Lipids in Health and Disease

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Comparing the impact of cumulative insulin resistance surrogates exposure on stroke: optimizing prevention strategies

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Abstract

Background Insulin resistance (IR) plays a major role in increasing the risk of stroke. The objective of this research is to systematically evaluate and compare the impact of cumulative exposure over time to four commonly used IR surrogates—triglyceride-glucose (CumTyG) index, metabolic score for IR (CumMetS-IR), estimated glucose disposal rate (CumeGDR) and triglyceride to high-density lipoprotein cholesterol (CumTG/HDL-C) ratio—on stroke risk, providing insights for optimizing monitoring strategies for primary stroke prevention.

Methods The study population was sourced from the China Health and Retirement Longitudinal Study (CHARLS2011-2018). Cumulative exposure to IR (CumIR) surrogates was calculated as the mean value of IR surrogates measured in the first and third waves of CHARLS, multiplied by the total exposure duration. The primary endpoint was incident stroke, determined through questionnaires in the third and fourth waves of CHARLS. Multivariable Cox regression models were applied to estimate and compare HRs and 95% CIs for stroke across quartiles of CumIR surrogates.

Results A total of 4,669 participants with no history of stroke at baseline were included. During a median follow-up of 6 years, 347 new stroke events (7.43%) were recorded. The incidence rates of stroke in the highest quartiles of CumTyG index, CumTG/HDL-C ratio, and CumMetS-IR, as well as the lowest quartile of CumeGDR, were 9.67%, 9.93%, 10.45%, and 13.02%, respectively. In terms of risk assessment, the multivariable Cox regression analysis showed that the highest quartiles of CumTyG index, CumTG/HDL-C ratio, and CumMetS-IR and the lowest quartile of CumeGDR were associated with stroke risk, with corresponding HR (95% CI) of 1.48(1.05–2.10), 1.61(1.15–2.24), 1.72(1.21–2.43), and 3.57(2.25–5.68), respectively. In terms of event prediction, receiver operating characteristic analysis revealed that CumeGDR had the highest predictive accuracy for incident stroke compared with other common IR surrogates.

Conclusions In assessing stroke risk and predicting events in middle-aged and elderly populations, cumulative exposure to eGDR demonstrates significant advantages over other common IR surrogates. Incorporating eGDR as an IR monitoring marker is recommended for primary stroke prevention.

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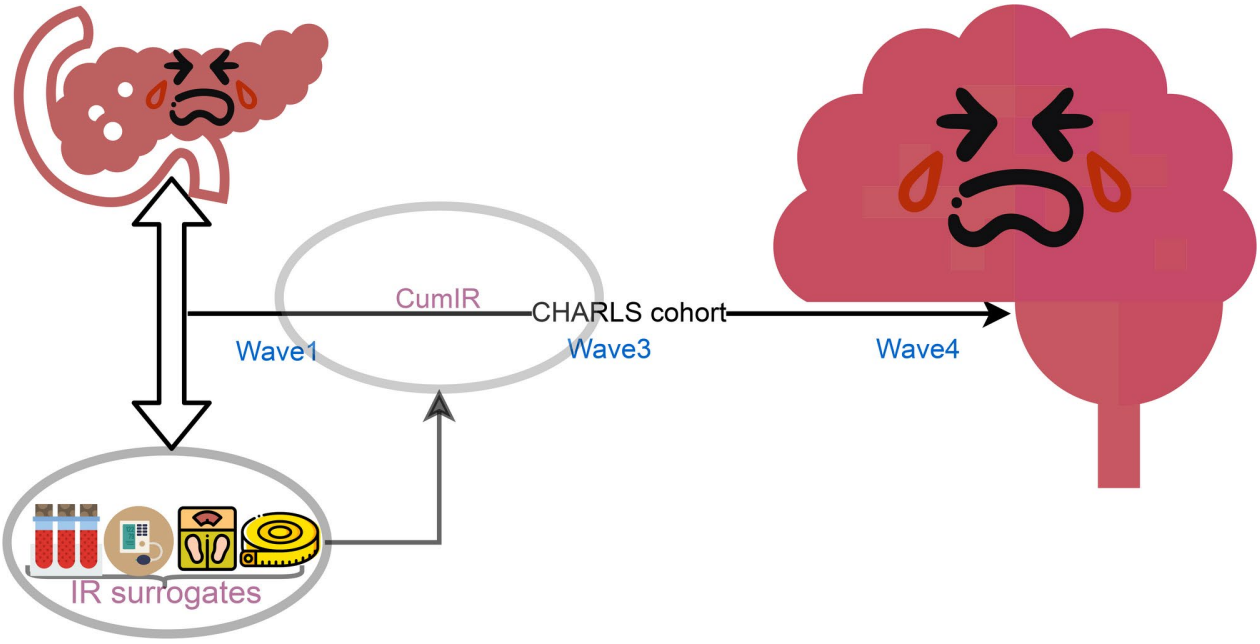
Graphic abstract



