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Association of novel triglyceride-glucose-related indices with incident stroke in early-stage cardiovascular-kidney-metabolic syndrome

Yong Yue^{1,2†}, Pengcheng Li^{3†}, Zhengyu Sun^{4†}, Rumi Murayama², Zongping Li¹, Kenji Hashimoto^{2*} and Ye Zhang^{1*}

Abstract

Background Emerging triglyceride-glucose (TyG)-related indices, such as the TyG-related body roundness index (TyG-BRI), a body shape index (TyG-ABSI), weight-adjusted waist index (TyG-WWI), and Chinese visceral adiposity index (TyG-CVAI), have gained attention as promising predictors of diverse cardiometabolic conditions. Nevertheless, their prospective associations with stroke onset remain insufficiently characterized, especially in individuals affected by cardiovascular-kidney-metabolic (CKM) syndrome.

Methods This prospective cohort study included 7,503 middle-aged and older adults with CKM syndrome stages 0–3 (see Methods: Definition of CKM Stages 0 to 4) from the China Health and Retirement Longitudinal Study (CHARLS). Cox proportional hazards models were used to evaluate the associations between TyG-related indices and incident stroke, with potential non-linear relationships examined via restricted cubic splines (RCS). Discriminative performance was compared using receiver operating characteristic (ROC) curves. Mediation analysis was conducted to assess whether systolic blood pressure (SBP) mediated the associations. Subgroup and sensitivity analyses were also performed to verify robustness.

Results Over a median follow-up of 5.2 years, 625 participants (8.33%) experienced a first stroke (incidence rate 102.18 per 10,000 person-years). In fully adjusted models, each 1-SD increase in TyG-BRI, TyG-ABSI, TyG-WWI, and TyG-CVAI was associated with stroke hazards of 1.16 (95% CI, 1.06–1.27), 1.10 (1.01–1.21), 1.13 (1.03–1.25), and 1.20 (1.10–1.31), respectively. Participants in the highest TyG-CVAI quartile had a 67% higher risk than those in the lowest (HR, 1.67; 95% CI, 1.28–2.18). Nonlinear thresholds were identified at TyG-BRI 18.16 and TyG-WWI 78.93. ROC analysis indicated that TyG-CVAI had the greatest discriminative ability for predicting stroke. SBP mediated 26.3–32.9% of these associations. The findings were consistent across multiple subgroup and sensitivity analyses.

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Conclusion Novel TyG-related indices, particularly TyG-CVAI, showed significant and incremental predictive value for stroke risk among individuals with CKM syndrome stages 0–3. Their incorporation into risk stratification frameworks may enhance early detection and prevention of cerebrovascular events in metabolically vulnerable populations.

Keywords CKM syndrome, Stroke risk, systolic blood pressure, TyG-related indices, Visceral adiposity.

Introduction

Stroke poses a major and growing global health challenge. According to the Global Burden of Disease (GBD) Study 2021, there were 11.9 million first-ever stroke cases and 7.3 million stroke-related deaths worldwide, accounting for 10.7% of all global mortality. Worldwide, stroke ranked third among causes of death, after ischemic heart disease and COVID-19 [1]. Although age-standardized rates of stroke incidence and mortality have declined over the past three decades, the absolute numbers of cases and deaths continue to rise. These trends underscore the urgent need for effective prevention strategies and long-term healthcare planning.

In 2023, the American Heart Association (AHA) introduced the concept of Cardiovascular–Kidney–Metabolic (CKM) syndrome to capture the intertwined progression of metabolic dysregulation, chronic kidney disease, and cardiovascular disease (CVD) [2]. This framework highlights bidirectional, synergistic interactions among these systems that accelerate disease and worsen outcomes [3, 4]. To facilitate early intervention, the AHA defined five CKM stages (see Methods: Definition of CKM Stages 0 to 4). Stages 0–3 encompass preclinical or early clinical phases during which preventive measures may be most effective [2]. Epidemiological data indicate that CKM syndrome is highly prevalent, with approximately 90% of U.S. adults meeting the criteria for stage 1 or higher. Around 15% of individuals progress to advanced stages, largely driven by cardiovascular complications such as coronary artery disease, heart failure, and stroke [3–8]. Given stroke's prominent role among CKM-related outcomes, identifying early predictors in stages 0–3 is critical.

Insulin resistance (IR), defined by reduced responsiveness of peripheral tissues to insulin, plays a central role in metabolic dysfunction and significantly increases the risk of cardiovascular disease [9–12]. The triglyceride–glucose (TyG) index, calculated from fasting triglyceride (TG) and fasting blood glucose (FBG) levels, is a validated and cost-effective surrogate marker of IR [13, 14]. Elevated TyG has been linked to acute coronary syndrome, coronary artery disease, heart failure, and stroke [15–20]. Building on this, composite TyG-related indices that integrate anthropometric measures (e.g., BMI, waist circumference (WC), waist-to-height ratio) demonstrate enhanced CVD prediction compared with TyG alone [21–23]. More recently, novel indices, such as TyG-BRI (triglyceride–glucose–body roundness index), TyG-ABSI

(triglyceride–glucose–a body shape index), TyG-WWI (triglyceride–glucose–weight-adjusted waist index), and TyG-CVAI (triglyceride–glucose–Chinese visceral adiposity index), have been associated with diverse adverse outcomes, including stroke, periodontitis, anxiety, and metabolic dysfunction-associated steatotic liver disease [24–31]. However, no study has yet examined whether these novel TyG-related indices predict new-onset stroke in individuals at early CKM stages.

Using data from the nationally representative China Health and Retirement Longitudinal Study (CHARLS), we evaluated the associations between these four emerging TyG-related indices and incident stroke among participants with CKM syndrome stages 0–3. Clarifying their prognostic value may improve early risk stratification and guide preventive efforts in this high-risk population.

Methods

Study population

CHARLS is a nationally representative, population-based cohort designed to monitor long-term changes in health status, socioeconomic conditions, and demographic characteristics among Chinese adults aged 45 years and older [32]. Participants were selected through a multistage, stratified probability sampling method from 150 counties and 450 communities across 28 provinces, ensuring comprehensive national coverage. The baseline survey was conducted from June 2011 to March 2012 (Wave 1), followed by four follow-up waves in 2013 (Wave 2), 2015 (Wave 3), 2018 (Wave 4), and 2020 (Wave 5). The study protocol received ethical approval from the Institutional Review Board of Peking University (IRB00001052-11015), and all participants provided written informed consent prior to data collection. In the present study, we utilized data from the baseline and all subsequent waves through 2020. A total of 17,708 individuals were initially enrolled in the baseline cohort. To construct the final analytic sample, we applied the following exclusion criteria: (1) age less than 45 years at baseline; (2) classified as CKM stage 4 or missing CKM data at baseline; (3) Missing key variables required to calculate novel TyG-related indices, including weight, height, WC, age, sex, TG, FBG, and high-density lipoprotein cholesterol (HDL-C); (4) missing stroke status at baseline; (5) absence of follow-up data on new-onset stroke in subsequent waves. After exclusion, a total of 7,503 participants were eligible for inclusion in the final cohort. A schematic

diagram detailing the selection process was presented in Fig. 1.

Definition of four novel TyG-related indices

Four TyG-related indices are novel markers that integrate the TyG index with anthropometric parameters to enhance the evaluation of metabolic dysfunction and visceral adiposity. The following formulas were used for calculation [28, 29, 33, 34]:

$$TyG - BRI = TyG \times BRI$$

$$TyG - ABSI = TyG \times ABSI$$

$$TyG - WWI = TyG \times WWI$$

$$TyG - CVAI = TyG \times CVAI$$

$$TyG = \ln [TG (mg/dL) \times FBG(mg/dL)/2]$$

$$BRI = 364.2 - 365.5 \times \sqrt{1 - (WC (cm) / 2\pi)^2 / (height (cm) / 2)^2}$$

