use of a large, nationally representative cohort and the evaluation of longitudinal TyG index changes, which provide a more comprehensive understanding of its prognostic value in patients with CKM syndrome stages 0–3. However, our study had certain limitations. Firstly, only two blood tests were conducted, preventing more detailed characterization of TyG index trajectories. The TyG index was assessed at specific time points, and its continuous variation over time was not fully captured. Future studies with more frequent measurements could provide deeper insights into the dynamic nature of metabolic dysregulation. Secondly, while we adjusted for multiple confounders, residual confounding cannot be entirely ruled out. Thirdly, our findings were specifically applicable to the elderly Chinese population. Future validation in multinational cohorts—such as the UK Biobank, Health and Retirement Study (HRS), and English Longitudinal Study of Ageing (ELSA) databases will be necessary. Fourthly, Stroke was ascertained through self-reported physician diagnosis rather than based on imaging (CT or MRI), which introduces potential misclassification bias, but the credibility of self-reported stroke events has been validated, providing some assurance of reliability [65, 66]. Additionally, the information on ischemic and hemorrhagic subtypes was lacking given data limitations. Finally, our study employed strict exclusion criteria (incomplete CKM data or missing stroke records), the criteria were consistent with the previous study [40, 45, 49]. The exclusion of certain participants may not have introduced bias to the study results.

Conclusion

Our findings demonstrate that cumTyG are robust predictors of stroke risk in individuals with CKM syndrome stages 0-3. The identification of high-risk subgroups underscores the importance of personalized approaches to stroke prevention. These findings emphasize the importance of monitoring the longitudinal changes in TyG index to most effectively identify individuals who are at high risk of developing stroke in individuals with CKM syndrome stages 0-3.

Abbreviations

TyG	Triglyceride glucose
CVD	Cardiovascular disease
CHARLS	China Health and Retirement Longitudinal Study
LDL-C	Low-density lipoprotein cholesterol
TC	Total cholesterol
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol

Supplementary Information

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Supplementary Material 1.

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Author contributions

FXD, LLF, LXC, CYB, and LBY conceived and designed the study. FXD, LLF, CYB, LBY, LXC, WJL, and NZC conducted the research. CYB, LLF and LXC analyzed

the data. LLF wrote the manuscript. All authors read and approved of the final 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 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.

Competing interests
The authors declare no competing interests.

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