Keywords Cumulative exposure to insulin resistance, Stroke, Estimated glucose disposal rate, CumeGDR

Introduction

The disease burden of stroke is one of the greatest global health challenges of the 21st century [1]. Over the past 30 years, the absolute number of new stroke cases has increased by 70%, and the number of people living with stroke has increased by 85% [2]. In 2019, stroke caused 6.55 million deaths and 143 million disability-adjusted life years worldwide, making it the second leading cause of death and disability globally [2–4]. Furthermore, it is important to note that the incidence of stroke increases with age [1]; given the rapid global aging trend, the number of deaths and disabilities worldwide is expected to rise significantly in the future [1]. Therefore, primary prevention should be a priority to mitigate the potential future burden of stroke-related diseases [5].

Insulin resistance (IR) refers to a condition in which insulin-targeted tissues exhibit reduced responsiveness to physiological levels of insulin [6], and it is a key characteristic in stroke patients [7]. Studies have shown that IR can lead to stroke by inducing hemodynamic disturbances, enhancing platelet adhesion, activation, and aggregation, as well as promoting atherosclerosis [7, 8]. There are currently various methods for assessing IR [9–11], including the hyperinsulinemic-euglycemic clamp [9], the quantitative insulin sensitivity check index [10], the homeostasis model assessment of IR [11], and IR surrogates such as triglyceride-glucose (TyG) index, triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio, metabolic score for IR (MetS-IR), and estimated glucose disposal rate (eGDR) [12–16]. Among these methods, IR surrogates are the most frequently used worldwide due to their simplicity, convenience, reproducibility, and better potential for widespread application. From a primary prevention perspective, identifying the optimal IR surrogates for stroke risk assessment and event prediction is crucial for reducing the burden of stroke. However, considering the dynamic nature of the metabolic factors involved in IR surrogates, such as blood glucose, lipids, blood pressure, and obesity [17], it is important to further explore the longitudinal changes in IR surrogates and their effects on stroke.

Cumulative exposure has become a widely used approach in recent years for handling repeated measurements in longitudinal studies, reflecting the intensity and duration of exposure to a given parameter over a period of time [18–22]. For example, prolonged high exposure to low-density lipoprotein cholesterol significantly increases the risk of atherosclerosis [23]. This differs from baseline single measurements, as cumulative exposure takes into account both the amount and duration of exposure during follow-up. Given the current severity of stroke and the importance of primary prevention, and the lack of systematic studies evaluating the relationship between cumulative exposure to IR surrogates and stroke, the present study aims to analyze and compare the impact of cumulative exposure to four common IR surrogates (TyG

index, TG/HDL-C ratio, MetS-IR, and eGDR) over time on stroke risk using national data from the China Health and Retirement Longitudinal Study (CHARLS). The goal is to provide valuable research data for optimizing monitoring strategies in primary stroke prevention.

Methods

Study population

We utilized data from the CHARLS project, a detailed description of which has been provided in previous publications [24]. The overall design and implementation framework of CHARLS are summarized in supplementary methods. Briefly, the baseline survey of the CHARLS study began in 2011–2012 and recruited 17,008 participants from 28 provinces across China, covering 150 counties, 450 villages, and approximately 10,000 households. The study population was selected through a multi-stage random sampling process, followed by random selection from a sampling frame reflecting all residential units within each village/community. Regarding follow-up, the CHARLS team conducts national tracking surveys every 2–3 years following the baseline survey. As of now, four waves of national tracking surveys have been completed, in 2013, 2015, 2018, and 2020, with blood sample measurements available from the baseline survey and the 2015 survey.

For the present study, we included baseline data from the first wave of CHARLS and follow-up data from the third and fourth waves of the national surveys. Cumulative IR (CumIR) surrogates were developed based on data from the first and third waves. The inclusion process for the study population is as follows: Step 1: We included participants aged ≥ 45 years from the baseline data of the first CHARLS wave who were followed up in the third wave. Step 2: We excluded participants who were diagnosed with stroke in the first wave or had an uncertain stroke status in either the first or third wave. Step 3: To calculate IR surrogates, participants were required to have fasting blood samples and obesity measurements, so we excluded those who did not undergo measurements of obesity parameters or blood tests, or who only completed non-fasting blood tests (i.e., did not have Cum-IR measured). A detailed flowchart of the study process was shown in Fig. 1.