$$ABSI = WC (m) / (BMI(kg/m^2)^{2/3} \times height (m)^{1/2})$$

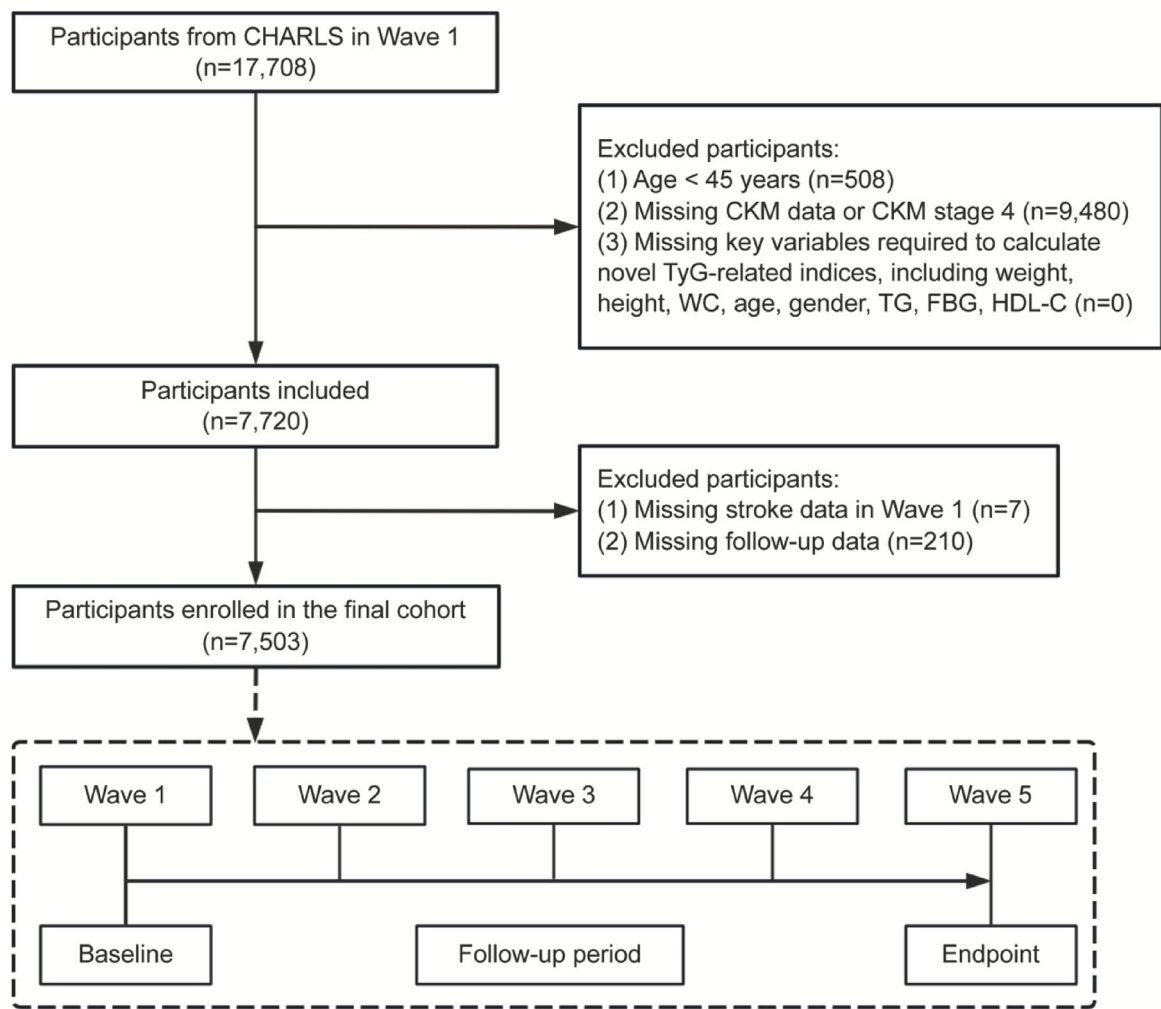


Fig. 1 Flowchart of participant selection

$$WWI = WC \text{ (cm)} / \sqrt{\text{weight (kg)}}$$

$$\begin{aligned} CVAI = & -267.93 + 0.68 \times \text{age (years)} + 0.03 \times BMI \text{ (kg/m}^2\text{)} \\ & + 4.00 \times WC \text{ (cm)} + 22.00 \times \log_{10}(TG) \text{ (mmol/L)} \\ & - 16.32 \times HDL-C \text{ (mmol/L) in male} \end{aligned}$$

$$\begin{aligned} CVAI = & -187.32 + 1.71 \times \text{age (years)} + 4.23 \times BMI \text{ (kg/m}^2\text{)} \\ & + 1.12 \times WC \text{ (cm)} + 39.76 \times \log_{10}(TG) \text{ (mmol/L)} \\ & - 11.66 \times HDL-C \text{ (mmol/L) in female} \end{aligned}$$

Definition of CKM syndrome stages 0 to 4

Based on the American Heart Association's advisory framework [2], CKM syndrome is categorized into five stages (0 to 4). Stage 0 includes individuals without any identifiable CKM-related risk factors; Stage 1 is defined by early metabolic disturbances such as overweight, abdominal obesity and/or impaired glucose tolerance; Stage 2 comprises those with established metabolic conditions, including type 2 diabetes mellitus, hypertension, or hypertriglyceridemia, as well as individuals with chronic kidney disease; Stage 3 represents the presence of subclinical cardiovascular abnormalities, such as asymptomatic atherosclerosis or cardiac remodeling, arising within the context of metabolic or renal dysfunction; Stage 4 corresponds to overt clinical cardiovascular disease, including diagnoses of coronary artery disease, heart failure, stroke, peripheral arterial disease, or atrial fibrillation, in individuals with underlying CKM-related pathology [35].

Outcome ascertainment

The primary endpoint of this study was the occurrence of new-onset stroke. During the follow-up period (Wave 2–5), incident stroke cases were identified based on participants' self-reports. Specifically, participants who answered "yes" to the question "Have you been diagnosed with a stroke by a doctor?" or "Are you currently receiving any treatment (traditional Chinese medicine/Western medicine/physical therapy/acupuncture and moxibustion/occupational therapy) to control your stroke?" were identified as having a stroke event. This method of outcome ascertainment has been adopted in prior population-based studies and is considered valid for stroke surveillance in large cohort settings [15, 28].

Data collection

At baseline, trained interviewers administered standardized questionnaires to collect information on demographic characteristics (including age, gender, education level, hukou, geographic region and marital status), health-related behaviors (such as activity, smoking, and alcohol intake), and self-reported medical history (including diabetes mellitus (DM), hypertension, heart

disease, stroke, dyslipidemia, and uses of antidiabetic agents, antihyperlipidemic agents and antihypertensive agents). Anthropometric measurements, including height, weight, and WC, were obtained by trained healthcare personnel using standardized protocols. Additionally, laboratory biomarkers were collected from fasting venous blood samples provided by all participants after an overnight fast of at least 8 h [36]. These included TG, FBG, glycated hemoglobin (HbA1c), hemoglobin (Hb), HDL-C, low-density lipoprotein cholesterol (LDL-C), creatinine (Cr), blood urea nitrogen (BUN), C-reactive protein (CRP), uric acid (UA), estimated glomerular filtration rate (eGFR), and total cholesterol (TC).

Educational level was categorized as no formal education, primary school, middle school, or high school and above. Hukou status was classified as agricultural or non-agricultural, based on China's household registration system, which influences access to social services and healthcare based on residency. Marital status was defined as married or other, with the latter including separated, divorced, widowed, and never-married individuals. Geographic region was divided into northern and southern China, based on the Qinling Mountains–Huaihe River Line. Activity was defined based on participation in any of the following activities: visiting friends or neighbors, playing mahjong or cards, providing unpaid help to non-cohabiting relatives or friends, doing group exercises (e.g., dancing or Qigong), attending community or club activities, volunteering, taking classes or training, and other forms of social interaction. Participants who reported engaging in at least one activity were classified as socially active. Smoking was determined based on lifetime cigarette use. Individuals who had smoked more than 100 cigarettes were considered ever smokers and further classified as never, former, or current smokers [37]. Alcohol intake was categorized into never drinkers (those who never or rarely consumed alcohol, defined as less than once per month), former drinkers (those who previously drank more than once per month but had quit within the past year), and current drinkers (those who drank more than once per month) [37]. DM was defined as FPG ≥ 126 mg/dL, and/or HbA1c $\geq 6.5\%$, current use of antidiabetic medication, or self-reported diagnosis [38]. Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, current use of antihypertensive medication, or self-reported diagnosis [38]. Dyslipidemia was defined as TC ≥ 240 mg/dL, TG ≥ 150 mg/dL, LDL-C ≥ 160 mg/dL, HDL-C < 40 mg/dL, current use of lipid-lowering therapy, or a self-reported history of dyslipidemia [39].

Handling of Missing Data and data preprocessing

As shown in Figure S1, most variables had relatively low proportions of missing data. The missing rates were as follows: Hukou ($< 0.1\%$), dyslipidemia (1%), smoking

(<0.1%), physical activity (1%), white blood cell count (2%), platelet count (2%), blood urea nitrogen (<0.1%), hemoglobin (2%), educational level (<0.1%), and use of antihyperlipidemic agents (1%). These procedures were conducted following the framework established by White and Groenwald to reduce potential bias and improve the accuracy of model estimation [40, 41].

During data preprocessing, we identified extreme values in several TyG-related indices. To reduce the influence of outliers and enhance the robustness of the analysis, we applied a percentile-based Winsorization approach. Specifically, we retained the central 98% of the data distribution and replaced the values below the 1st percentile and above the 99th percentile with the respective threshold values. This transformation was applied to TyG-BRI, TyG-ABSI, TyG-WWI, and TyG-CVAI prior to statistical analysis (Figure S2).

Statistical analysis

Continuous variables with skewed distributions were summarized as medians with interquartile ranges (IQR). Categorical variables were reported as counts and percentages. Baseline characteristics were compared between participants with and without new-onset stroke. To further examine the association between TyG-related indices and the risk of incident stroke, participants were stratified into quartiles for each index: TyG-BRI, TyG-ABSI, TyG-WWI, and TyG-CVAI. Differences between groups were assessed using the χ^2 test for categorical variables and Kruskal-Wallis or Mann-Whitney test for continuous variables. Furthermore, the interrelationships among TyG, TyG-BRI, TyG-ABSI, TyG-WWI, and TyG-CVAI were evaluated using Spearman correlation coefficients.

Kaplan–Meier analysis was performed to visualize the cumulative incidence of new-onset stroke across quartiles of TyG-related indices, and differences were assessed using the log-rank test. In addition, multivariable Cox regression analysis was conducted to evaluate the association between TyG-related indices and the risk of new-onset stroke across the three models. Results were presented as hazard ratios (HR) with corresponding 95% confidence intervals (CI). To enhance comparability across models, the four TyG-related indices were standardized to z-scores, allowing effect estimates to represent the change in stroke risk per one SD increase in each index. Model 1 was unadjusted; Model 2 adjusted for age, gender and education level; and Model 3 adjusted for age, gender, education level, alcohol intake, smoking, hypertension, DM, antidiabetic agents, antihypertensive agents, SBP, DBP, PLT, BUN, Cr, LDL_C, CRP, HbA1C, UA, Hb, eGFR. Covariate selection was based on the Boruta feature selection algorithm, which identified the most relevant predictors for model inclusion

(Figure S3). To mitigate multicollinearity, variance inflation factors (VIFs) were calculated for each continuous covariate retained after feature selection, excluding the TyG-related indices and their individual components. As all VIFs were below the threshold of 5, the selected variables were included in the final models.