Ethics statement

All participants in the CHARLS study provided written informed consent before participation, and subsequent surveys, physical measurements, blood collection, and follow-up were carried out after approval. The implementation of CHARLS was authorized by the Ethics Committee of Peking University (No. 00001052–11015), and all research data were de-identified.

Assessment of covariates and independent variables

Various covariates were assessed from the CHARLS questionnaires and datasets, including basic demographic characteristics (gender, age, education, marital status, and residence), lifestyle factors (smoking and drinking status), comorbidities (hypertension, diabetes, and heart disease), simple body measurements [systolic blood pressure, diastolic blood pressure, height, weight, body mass index (BMI), waist circumference (WC)], and blood biomarkers. Detailed assessments of lifestyle factors, comorbidities, and simple body measurements were summarized in supplementary methods.

Blood samples were collected after overnight fasting. Venous blood samples were collected by trained staff. To maintain sample stability, all samples were stored at -80 °C. Blood sample analysis was performed in the laboratory of Peking University, where biomarkers including glycated hemoglobin, fasting plasma glucose (FPG), HDL-C, low-density lipoprotein cholesterol, total cholesterol, TG, uric acid, and creatinine were measured. The CHARLS team performs weekly quality control checks, ensuring the stability of sample analysis during the study period. Detailed analytical methods, laboratory coefficients of variation, and upper detection limits have been reported in previous studies [25].

The calculation methods for IR surrogates and CumIR surrogates were shown in Table 1 [12–15, 20–22].

Outcome determination

The primary outcome in this study was incident stroke, which was assessed based on questionnaires from the third and fourth waves. Participants were asked, "Have you been diagnosed with stroke by a doctor?" and responded with "Yes" or "No." A response of "Yes" indicated a stroke diagnosis.

Missing data assessment

In this study, the total missing data accounted for 1.91% of the study population, with the highest missing value being 34 (supplementary Table 1). Given the relatively low proportion of missing data, all analyses were performed on the original dataset. Data analysis was conducted between October and November 2024.

Statistical analysis

A two-tailed significance level of 5% was used for all statistical tests. Data analysis was conducted using R language (version 4.2.1) and Empower(R) (version 4.2). Baseline characteristics of the study population are presented as frequencies (percentages), mean ± standard deviation, or median and interquartile range, with appropriate statistical tests selected based on the nature of the data.