To explore potential non-linear associations between TyG-related indices and the risk of new-onset stroke, restricted cubic spline (RCS) models were fitted within the Cox proportional hazards framework. Four knots were placed at the 5th, 35th, 65th, and 95th percentiles of TyG-related indices, using the median as the reference point. In cases where non-linearity was detected, threshold effect analysis was performed using a two-piecewise Cox regression model. The inflection point was identified through a recursive algorithm, and a likelihood ratio test was conducted to compare the fit of the linear model with that of the segmented model, allowing for separate estimation of risk associations below and above the threshold.

To further assess the discriminatory performance of different metabolic indices in predicting new-onset stroke, receiver operating characteristic (ROC) curve analysis was conducted. The area under the curve (AUC) was calculated for each index, including TyG, TyG-BMI, TyG-BRI, TyG-ABSI, TyG-WWI, TyG-CVAI, and METS-IR. Additionally, ROC curves were generated based on the three Cox proportional hazards models to compare their predictive performance.

Subgroup analyses were performed to evaluate the consistency of associations across clinically relevant categories, including gender, CKM stage, alcohol intake, smoking, hypertension, DM, use of antidiabetic agents, use of antihypertensive agents, BMI (<24, 24–28, $\geq$ 28), and age (<60, $\geq$ 60). Interaction terms between TyG-related indices and each subgroup variable were incorporated into the Cox models to test for effect modification. All subgroup models were adjusted for the same covariates included in Model 3, except for the stratification variable itself, which was excluded to avoid over-adjustment.

A Bayesian mediation analysis was conducted to investigate whether SBP mediated the association between TyG-related indices and new-onset stroke. The analysis was based on 1,000 posterior simulations to estimate the distribution of mediation effects. The average causal mediation effect (ACME), average direct effect (ADE), and the proportion mediated were calculated, with corresponding p-values used to assess statistical significance.

Finally, sensitivity analyses were carried out to evaluate the robustness of the primary findings. First, logistic regression models were applied as an alternative method to replicate the associations. Second, analyses were repeated using a complete-case dataset after excluding participants with missing values. Third, to evaluate the

potential impact of extreme values, Cox regression models were re-estimated using the original, unprocessed TyG-related indices prior to Winsorization. Fourth, E-values were computed to quantify the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome to explain away the observed associations.

All statistical analyses were conducted using R software version 4.3.3 (Vienna, Austria). A two-tailed *P* value less than 0.05 was regarded as statistically significant.

Results

Participant characteristics

Of the 7,503 participants (3,549 men and 3,954 women; median age 58.0 years [IQR 52.0–65.0]), those who developed new-onset stroke ($n=625$) differed markedly at baseline (Table 1). Compared with stroke-free participants, cases had higher median values of age, systolic and diastolic blood pressure, BMI, white blood cell count, fasting blood glucose, creatinine, total cholesterol, triglycerides, LDL-C, CRP, HbA1c, uric acid, hemoglobin, the TyG index, and all four novel TyG-related indices (BRI, TyG-BRI, ABSI, TyG-ABSI, WWI, TyG-WWI, CVAI, and TyG-CVAI) (all $p<0.05$). In contrast, HDL-C and eGFR were lower among stroke cases (both $p<0.05$).

Compared to participants who did not experience stroke, those who developed stroke were less likely to reside in southern China (52.64% vs. 58.48%). Additionally, stroke cases had a significantly higher prevalence of CKM stage 3, dyslipidemia, hypertension, and diabetes mellitus, with all differences reaching statistical significance ($p<0.05$). Use of antidiabetic, antihyperlipidemic, and antihypertensive medications was more frequent in the stroke group, as were former or current smoking and alcohol consumption (all $p<0.05$). Participants were divided into quartiles (Q1–Q4) for TyG-related indices (TyG-BRI, TyG-ABSI, TyG-WWI, and TyG-CVAI). Baseline characteristics across these quartiles are presented in Supplementary Tables S1–S4.

Spearman correlation analysis (Figure S4) showed moderate associations between the TyG index and its derivatives, with coefficients ranging from 0.41 to 0.72. TyG-ABSI correlated most strongly with TyG ($r=0.73$), followed by TyG-WWI ($r=0.72$), TyG-CVAI ($r=0.61$), and TyG-BRI ($r=0.47$).

The incidence rate of stroke

As shown in Table 2, a total of 625 participants experienced new-onset stroke during the follow-up period, corresponding to an overall incidence rate of 102.18 cases per 10,000 person-years, and an overall cumulative incidence of 8.33%. When stratified by quartiles of TyG-related indices, a progressive increase in stroke incidence was observed across higher quartiles. Specifically, the

stroke incidence rates per 10,000 person-years by TyG-BRI quartiles were: Q1, 60.37; Q2, 87.23; Q3, 113.75; and Q4, 147.57. For TyG-ABSI, the corresponding rates were: Q1, 65.35; Q2, 94.16; Q3, 112.48; and Q4, 138.72. Similarly, stroke incidence rates across TyG-WWI quartiles were: Q1, 57.91; Q2, 101.11; Q3, 110.60; and Q4, 140.72. For TyG-CVAI, the rates were: Q1, 57.73; Q2, 80.04; Q3, 115.31; and Q4, 157.39 per 10,000 person-years.

As shown in Figure S5, participants in the lowest quartile of TyG-related indices had markedly lower stroke incidence than those in the highest quartile.

Relationship between TyG-related indices and the risk of new-onset stroke

Figure 2 displayed Kaplan–Meier curves for TyG-related indices, stratified by quartile. In all cases, higher quartiles corresponded to progressively greater cumulative stroke incidence. Participants in the top quartile (Q4) experienced the highest risk over time, while those in the bottom quartile (Q1) had the lowest. Log-rank tests confirmed significant differences across quartiles for all four indices ($P<0.001$).

To investigate the associations between TyG-related indices and the risk of new-onset stroke, three Cox proportional hazards regression models were constructed (Table 3). In the unadjusted model (Model 1), each 1-SD increase in TyG-BRI was associated with a 33% higher risk of stroke (HR = 1.33, 95% CI: 1.23–1.43). This association remained significant after adjusting for age, sex, and education level in Model 2 (HR = 1.37, 95% CI: 1.27–1.49), and was slightly attenuated but still statistically significant in the fully adjusted model (Model 3), which accounted for demographic, clinical, and laboratory covariates (HR = 1.16, 95% CI: 1.06–1.27). When TyG-BRI was analyzed as a categorical variable, participants in Q2, Q3, and Q4 had higher stroke risks compared with Q1, with adjusted hazard ratios of 1.39 (95% CI: 1.07–1.82), 1.63 (95% CI: 1.25–2.11), and 1.87 (95% CI: 1.43–2.44), respectively (*P* for trend = 0.048). Similarly, for TyG-ABSI, a 1-SD increase was associated with a 30% higher risk of stroke in Model 1 (HR = 1.30, 95% CI: 1.19–1.42), and remained significant in Model 3 after full adjustment (HR = 1.10, 95% CI: 1.01–1.21). In the quartile-based analysis, Q3 and Q4 were significantly associated with elevated stroke risk compared with Q1, with HRs of 1.37 (95% CI: 1.07–1.76) and 1.45 (95% CI: 1.12–1.86), respectively. For TyG-WWI, each 1-SD increment was associated with a 32% higher stroke risk in the unadjusted model (HR = 1.32, 95% CI: 1.21–1.44), and a 13% increase in the fully adjusted model (HR = 1.13, 95% CI: 1.03–1.25). The adjusted HRs for Q2, Q3, and Q4 were 1.60 (95% CI: 1.23–2.08), 1.60 (95% CI: 1.23–2.08), and 1.74 (95% CI: 1.33–2.29), respectively. As for TyG-CVAI, a 1-SD increase was associated with a 45% increase in