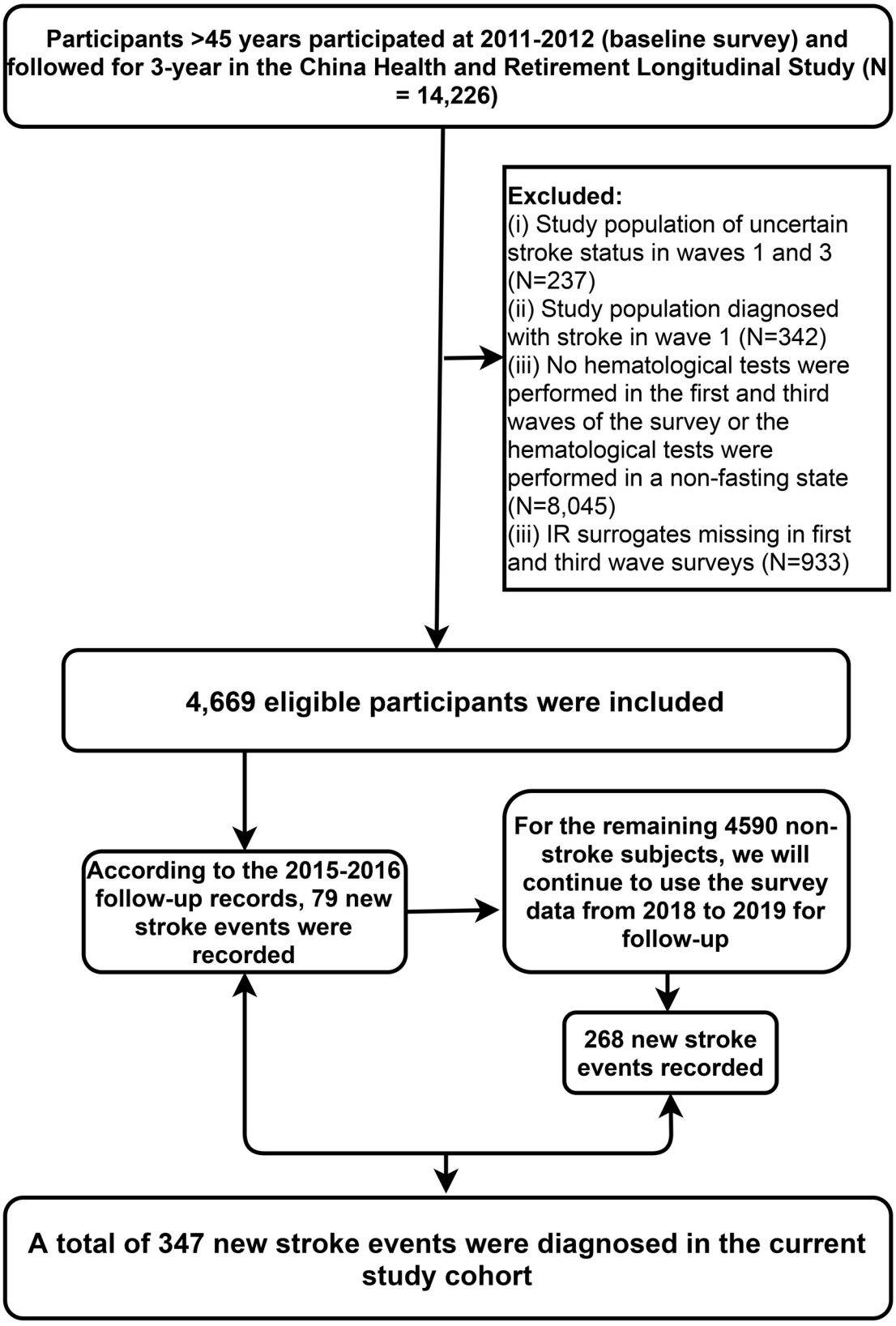


Fig. 1 Flow chart of study participants

Table 1 Calculation method of IR surrogates and CumIR surrogates

	Calculation method	Reference
TyG index	TyG index = ln [TG (mg/dL) × FPG (mg/dL)/2]	[12]
TG/HDL-C ratio	TG/HDL-C ratio = TG (mg/dL) / HDL-C (mg/dL)	[13]
MetS-IR	MetS-IR = Ln [(2 × FPG (mg/dL)) + fasting TG (mg/dL)] × BMI (kg/m^2) / (Ln [HDL-C (mg/dL)]).	[14]
eGDR	eGDR = 21.158 – (0.09 × WC) – (3.407 × hypertension) – (0.551 × HbA1c) [WC (cm), hypertension (yes = 1/no = 0), and HbA1c (%)].	[15]
CumTyG index	CumTyG index = (TyG index2012 + TyGindex2015)/2* time (2012 – 2015)	[20]
CumTG/HDL-C ratio	CumTG/HDL-C ratio = (TG/HDL-C ratio2012 + TG/HDL-C ratio2015)/2* time (2012 – 2015)	
CumMetS-IR	CumMetS-IR = (MetS-IR2012 + MetS-IR2015)/2* time (2012 – 2015)	[21]
CumeGDR	CumeGDR = (eGDR2012 + eGDR2015)/2* time (2012 – 2015)	[22]

Abbreviations: IR: insulin resistance; CumIR: cumulative insulin resistance; TyG: triglyceride-glucose; TG/HDL-C: triglyceride to high-density lipoprotein cholesterol; MetS-IR: metabolic score for insulin resistance; eGDR: estimated glucose disposal rate; CumTyG: cumulative triglyceride-glucose; CumMetS-IR: cumulative metabolic score for insulin resistance; CumTG/HDL-C: cumulative triglyceride to high-density lipoprotein cholesterol; CumeGDR: cumulative estimated glucose disposal rate

Cox regression models were used to estimate the multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals for stroke associated with IR surrogates and CumIR surrogates. Given the large differences in the units of various IR surrogates and CumIR surrogates, we chose to assess the association between the quartiles of these surrogates and stroke risk for easier comparison of results. Following the STROBE guidelines, a stepwise adjustment approach was applied for model building [26]. To minimize the impact of collinearity, the components of the IR surrogates and potential collinear covariates (supplementary Tables 2–9) were excluded from the models [27].

Three adjusted models were constructed for data analysis: Model I adjusted for basic demographic characteristics; Model II further adjusted for potential confounders including lifestyle factors and comorbidities; Model III, the final model, adjusted for all covariates while excluding those covariates with high collinearity.

Receiver operating characteristic (ROC) analysis was applied to assess the predictive value of IR surrogates and their cumulative exposure for stroke events, calculating the corresponding area under the curve, sensitivity, specificity, and optimal threshold. Differences in area under the curve values were compared using the DeLong test [28].

Sensitivity analyses

(1) Stratified analyses by age and gender were performed to assess the associations mentioned above, with likelihood ratio tests to detect potential differences across populations.
(2) To minimize the impact of medication on the results [29], we excluded participants using antihypertensive, antidiabetic, or lipid-lowering medications at baseline.
(3) Multiple imputation was applied to handle missing data [30], and multivariable Cox regression models were run on the imputed datasets.
(4) To reduce the influence of cardiovascular disease on stroke incidence [31], the analysis was repeated excluding individuals with cardiovascular disease.
(5) To minimize the potential impact of altered insulin secretion patterns in diabetic patients on the measurement of IR [32], the analysis was repeated for non-diabetic participants at baseline.
(6) Considering potential reverse causality, the analysis was repeated excluding participants diagnosed with stroke in the third wave survey.

Results

Study participants

A total of 4,669 participants with complete follow-up data were included in this study, with a mean age of 59 years and a male-to-female ratio of 0.82:1. During a median follow-up of 6 years, 347 new stroke events (7.43%) were recorded. Grouping participants by the quartiles of CumIR surrogates revealed a progressive increase in the stroke incidence for CumTyG index, CumTG/HDL-C ratio, and CumMetS-IR, while the stroke incidence for CumeGDR decreased with increasing quartiles (Fig. 2). Notably, the stroke incidence in the highest quartiles of CumTyG index, CumTG/HDL-C ratio, and CumMetS-IR was 9.67%, 9.93%, 10.45%, respectively, while the lowest quartile of CumeGDR had a stroke incidence of 13.02%, suggesting that lower CumeGDR was associated with a higher stroke risk.

Table 2 shows the baseline characteristics of the study population, comparing those who had a stroke during follow-up with those who did not. Typically, patients who experienced a future stroke were older at the time of the baseline survey. They were also more likely to be overweight or obese, have poorer insulin resistance status, have more underlying diseases, and exhibit higher levels of blood pressure, blood uric acid, blood glucose, and lipids other than HDL-C.

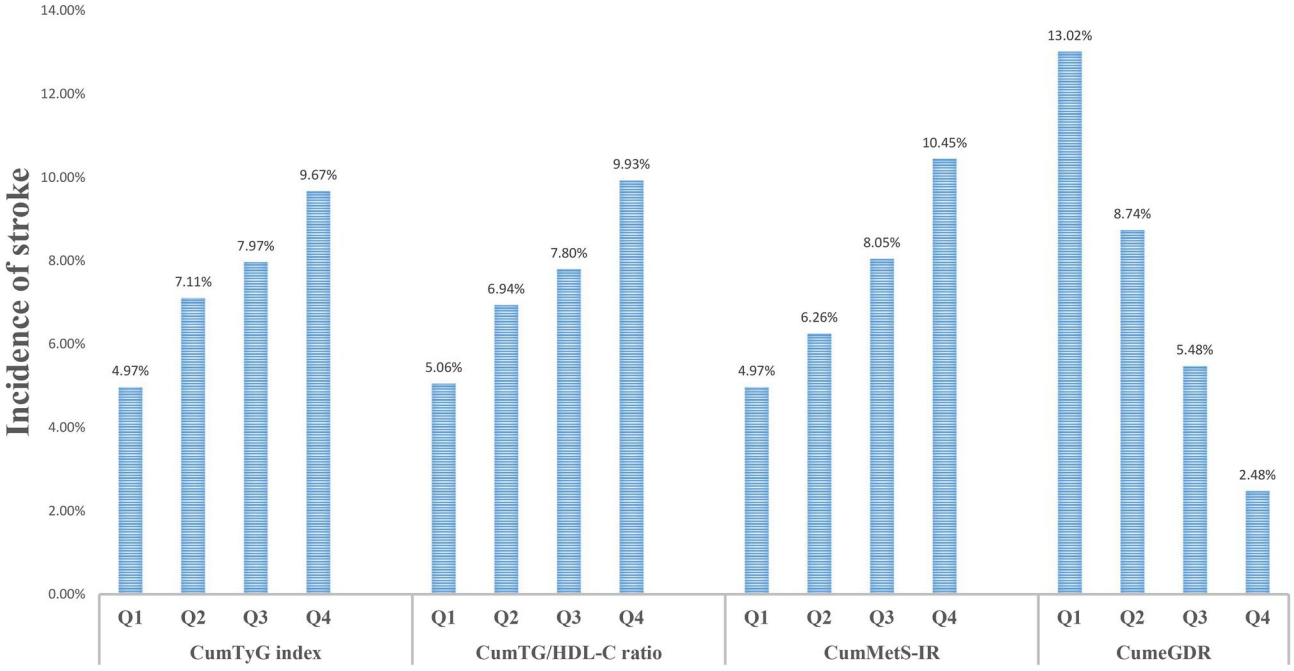


Fig. 2 Stroke incidence in the study population according to CumIR quartile groupings. CumIR: Cumulative insulin resistance; CumTyG: cumulative triglyceride-glucose; CumMetS-IR: cumulative metabolic score for insulin resistance; CumTG/HDL-C: cumulative triglyceride to high-density lipoprotein cholesterol; CumeGDR: cumulative estimated glucose disposal rate; CumIR: cumulative insulin resistance