Table 1 The baseline characteristics of participants

Variables	Total (n = 7503)	Non-stroke (n = 6878)	New onset stroke (n = 625)	P value
Age, years	58.00 (52.00, 65.00)	58.00 (51.00, 65.00)	61.00 (55.00, 67.00)	< 0.001
Gender, n (%)				0.088
Male	3549 (47.30)	3233 (47.00)	316 (50.56)	
Female	3954 (52.70)	3645 (53.00)	309 (49.44)	
Marital status, n (%)				0.088
Married	6650 (88.63)	6109 (88.82)	541 (86.56)	
Other	853 (11.37)	769 (11.18)	84 (13.44)	
Hukou, n (%)				0.761
Agricultural	6343 (84.54)	5812 (84.50)	531 (84.96)	
Non-agricultural	1160 (15.46)	1066 (15.50)	94 (15.04)	
Education level, n (%)				0.277
No formal education	3621 (48.26)	3311 (48.14)	310 (49.60)	
Primary school	1634 (21.78)	1486 (21.61)	148 (23.68)	
Middle school	1518 (20.23)	1407 (20.46)	111 (17.76)	
High school or above	730 (9.73)	674 (9.80)	56 (8.96)	
Geographic position, n (%)				0.005
North	3152 (42.01)	2856 (41.52)	296 (47.36)	
South	4351 (57.99)	4022 (58.48)	329 (52.64)	
Alcohol intake, n (%)				0.010
Never	4356 (58.06)	4015 (58.37)	341 (54.56)	
Former	582 (7.76)	515 (7.49)	67 (10.72)	
Current	2565 (34.19)	2348 (34.14)	217 (34.72)	
Smoking, n (%)				< 0.001
Never	4546 (60.59)	4203 (61.11)	343 (54.88)	
Former	604 (8.05)	529 (7.69)	75 (12.00)	
Current	2353 (31.36)	2146 (31.20)	207 (33.12)	
Activity, n (%)				0.805
No	3734 (49.77)	3420 (49.72)	314 (50.24)	
Yes	3769 (50.23)	3458 (50.28)	311 (49.76)	
Hypertension, n (%)				< 0.001
No	4102 (54.67)	3872 (56.30)	230 (36.80)	
Yes	3401 (45.33)	3006 (43.70)	395 (63.20)	
DM, n (%)				< 0.001
No	6470 (86.23)	5965 (86.73)	505 (80.80)	
Yes	1033 (13.77)	913 (13.27)	120 (19.20)	
Dyslipidemia, n (%)				< 0.001
No	6952 (92.66)	6416 (93.28)	536 (85.76)	
Yes	551 (7.34)	462 (6.72)	89 (14.24)	
Antidiabetic agents, n (%)				< 0.001
No	7296 (97.24)	6708 (97.53)	588 (94.08)	
Yes	207 (2.76)	170 (2.47)	37 (5.92)	
Antihyperlipidemic agents, n (%)				< 0.001
No	7274 (96.95)	6692 (97.30)	582 (93.12)	
Yes	229 (3.05)	186 (2.70)	43 (6.88)	
Antihypertensive agents, n (%)				< 0.001
No	6397 (85.26)	5945 (86.44)	452 (72.32)	
Yes	1106 (14.74)	933 (13.56)	173 (27.68)	
CKM stage, n (%)				< 0.001
0	292 (3.89)	281 (4.09)	11 (1.76)	
1	789 (10.52)	754 (10.96)	35 (5.60)	
2	2087 (27.82)	1931 (28.08)	156 (24.96)	
3	4335 (57.78)	3912 (56.88)	423 (67.68)	
SBP, mmHg	126.00 (113.50, 140.50)	125.00 (113.00, 139.50)	135.00 (120.00, 151.00)	< 0.001

Table 1 (continued)

Variables	Total (n = 7503)	Non-stroke (n = 6878)	New onset stroke (n = 625)	P value
DBP, mmHg	74.00 (66.50, 82.50)	74.00 (66.50, 82.00)	78.00 (70.00, 86.50)	< 0.001
BMI, kg/m ²	23.02 (20.80, 25.57)	22.95 (20.72, 25.48)	23.89 (21.60, 26.58)	< 0.001
WBC, 10 ⁹ /L	6.00 (5.00, 7.20)	6.00 (4.98, 7.20)	6.10 (5.17, 7.50)	0.002
PLT, 10 ⁹ /L	207.38 (163.00, 254.00)	207.00 (162.00, 253.00)	211.00 (168.00, 264.00)	0.068
BUN, mg/dL	15.15 (12.55, 18.21)	15.15 (12.55, 18.23)	15.21 (12.63, 17.90)	0.924
FBG, mg/dL	102.24 (94.32, 112.86)	102.06 (94.14, 112.50)	104.76 (95.94, 117.72)	< 0.001
Cr, mg/dL	0.76 (0.64, 0.88)	0.76 (0.64, 0.88)	0.78 (0.67, 0.90)	< 0.001
TC, mg/dL	190.59 (167.01, 215.34)	190.21 (167.01, 214.95)	194.46 (169.72, 220.75)	0.004
TG, mg/dL	104.43 (74.34, 152.22)	103.10 (73.46, 150.45)	115.05 (84.96, 164.61)	< 0.001
HDL-C, mg/dL	49.87 (40.98, 60.31)	49.87 (40.98, 60.70)	47.17 (39.05, 56.44)	< 0.001
LDL-C, mg/dL	114.05 (93.17, 136.86)	113.66 (92.78, 136.47)	118.69 (95.10, 142.27)	< 0.001
CRP, mg/dL	0.99 (0.54, 2.10)	0.96 (0.53, 2.04)	1.28 (0.66, 2.70)	< 0.001
HbA1C, %	5.10 (4.90, 5.40)	5.10 (4.90, 5.40)	5.20 (4.90, 5.50)	< 0.001
UA, mg/dL	4.28 (3.57, 5.13)	4.28 (3.56, 5.11)	4.35 (3.59, 5.33)	0.037
Hb, g/L	14.20 (13.00, 15.50)	14.20 (13.00, 15.50)	14.40 (13.20, 15.70)	0.010
eGFR, mL/min/1.73m ²	95.17 (84.79, 102.64)	95.35 (85.14, 102.87)	92.26 (81.67, 99.51)	< 0.001
TyG	8.59 (8.21, 9.03)	8.57 (8.20, 9.02)	8.74 (8.37, 9.14)	< 0.001
BRI	3.97 (3.16, 5.01)	3.93 (3.13, 4.96)	4.46 (3.58, 5.40)	< 0.001
TyG-BRI	34.33 (26.47, 44.30)	33.91 (26.22, 43.81)	38.56 (30.75, 48.77)	< 0.001
ABSI	0.08 (0.08, 0.09)	0.08 (0.08, 0.09)	0.08 (0.08, 0.09)	< 0.001
TyG-ABSI	0.71 (0.67, 0.76)	0.71 (0.66, 0.76)	0.73 (0.69, 0.79)	< 0.001
WWI	11.09 (10.54, 11.68)	11.07 (10.53, 11.67)	11.27 (10.73, 11.83)	< 0.001
TyG-WWI	95.61 (88.42, 103.65)	95.36 (88.06, 103.44)	99.09 (91.58, 107.28)	< 0.001
CVAI	91.21 (64.94, 120.32)	89.91 (63.96, 118.52)	108.36 (80.08, 136.63)	< 0.001
TyG-CVAI	784.86 (545.46, 1067.83)	771.01 (534.39, 1051.59)	947.74 (683.28, 1234.56)	< 0.001

Continuous variables were presented as median (IQR), and categorical variables were presented as number (percentage). Statistical comparisons were performed using Mann-Whitney test (for continuous variables) or Chi-square test (for categorical variables).

DM: diabetes mellitus, CKM: cardiovascular-kidney-metabolic syndrome, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, WBC: white blood cell, PLT: platelet, BUN: blood urea nitrogen, FBG: fasting blood glucose, Cr: creatinine, TC: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, CRP: C-reactive protein, HbA1C: glycated hemoglobin, UA: uric acid, Hb: hemoglobin, eGFR: estimated glomerular filtration rate, TyG: triglyceride-glucose index, BRI: body roundness index, ABSI: a body shape index, WWI: weight-adjusted waist index, CVAI: Chinese visceral adiposity index, TyG-BRI: triglyceride-glucose index-body roundness index, TyG-ABSI: triglyceride-glucose index-a body shape index, TyG-WWI: triglyceride-glucose index-weight-adjusted waist index, TyG-CVAI: triglyceride-glucose index-Chinese visceral adiposity index.

stroke risk in Model 1 (HR = 1.45, 95% CI: 1.34–1.56), which decreased to 20% in Model 3 (HR = 1.20, 95% CI: 1.10–1.31). In the categorical analysis, participants in Q3 and Q4 had significantly higher risks compared with Q1, with HRs of 1.59 (95% CI: 1.22–2.07) and 1.67 (95% CI: 1.28–2.18), respectively.

Nonlinear associations between TyG-related indices and stroke risk

RCS analyses were conducted to evaluate potential nonlinear relationships between TyG-related indices and the risk of new-onset stroke. As shown in Fig. 3, a significant nonlinear association was observed for TyG-BRI and TyG-WWI (P for nonlinearity < 0.05), while no evidence of nonlinearity was detected for TyG-ABSI and TyG-CVAI (P for nonlinearity > 0.05).

Given the presence of nonlinearity, a threshold effect analysis was further performed using a two-piecewise Cox regression model. For TyG-BRI, an inflection point was identified at 18.16. Below this threshold, the

association between TyG-BRI and stroke risk was not statistically significant (HR = 0.975, 95% CI: 0.938–1.014, $P = 0.215$), whereas above the threshold, stroke risk increased significantly with each unit increment in TyG-BRI (HR = 1.014, 95% CI: 1.007–1.022, $P < 0.001$). The log-likelihood ratio test indicated that the two-piecewise model provided a better fit than the linear model ($P = 0.048$). Similarly, for TyG-WWI, the inflection point was estimated at 78.93. Below this value, no significant association was observed (HR = 0.994, 95% CI: 0.977–1.012, $P = 0.537$); however, above the threshold, TyG-WWI was significantly associated with increased stroke risk (HR = 1.016, 95% CI: 1.007–1.025, $P < 0.001$). The log-likelihood ratio test also supported the presence of a threshold effect ($P = 0.018$). These threshold effects are detailed in Table 4.