Association between baseline IR surrogates quartiles and stroke

In the three adjusted multivariable models, higher levels of TyG index, TG/HDL-C ratio, MetS-IR, and lower levels of eGDR were significantly associated with a higher risk of stroke (supplementary Table 10). Among these, the lowest quartile of eGDR had the highest HR for stroke, followed by the highest quartile of MetS-IR, TG/HDL-C ratio, and TyG index (Model III: HR2.42 vs. 1.86 vs. 1.59 vs. 1.55).

Association between CumIR surrogates quartiles and stroke

Supplementary Fig. 1 shows the histogram distribution of CumIR surrogates and the pairwise correlation coefficients between CumIR surrogates. The correlation matrix revealed that CumeGDR was negatively correlated with the other three CumIR surrogates.

As with baseline IR surrogates, the association between CumIR surrogates' quartiles and stroke showed similar results across all models (Table 3). Higher levels of CumTyG index, CumTG/HDL-C ratio, CumMetS-IR, and lower levels of CumeGDR were significantly associated with increased stroke risk. Specifically, the lowest quartile of CumeGDR had the highest HR for stroke, followed by the highest quartiles of CumMetS-IR, CumTG/HDL-C ratio, and CumTyG index (Model III: HR3.57 vs. 1.72 vs. 1.61 vs. 1.48). Notably, compared to baseline eGDR, CumeGDR showed a higher HR for stroke.

ROC analysis for IR surrogates and CumIR surrogates in predicting stroke

Figure 3 shows the ROC analysis for baseline IR surrogates and CumIR surrogates in predicting stroke events. Among baseline IR surrogates, eGDR showed the highest accuracy for predicting stroke, with an optimal threshold of 9.5555. For CumIR surrogates, CumeGDR demonstrated the highest accuracy for predicting stroke events, with an optimal threshold of 23.7991, outperforming CumTyG index, CumTG/HDL-C ratio, and CumMetS-IR (Table 4).

Sensitivity analysis

In the first sensitivity analysis, we found that the association between CumIR surrogates and stroke did not differ by age or gender (supplementary Table 11, all *P*-interaction > 0.05). In the second sensitivity analysis, we excluded participants using antihypertensive, antidiabetic, or lipid-lowering medications, and the results remained consistent with the main analysis (sensitivity analysis 2: supplementary Tables 12 and 13). After conducting multiple imputation (sensitivity analysis 3), the results were similar to the main analysis (supplementary Table 14). Repeating the analysis after excluding participants with cardiovascular disease (sensitivity analysis 4: supplementary Tables 15 and 16) and diabetes (sensitivity analysis 5: supplementary Tables 17 and 18) did not lead to any significant changes in the results. Finally, after excluding participants diagnosed with stroke in the third

Table 2 Summary of baseline characteristics of the study population according to occurrence of stroke

	Total population	Non-stroke	Stroke	*P*-value
No. of subjects	4,669	4,322	347	
Age, years	58.99 (8.69)	58.82 (8.67)	61.12 (8.61)	< 0.001
Height, m	1.58 (0.08)	1.58 (0.08)	1.58 (0.09)	0.519
Weight, kg	59.28 (11.42)	59.06 (11.29)	61.97 (12.64)	< 0.001
BMI, kg/m^2	23.71 (3.92)	23.62 (3.83)	24.75 (4.81)	< 0.001
WC, cm	84.64 (12.43)	84.35 (12.38)	88.19 (12.48)	< 0.001
SBP, mmHg	128.61 (20.77)	127.88 (20.41)	137.73 (23.06)	< 0.001
DBP, mmHg	75.08 (11.96)	74.74 (11.83)	79.32 (12.81)	< 0.001
FPG, mmol/L	102.42 (94.86-111.96)	102.24 (94.68–111.60)	104.94 (96.30-118.08)	< 0.001
HbA1c, %	5.29 (0.80)	5.28 (0.79)	5.42 (0.94)	0.002
Cr, mg/dL	0.75 (0.64–0.86)	0.75 (0.64–0.86)	0.75 (0.66–0.88)	0.278
UA, mg/dL	4.20 (3.51–5.03)	4.20 (3.51–5.02)	4.26 (3.55–5.21)	0.177
TC, mg/dL	191.37 (168.17–216.50)	190.98 (167.78-216.11)	196.39 (171.84-220.17)	0.041
TG, mg/dL	104.43 (74.34-152.22)	103.55 (73.45-150.45)	114.17 (84.96-171.25)	< 0.001
HDL-C, mg/dL	49.10 (40.59–59.92)	49.48 (40.59–60.31)	46.39 (39.05–55.28)	< 0.001
LDL-C, mg/dL	115.21 (93.94-137.63)	114.82 (93.94-137.63)	118.69 (94.72-140.53)	0.076
TyG index	8.68 (0.66)	8.67 (0.65)	8.85 (0.68)	< 0.001
TG/HDL-C ratio	2.11 (1.31–3.56)	2.08 (1.29–3.51)	2.43 (1.61–4.09)	< 0.001
MetS-IR	34.70 (29.98–40.51)	34.45 (29.84–40.30)	36.85 (31.86–43.42)	< 0.001
eGDR	9.85 (7.16–11.07)	9.97 (7.27–11.13)	7.53 (6.43–10.29)	< 0.001
Gender				0.490
Male	2097 (44.91%)	1935 (44.77%)	162 (46.69%)	
Female	2572 (55.09%)	2387 (55.23%)	185 (53.31%)	
Marital status				0.005
Married	4141 (88.69%)	3849 (89.06%)	292 (84.15%)	
Other	528 (11.31%)	473 (10.94%)	55 (15.85%)	
Living place				0.283
Rural	3107 (66.55%)	2867 (66.34%)	240 (69.16%)	
Urban	1562 (33.45%)	1455 (33.66%)	107 (30.84%)	
Education, n (%)				0.804
Below primary	2244 (48.07%)	2074 (48.00%)	170 (48.99%)	
Primary schools	1062 (22.75%)	979 (22.66%)	83 (23.92%)	
Middle school	932 (19.97%)	866 (20.04%)	66 (19.02%)	
High school and above	430 (9.21%)	402 (9.30%)	28 (8.07%)	
Drinking status				0.255
No	3127 (66.97%)	2885 (66.75%)	242 (69.74%)	
Yes	1542 (33.03%)	1437 (33.25%)	105 (30.26%)	
Smoking status				0.901
No	3290 (70.60%)	3044 (70.58%)	246 (70.89%)	
Yes	1370 (29.40%)	1269 (29.42%)	101 (29.11%)	
Hypertension				< 0.001
No	2753 (58.96%)	2625 (60.74%)	128 (36.89%)	
Yes	1916 (41.04%)	1697 (39.26%)	219 (63.11%)	
Diabetes				< 0.001
No	3940 (84.39%)	3670 (84.91%)	270 (77.81%)	
Yes	729 (15.61%)	652 (15.09%)	77 (22.19%)	
Heart disease				< 0.001
No	4089 (87.92%)	3818 (88.69%)	271 (78.32%)	
Yes	562 (12.08%)	487 (11.31%)	75 (21.68%)	

Values were expressed as mean (standard deviation) or medians (quartile interval) or n (%). Mann-Whitney U, Student's t test, or chi-square test were used for comparisons between groups

Abbreviations: BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; Cr: creatinine; UA: uric acid; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; TC: total cholesterol; TG: triglycerides; TyG: triglyceride-glucose; TG/HDL-C: triglyceride to high-density lipoprotein cholesterol; MetS-IR: metabolic score for insulin resistance; eGDR: estimated glucose disposal rate

Table 3 Cox regression model analyzes the association between CumIR surrogates and stroke

	HR (95%CI)		
	Model I	**Model II**	**Model III**
CumTyG index quartiles			
Q1	1.0	1.0	1.0
Q2	1.47 (1.05, 2.05)	1.43 (1.02, 2.00)	1.31 (0.93, 1.84)
Q3	1.73 (1.24, 2.41)	1.62 (1.16, 2.27)	1.38 (0.98, 1.93)
Q4	2.11 (1.53, 2.91)	1.84 (1.31, 2.59)	1.48 (1.05, 2.10)
CumTG/HDL-C ratio quartiles			
Q1	1.0	1.0	1.0
Q2	1.41 (1.01, 1.98)	1.38 (0.98, 1.93)	1.28 (0.91, 1.80)
Q3	1.63 (1.17, 2.26)	1.55 (1.11, 2.16)	1.31 (0.93, 1.83)
Q4	2.17 (1.58, 2.98)	1.91 (1.38, 2.65)	1.61 (1.15, 2.24)
CumMetS-IR quartiles			
Q1	1.0	1.0	1.0
Q2	1.38 (0.98, 1.95)	1.37 (0.97, 1.94)	1.30 (0.92, 1.84)
Q3	1.93 (1.38, 2.69)	1.83 (1.31, 2.56)	1.57 (1.11, 2.21)
Q4	2.57 (1.86, 3.55)	2.24 (1.61, 3.13)	1.72 (1.21, 2.43)
CumeGDR quartiles			
Q4	1.0	1.0	1.0
Q3	2.25 (1.45, 3.49)	2.28 (1.46, 3.56)	2.10 (1.34, 3.28)
Q2	3.47 (2.30, 5.26)	3.43 (2.25, 5.22)	2.79 (1.79, 4.34)
Q1	5.27 (3.53, 7.86)	4.91 (3.25, 7.43)	3.57 (2.25, 5.68)