Table 2 Incidence rate of stroke (% or per 10,000 person-year)

Index	Participants	New onset stroke events	Incidence rate (95% CI) (%)	Per 10,000 person-year
Overall	7503	625	8.33 (7.69, 8.96)	102.18
TyG-BRI				
Q1	1876	92	4.90 (3.95, 5.85)	60.37
Q2	1875	134	7.15 (5.97, 8.32)	87.23
Q3	1876	175	9.33 (8.00, 10.65)	113.75
Q4	1876	224	11.94 (7.79, 8.96)	147.57
P for trend			< 0.001	
TyG-ABSI				
Q1	1876	102	5.44 (4.43, 6.44)	65.35
Q2	1875	146	7.79 (6.60, 8.98)	94.16
Q3	1876	171	9.12 (7.86, 10.37)	112.48
Q4	1876	206	10.98 (9.58, 12.38)	138.72
P for trend			< 0.001	
TyG-WWI				
Q1	1876	90	4.8 (3.86, 5.75)	57.91
Q2	1875	155	8.27 (7.03, 9.52)	101.11
Q3	1876	170	9.06 (7.80, 10.32)	110.60
Q4	1876	210	11.19 (9.75, 12.64)	140.72
P for trend			< 0.001	
TyG-CVAI				
Q1	1876	89	4.74 (3.80, 5.69)	57.73
Q2	1875	124	6.61 (5.48, 7.73)	80.04
Q3	1876	176	9.38 (8.05, 10.71)	115.31
Q4	1876	236	12.58 (11.03, 14.12)	157.39
P for trend			< 0.001	

TyG-BRI: triglyceride-glucose index-body roundness index, TyG-ABSI: triglyceride-glucose index-a body shape index, TyG-WWI: triglyceride-glucose index-weight-adjusted waist index, TyG-CVAI: triglyceride-glucose index-Chinese visceral adiposity index, CI: confidence interval

Comparative predictive performance of TyG and related indices

ROC curve analysis (Fig. 4) revealed that TyG-CVAI had the strongest discrimination for new-onset stroke (AUC=0.62), followed by TyG-BRI (AUC=0.60). TyG-WWI, TyG-BMI, and METS-IR performed similarly, each with an AUC of approximately 0.59, while TyG and TyG-ABSI showed slightly lower predictive ability (AUC=0.58).

We evaluated the prognostic performance of the three Cox models over the 5-year follow-up (Figure S6). Discrimination improved with each incremental adjustment: Model 1 (unadjusted) showed the lowest AUC, Model 2 (age, sex, education level adjusted) was intermediate, and

Model 3 (fully adjusted) achieved the highest predictive accuracy throughout the follow-up period.

Mediation of SBP in the TyG-related indices-stroke relationship

Bayesian mediation analyses (Fig. 5) demonstrated that systolic blood pressure (SBP) significantly mediated the associations between TyG-related indices and new-onset stroke. For TyG-BRI, the total effect was significant (estimate = -1.602, $P<0.001$), with an ADE of -1.078 ($P<0.001$) and an ACME of -0.523 ($P<0.001$). The proportion mediated by SBP was 32.9%. For TyG-ABSI, the total effect was -184.149 ($P<0.001$), composed of an ADE of -134.824 and an ACME of -49.325 ($P<0.001$), with 27.1% of the effect mediated by SBP. TyG-WWI showed a total effect of -1.993 ($P<0.001$), with an ADE of -1.418 and an ACME of -0.576 (both $P<0.001$), corresponding to a mediation proportion of 29.4%. TyG-CVAI had a smaller total effect (-0.079, $P<0.001$), with an ADE of -0.058 and an ACME of -0.021 (both $P<0.001$), and a mediation proportion of 26.3%. These results indicate that SBP explains approximately one-quarter to one-third of the links between elevated TyG-related indices and incident stroke.

Subgroup and sensitivity analyses

Figure 6A–D presents the results of subgroup analyses examining the associations between TyG-related indices and incident stroke. Positive associations were consistently observed across most subgroups, including sex, age, BMI, CKM stage, smoking status, alcohol intake, diabetes, and medication use. No significant interactions were detected (all P for interaction >0.05). However, hypertension status did modify the relationships for TyG-BRI (Fig. 6A), TyG-WWI (Fig. 6C), and TyG-CVAI (Fig. 6D): each index was more strongly associated with stroke risk in participants without hypertension (P for interaction = 0.027, 0.041, and 0.032, respectively).

We conducted several sensitivity checks to verify the robustness of our findings. First, using binary logistic regression in place of Cox models yielded results consistent with the primary analysis (Table S5). Second, restricting to participants with no missing covariates produced effect estimates similar to the main models (Table S6). Third, re-estimating the Cox models using the original, non-Winsorised TyG-related indices showed some divergence in effect estimates when treated as continuous variables, suggesting sensitivity to outliers. However, when categorized into quartiles, the estimates were largely consistent with those based on the Winsorised data, reinforcing the robustness of the main findings (Table S7). Fourth, based on the fully adjusted hazard ratios (Model 3), E-values suggested that unmeasured confounding would need to be unrealistically strong

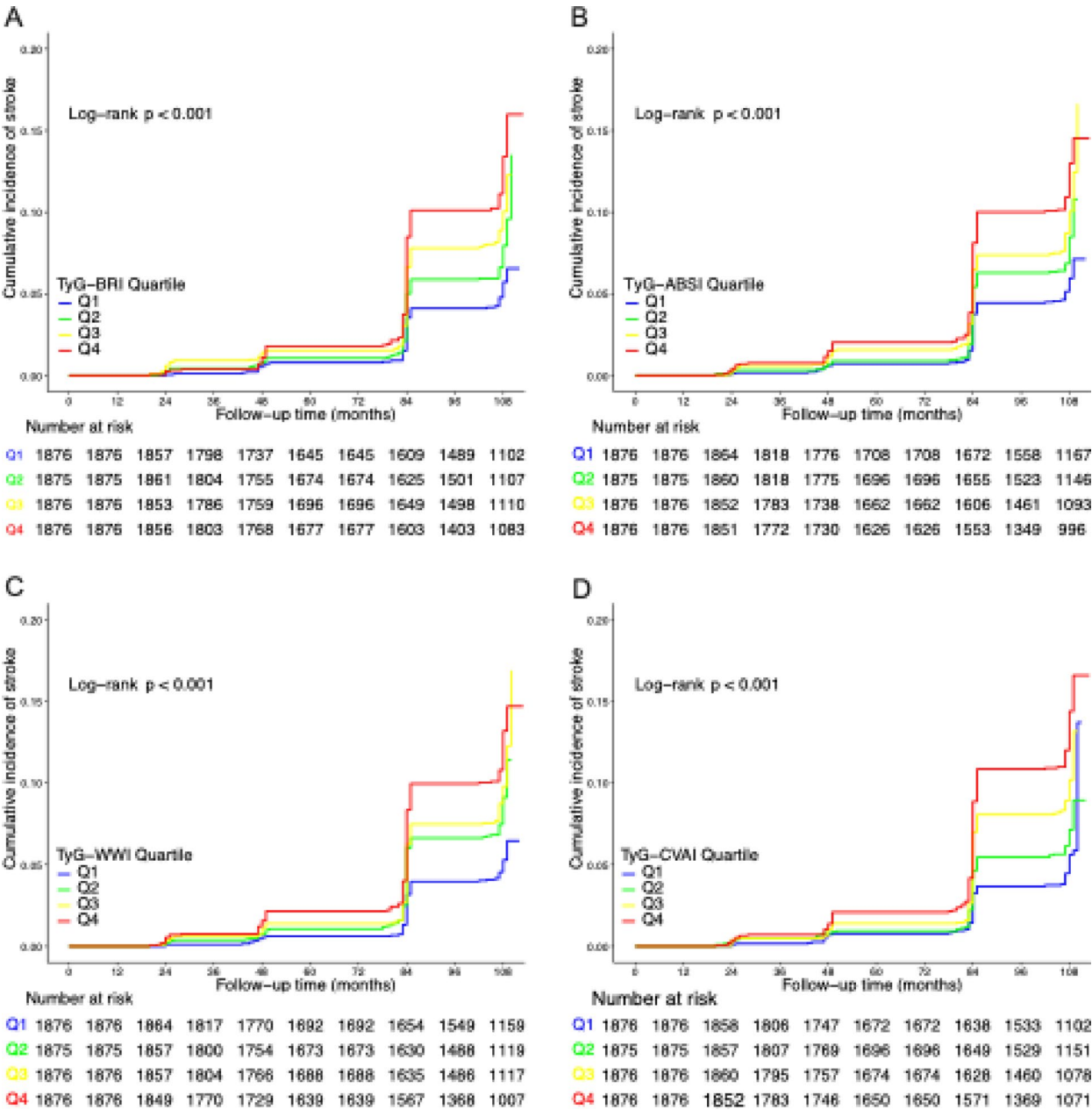


Fig. 2 Kaplan-Meier curves for new-onset stroke across quartiles of TyG-related indices: **(A)** TyG-BRI, **(B)** TyG-ABSI, **(C)** TyG-WWI, and **(D)** TyG-CVAI

to explain away the observed associations (Table S8). Together, these sensitivity analyses reinforce the stability and validity of our results.

Discussion

This study is among the first to evaluate four novel TyG-related indices—TyG-BRI, TyG-ABSI, TyG-WWI, and TyG-CVAI—in relation to incident stroke among individuals with CKM syndrome stages 0–3, using data from the nationally representative CHARLS cohort. Higher levels of each index were significantly associated with an increased risk of stroke, even after adjusting for

demographic, clinical, and metabolic factors. TyG-CVAI showed the strongest predictive performance. Nonlinear associations for TyG-BRI and TyG-WWI revealed marked risk increases in stroke risk above specific thresholds. Mediation analyses suggested that SBP partially underlies these associations, implying a blood-pressure-mediated pathway from metabolic dysregulation to stroke. Subgroup analyses confirmed these relationships across most participant groups, with particularly strong associations in those without hypertension. Overall, our findings support the utility of these novel TyG-based indices as accessible and reliable biomarkers for

Table 3 Cox regression analysis of TyG-related indices and the risk of new-onset stroke among individuals with CKM syndrome stages 0–3

	Model 1		Model 2		Model 3	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
TyG-BRI (per 1 SD)	1.33 (1.23, 1.43)	< 0.001	1.37 (1.27, 1.49)	< 0.001	1.16 (1.06, 1.27)	< 0.001
TyG-BRI quartile						
Q1	Reference		Reference		Reference	
Q2	1.44 (1.10, 1.88)	0.007	1.53 (1.17, 2.00)	0.002	1.39 (1.07, 1.82)	0.015
Q3	1.87 (1.45, 2.40)	< 0.001	2.04 (1.58, 2.64)	< 0.001	1.63 (1.25, 2.11)	< 0.001
Q4	2.47 (1.94, 3.15)	< 0.001	2.83 (2.19, 3.64)	< 0.001	1.87 (1.43, 2.44)	< 0.001
p for trend		< 0.001		< 0.001		0.048
TyG-ABSI (per 1 SD)	1.30 (1.19, 1.42)	< 0.001	1.24 (1.13, 1.36)	< 0.001	1.10 (1.01, 1.21)	0.038
TyG-ABSI quartile						
Q1	Reference		Reference		Reference	
Q2	1.45 (1.13, 1.87)	0.004	1.36 (1.06, 1.75)	0.017	1.25 (0.97, 1.61)	0.088
Q3	1.76 (1.38, 2.25)	< 0.001	1.63 (1.27, 2.08)	< 0.001	1.37 (1.07, 1.76)	0.014
Q4	2.22 (1.75, 2.81)	< 0.001	2.00 (1.57, 2.55)	< 0.001	1.45 (1.12, 1.86)	0.005
p for trend		< 0.001		< 0.001		< 0.001
TyG-WWI (per 1 SD)	1.32 (1.21, 1.44)	< 0.001	1.31 (1.20, 1.44)	< 0.001	1.13 (1.03, 1.25)	0.014
TyG-WWI quartile						
Q1	Reference		Reference		Reference	
Q2	1.76 (1.36, 2.29)	< 0.001	1.74 (1.34, 2.26)	< 0.001	1.60 (1.23, 2.08)	< 0.001
Q3	1.94 (1.50, 2.51)	< 0.001	1.99 (1.54, 2.58)	< 0.001	1.60 (1.23, 2.08)	< 0.001
Q4	2.53 (1.97, 3.24)	< 0.001	2.55 (1.97, 3.31)	< 0.001	1.74 (1.33, 2.29)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001
TyG-CVAI (per 1 SD)	1.45 (1.34, 1.56)	< 0.001	1.40 (1.30, 1.51)	< 0.001	1.20 (1.10, 1.31)	< 0.001
TyG-CVAI quartile						
Q1	Reference		Reference		Reference	
Q2	1.37 (1.04, 1.80)	0.023	1.37 (1.04, 1.80)	0.025	1.26 (0.95, 1.65)	0.105
Q3	2.01 (1.56, 2.60)	< 0.001	1.97 (1.52, 2.56)	< 0.001	1.59 (1.22, 2.07)	0.001
Q4	2.77 (2.17, 3.53)	< 0.001	2.56 (1.99, 3.28)	< 0.001	1.67 (1.28, 2.18)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001

Model 1: non-adjusted;

Model 2: adjusted for age, gender, education level;

Model 3: adjusted for age, gender, education level, alcohol intake, smoking, hypertension, DM, antidiabetic agents, antihypertensive agents, SBP, DBP, PLT, BUN, Cr, LDL_C, CRP, HbA1C, UA, Hb, eGFR.

TyG-BRI: triglyceride-glucose index-body roundness index, TyG-ABSI: triglyceride-glucose index-a body shape index, TyG-WWI: triglyceride-glucose index-weight-adjusted waist index, TyG-CVAI: triglyceride-glucose index-Chinese visceral adiposity index, HR: hazard ratio, CI: confidence interval.

identifying stroke risk in individuals with CKM syndrome stages 0–3.

A substantial body of evidence supports the use of the TyG index and its composite measures for predicting stroke risk. Several cohort studies have shown that higher TyG values are linked to greater incidence of CVD, including stroke [42–45]. For example, a U.S. prospective study found that each one-unit rise in the TyG index corresponded to a 32.1% increase in stroke risk after multivariable adjustment [45]. Likewise, a Chinese cohort reported that a one-SD increment in TyG was associated with a 34% higher risk of stroke (adjusted HR 1.34) [46].

Obesity, especially visceral adiposity, is also a well-established contributor to stroke development [47–49]. While BMI and waist circumference are widely used, they poorly capture abdominal fat distribution. To overcome this, researchers have developed novel adiposity

indices (BRI, ABSI, WWI, and CVAI) that better estimate visceral fat accumulation and demonstrate improved prediction of cardiovascular and cerebrovascular events [50–53].

Recent large-scale cohort studies have underscored the added value of combining TyG with adiposity measures. For example, jointly assessing TyG and BRI enhanced identification of individuals at high stroke risk, demonstrating how insulin resistance and central obesity together exacerbate cerebrovascular vulnerability [33]. Similarly, combining TyG with ABSI outperformed either metric alone for predicting incident stroke, supporting its use in early prevention strategies [34]. A nationwide analysis revealed that higher baseline and cumulative TyG-CVAI levels, as well as increasing trajectories over time, were associated with an elevated risk of new-onset stroke. They also reported a U-shaped relationship,

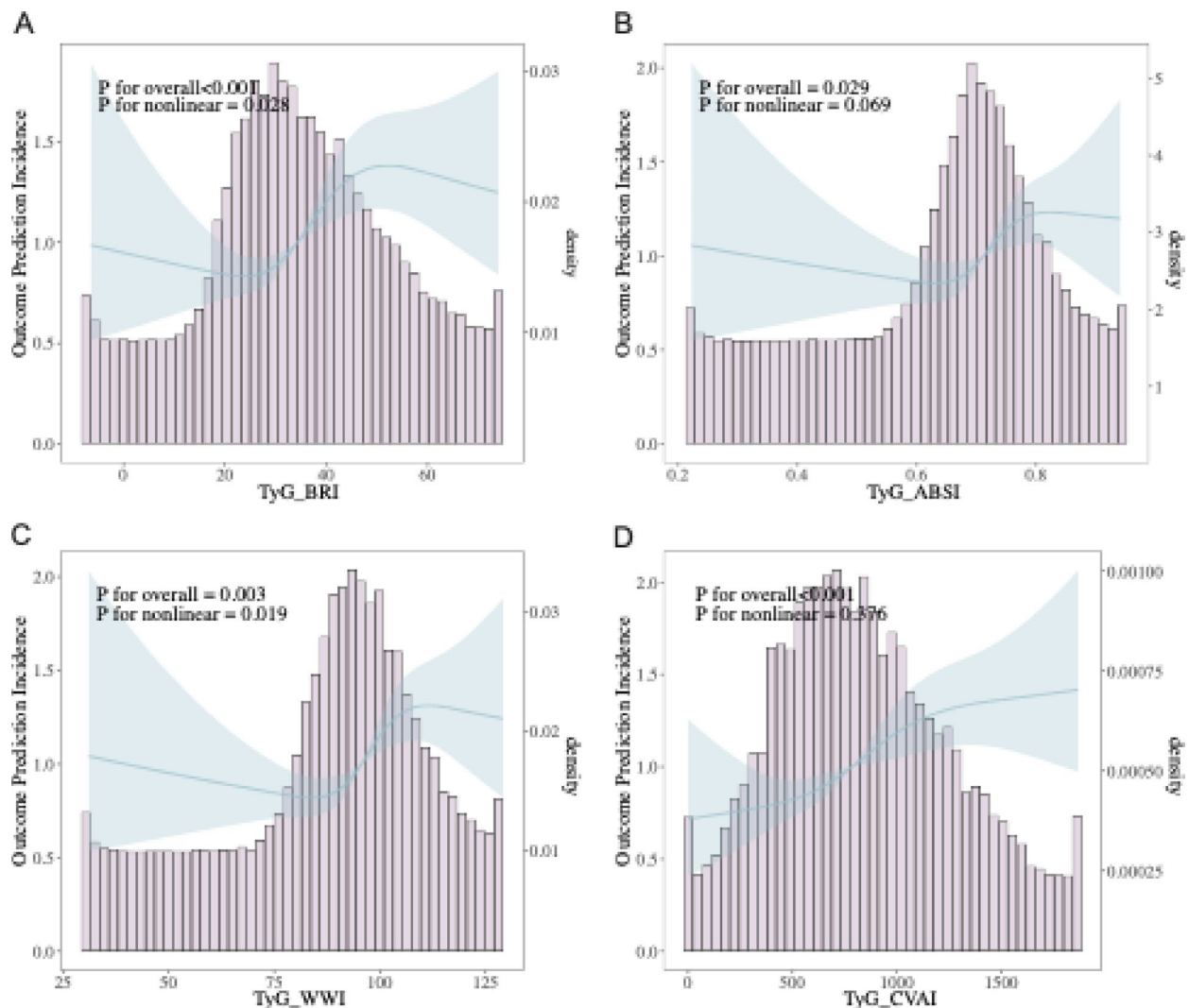


Fig. 3 Restricted cubic spline curves illustrating the associations between TyG-related indices and new-onset stroke risk. **(A)** TyG-BRI, **(B)** TyG-ABSI, **(C)** TyG-WWI, and **(D)** TyG-CVAI. Solid lines represented adjusted hazard ratios derived from multivariable Cox models, and shaded areas denote 95% confidence intervals. Adjusted for age, gender, education level, alcohol intake, smoking, hypertension, DM, antidiabetic agents, antihypertensive agents, SBP, DBP, PLT, BUN, Cr, LDL_C, CRP, HbA1C, UA, Hb, eGFR

indicating that both very low and very high TyG-CVAI levels may elevate stroke risk [28].

Although the underlying mechanisms remain unclear, the strong associations between the four TyG-related indices and stroke risk likely reflect the combined impact of insulin resistance and abdominal obesity—two key, interrelated components of CKM syndrome. In this syndrome, impaired insulin signaling reduces cellular glucose uptake, provoking compensatory hyperinsulinemia and chronic hyperglycemia [54]. These disturbances trigger a cascade of harmful molecular events: advanced glycation end-product formation and activation of the protein kinase C (PKC)–nicotinamide adenine dinucleotide phosphate oxidase (NADPH) pathway generate excess reactive oxygen species (ROS) [55–57], which diminish nitric oxide bioavailability, impair endothelial

function, and upregulate adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), thereby promoting vascular inflammation and atherosclerosis [9, 58, 59]. Concurrently, hyperinsulinemia activates the sympathetic nervous system and the renin–angiotensin–aldosterone system, leading to sodium retention, plasma volume expansion, hypertension, heightened platelet reactivity, and prothrombotic tendencies [60, 61]. Dyslipidemia—marked by elevated triglycerides, low HDL-C, and an abundance of small dense LDL particles—further compounds vascular injury [62].

Visceral adipose tissue exacerbates these processes by secreting proinflammatory cytokines (e.g., TNF- α , IL-6) and free fatty acids, which interfere with insulin signaling, fuel systemic inflammation, and promote macrophage-mediated vascular damage [63]. Hepatic uptake

Table 4 Threshold effect analysis of TyG-related indices on new-onset stroke using a two-piecewise linear regression model

	Adjusted HR (95% CI)	P value
TyG-BRI		
Total	1.011 (1.004, 1.017)	0.001
Inflection point	18.16	
< 18.16	0.975 (0.938, 1.014)	0.215
≥ 18.16	1.014 (1.007, 1.022)	<0.001
P for Log-likelihood ratio	0.048	
TyG-WWI		
Total	1.009 (1.002, 1.016)	0.014
Inflection point	78.93	
< 78.93	0.994 (0.977, 1.012)	0.537
≥ 78.93	1.016 (1.007, 1.025)	<0.001
P for Log-likelihood ratio	0.018	

TyG-BRI: triglyceride-glucose index-body roundness index, TyG-WWI: triglyceride-glucose index-weight-adjusted waist index, HR: hazard ratio, CI: confidence interval Adjusted for age, gender, education level, alcohol intake, smoking, hypertension, DM, antidiabetic agents, antihypertensive agents, SBP, DBP, PLT, BUN, Cr, LDL_C, CRP, HbA1C, UA, Hb, eGFR.

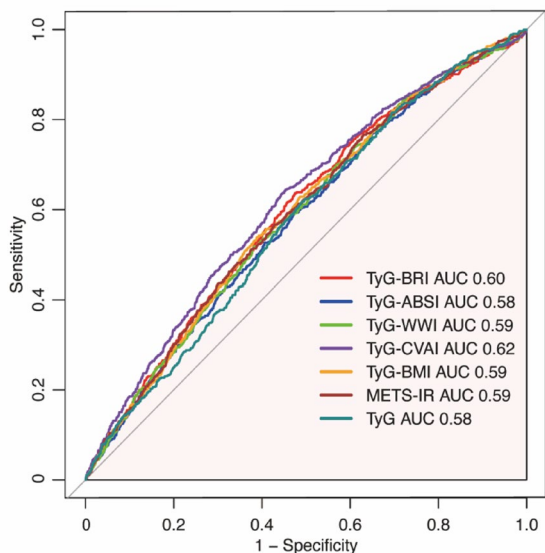


Fig. 4 Comparison of the discriminatory performance of different IR indices for predicting new-onset stroke

of excess free fatty acids intensifies lipotoxic stress and sustains a proinflammatory state, perpetuating IR [64]. Together, IR and visceral fat accumulation contribute to a vicious cycle involving endothelial dysfunction, chronic inflammation, accelerated atherogenesis, hypertension, and thrombosis—all of which increase the risk of stroke.

Our mediation analysis revealed that systolic blood pressure (SBP) accounted for 26.3–32.9% of the association between TyG-related indices and stroke risk, indicating that hypertension is a key intermediary linking metabolic dysregulation to cerebrovascular pathology. These findings support an integrated CKM model in which both metabolic and hemodynamic disturbances

contribute to vascular compromise. Moreover, hypertension might aggravate endothelial injury and vascular remodeling in the context of IR and chronic inflammation, thereby further elevating stroke susceptibility [65, 66]. Although the CHARLS dataset did not permit estimation of the precise reduction in stroke risk achievable by targeting specific SBP thresholds, our results underscore the potential clinical value of early blood pressure control in metabolically vulnerable individuals. Future interventional studies are needed to quantify the preventive impact of SBP reduction in this high-risk population.

We observed strong associations between all four TyG-related indices and incident stroke risk over a median follow-up (incidence 102.18 per 10,000 person-years; cumulative incidence 8.33%). Stroke hazards increased in a graded fashion across index quartiles: participants in the highest quartile of TyG-BRI had an 87% higher risk than those in the lowest (HR 1.87, 95% CI 1.43–2.44), with similar effects for TyG-WWI (HR 1.74, 1.33–2.29), TyG-CVAI (HR 1.67, 1.28–2.18), and TyG-ABSI (HR 1.45, 1.12–1.86). When analyzed continuously, each 1-SD increase in TyG-BRI, TyG-WWI, TyG-CVAI, and TyG-ABSI was associated with 16%, 13%, 20%, and 10% higher stroke hazards, respectively.

Restricted cubic spline models identified threshold effects for TyG-BRI (18.16) and TyG-WWI (78.93), beyond which stroke risk increased sharply. These inflection points may represent critical metabolic thresholds where insulin resistance and adiposity begin to synergistically impair vascular function. However, due to the absence of mechanistic biomarkers (e.g., IL-6, TNF- α), the underlying biological pathways remain unclear and warrant further investigation. Additional studies are needed to determine whether these thresholds correspond to specific stages of metabolic dysfunction and to validate their relevance in other populations. Clinically, the observed non-linear associations may help identify individuals who fall outside conventional high-risk classifications but exhibit elevated metabolic profiles that cross these critical thresholds—potentially benefiting from earlier preventive interventions. If confirmed by future research, these inflection points could inform more personalized risk assessment strategies and guide targeted preventive measures in metabolically vulnerable populations. In contrast, TyG-ABSI and TyG-CVAI exhibited approximately linear risk patterns. Prior Chinese cohort studies likewise reported a U-shaped TyG-CVAI–stroke relationship [28], whereas TyG-WWI and TyG-BRI generally showed linear trends despite occasional visual indications of nonlinearity [24, 67]. A recent UK cohort also identified a significant nonlinear association for TyG-BRI [25], underscoring potential population differences.

Consistent with earlier reports, TyG-CVAI demonstrated the highest predictive accuracy in our ROC

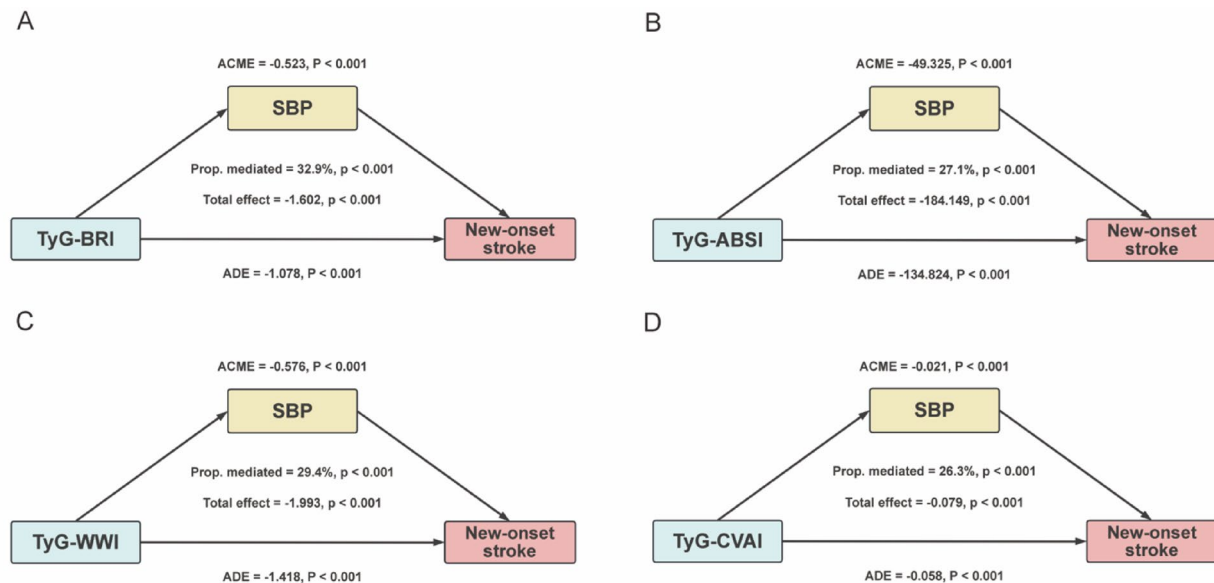


Fig. 5 Mediation analysis of SBP in the association between TyG-related indices and new-onset stroke

analysis (AUC=0.62). For example, Ren et al. found CVAI outperformed other adiposity metrics for CVD risk prediction [52], and Wang et al. reported TyG-CVAI achieved the highest AUC (0.636) among several TyG-related indices [28]. Subgroup analyses confirmed stability across most strata; notably, associations were stronger among participants without hypertension, suggesting that TyG-related indices may help identify metabolically at-risk individuals who fall below conventional blood pressure thresholds and refine early primary prevention efforts.

Strengths and limitations

This study offers several strengths. First, it utilizes a nationally representative cohort of middle-aged and older Chinese adults—a population with a high prevalence of CKM syndrome—which enhances the generalizability of our findings. Second, by examining four distinct TyG-related indices, including those that capture visceral adiposity, we provide a more nuanced evaluation of both metabolic and anatomical contributors to stroke risk. Third, our prospective design, extensive covariate adjustment, and comprehensive sensitivity and subgroup analyses bolster the validity and consistency of the results. Fourth, the use of restricted cubic spline modeling uncovered nonlinear and threshold effects that standard regression approaches might overlook. Finally, mediation analysis identified systolic blood pressure as a partial intermediary, lending mechanistic support to the integrated CKM framework.

However, several limitations warrant consideration. We measured TyG-related indices only at baseline, which may not capture temporal changes in metabolic

status or fat distribution and could underestimate cumulative exposure. Stroke outcomes relied primarily on self-report, potentially introducing misclassification, though prior validation in CHARLS suggests acceptable accuracy. Our cohort was limited to middle-aged and older Chinese adults, so extrapolation to younger or non-Chinese populations should be done cautiously. As an observational study, residual confounding from unmeasured factors cannot be completely excluded despite rigorous adjustment. Moreover, external validation was not feasible due to the absence of an independent cohort within the CHARLS framework. Additionally, comparator models such as the Framingham Stroke Risk Score could not be assessed, as key variables (e.g., atrial fibrillation, left ventricular hypertrophy) were unavailable—limiting the comparative interpretability and generalizability of our findings.

Future research should validate these associations in more ethnically and age-diverse cohorts and investigate how TyG-related indices evolve over time in relation to cerebrovascular events. Incorporating clinically confirmed or imaging-verified stroke diagnoses, along with standardized diagnostic criteria, will help reduce misclassification and recall bias, thereby improving the accuracy and reliability of stroke incidence estimates. Additionally, mechanistic studies are needed to elucidate how insulin resistance and central adiposity interact to promote vascular injury. Further investigations should also assess whether TyG-CVAI offers incremental predictive value beyond existing clinical risk models, such as the Framingham Stroke Risk Score, in independent and diverse cohorts. Ultimately, integrating novel TyG-related indices into early risk stratification algorithms may aid in

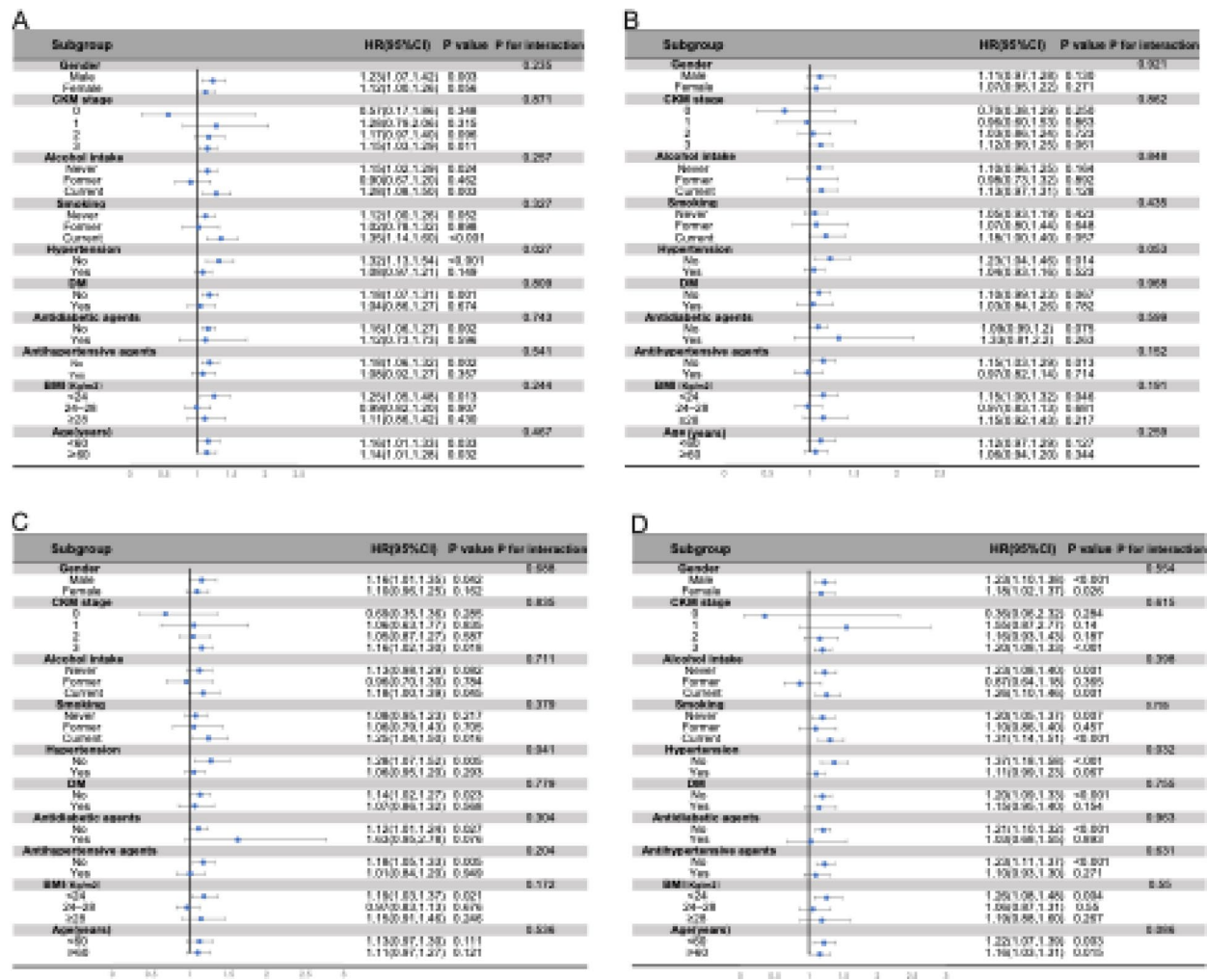


Fig. 6 Subgroup analyses of the association between TyG-related indices and new-onset stroke. **(A)** TyG-BRI, **(B)** TyG-ABSI, **(C)** TyG-WWI, and **(D)** TyG-CVAI. Models were adjusted based on Model 3, with the stratification variable itself excluded from adjustment

identifying metabolically vulnerable individuals—particularly those without overt hypertension or diabetes—and support targeted prevention strategies within the CKM syndrome stage 0–3 population.

Conclusion

In this large prospective cohort of Chinese adults with early-stage CKM syndrome, four novel TyG-related indices—TyG-BRI, TyG-ABSI, TyG-WWI, and TyG-CVAI—were each independently associated with an increased risk of new-onset stroke. Among them, TyG-CVAI demonstrated the strongest predictive performance, while TyG-BRI and TyG-WWI showed threshold effects beyond which stroke risk rose sharply. Mediation analysis indicated that systolic blood pressure accounted for approximately 26–33% of these associations, underscoring hypertension as a key intermediary. These findings support the incorporation of TyG-related indices into early risk stratification strategies to enhance stroke

prevention among individuals with CKM syndrome stages 0–3.

Abbreviations

ABSI	A body shape index
ACME	Average causal mediation effect
ADE	Average direct effect
AHA	American Heart Association
AUC	Area under the curve
BMI	Body mass index
BRI	Body roundness index
BUN	Blood urea nitrogen
CHARLS	China Health and Retirement Longitudinal Study
CI	Confidence interval
CKM	Cardiovascular-kidney-metabolic syndrome
CRP	C-reactive protein
Cr	Creatinine
CVAI	Chinese visceral adiposity index
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
FBG	Fasting blood glucose
GBD	Global Burden of Disease

Hb	Hemoglobin
HbA1c	Glycated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
HRs	Hazard ratios
IQR	Interquartile range
IR	Insulin resistance
LDL-C	Low-density lipoprotein cholesterol
NADPH	Nicotinamide adenine dinucleotide phosphate oxidase
PKC	Protein kinase C
PLT	Platelet
RCS	Restricted cubic splines
ROC	Receiver operating characteristic
ROS	Reactive oxygen species
SBP	Systolic blood pressure
SD	Standard deviation
TC	Total cholesterol
TG	Triglycerides
TyG	Triglyceride-glucose index
TyG-ABSI	Triglyceride-glucose index–a body shape index
TyG-BRI	Triglyceride-glucose index–body roundness index
TyG-CVAI	Triglyceride-glucose index–Chinese visceral adiposity index
TyG-WWI	Triglyceride-glucose index–weight-adjusted waist index
UA	Uric acid
VCAM-1	Vascular cell adhesion molecule-1
VIF	Variance inflation factor
WC	Waist circumference
WBC	White blood cell
WWI	Weight-adjusted waist index

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12933-025-02854-x>.

Supplementary Material 1

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Author contributions

YY, PL, and ZS designed the study. YY, ZS and PL extracted, collected, and analyzed data. YY, ZS and PL prepared tables and figures. YY, PL, ZS, RM and ZL drafted the initial manuscript. KH and YZ reviewed and revised the manuscript. All authors approved the final version of the manuscript for submission.

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Data availability

The dataset utilized in this study is publicly available from the official CHARLS website (<https://charls.pku.edu.cn/>). Upon registration and approval, users may access and download the data in accordance with the platform's guidelines.

Declarations

Consent for publication

Not applicable.

Competing interests

Dr. Hashimoto reports receiving research funding from Otsuka (Japan) and speaker honoraria from Abbott (Costa Rica) outside the submitted work. All other authors declare no conflicts of interest.

Ethics statement

The study involving human participants was reviewed and approved by the Ethics Committee of Peking University. All participants provided written informed consent prior to their inclusion in the study.

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