Abbreviations: HR: hazard ratios; CI: confidence interval; CumIR: cumulative insulin resistance; CumTyG: cumulative triglyceride-glucose; CumMetS-IR: cumulative metabolic score for insulin resistance; CumTG/HDL-C: cumulative triglyceride to high-density lipoprotein cholesterol; CumeGDR: cumulative estimated glucose disposal rate;

Model I adjust for age, gender, education, marital status, living place

Model II adjust for age, gender, education, marital status, living place, smoking status, drinking status, diabetes, heart disease

Model III adjust for age, gender, education, marital status, living place, smoking status, drinking status, diabetes, heart disease, height, SBP, DBP, Cr, UA, LDL-C

wave survey (sensitivity analysis 6: supplementary Tables 19 and 20), the findings remained highly consistent.

Discussion

Based on the CHARLS national prospective cohort study, we found that the cumulative exposure of IR surrogates—TyG index, TG/HDL-C ratio, MetS-IR, and eGDR—over time is associated with the incidence of stroke. Among these, CumeGDR appears to provide additional risk stratification and is more accurate for predicting stroke events. From a primary prevention perspective, we recommend including the IR surrogate eGDR as a key factor in stroke monitoring.

As global populations age, stroke is becoming an increasingly common condition. By 2050, the absolute number of stroke-related deaths worldwide is expected to reach 9.7 million, placing a heavy burden on families and public health systems [1, 33]. Previous studies have shown that insulin resistance (IR) is an important risk factor for stroke and that there is a causal relationship between the two [7, 34–36]. Numerous studies have evaluated various IR surrogates for stroke risk assessment, demonstrating the utility of these surrogates in real-world settings [37–41]. However, a systematic comparative analysis of IR surrogates for stroke risk assessment remains lacking. It is important to note that in a recent longitudinal study based in rural China, Zhao et al. used the TyG index, visceral adiposity index (VAI), lipid accumulation product (LAP), and Chinese VAI (CVAI) as surrogate IR indices to compare their effectiveness in stroke risk assessment [41]. Their results showed that all these surrogates were independently associated with stroke risk, with TyG index providing the most informative risk assessment (each increase in standard deviation). It should be noted that, CVAI, VAI, and LAP are rarely classified as IR surrogate indices, and they are more appropriately classified as obesity indices. Overall, the TyG index has good application potential as an IR alternative index in stroke risk assessment. In the current study, we systematically evaluated and compared the baseline IR surrogates—TyG index, TG/HDL-C ratio, MetS-IR, and eGDR—and concluded that baseline eGDR had the strongest association with stroke, making it the most suitable for early stroke risk assessment.

In addition to comparing baseline IR surrogates for stroke risk, our study also investigated and compared the relationship between the cumulative exposure of IR surrogates over time and incident stroke—a relationship that has not been systematically examined before. Cumulative exposure is a new concept used in the analysis of repeated measures data, reflecting the sustained intensity of exposure to a given parameter over a specified period [18–20]. Several recent studies have explored the association between individual cumulative IR surrogates such as CumTyG index, CumMetS-IR, and CumeGDR with stroke risk. Specifically, studies from the Kailuan cohort reported HRs of 1.30–1.35 for high CumTyG index and 1.70 for high CumMetS-IR in relation to stroke risk [42, 43]. Our findings are consistent with these results, with CumMetS-IR showing a slightly stronger association with stroke risk compared to CumTyG index. Regarding the association between CumeGDR and stroke, a recent study by Yao et al. reported findings where the HRs associated with stroke across CumeGDR quintiles were Q1:1, Q2:0.78, Q3:0.78, Q4:0.43, and Q5:0.37, respectively [22]; these recalculated results align with our findings. Compared to previous studies that individually analyzed these IR surrogates [21, 22, 42, 43], our study has the advantage of systematically evaluating the cumulative exposure of multiple IR surrogates in a homogeneous study population, including CumTG/HDL-C ratio. We used quartiles for group categorization and calculated the HRs, which

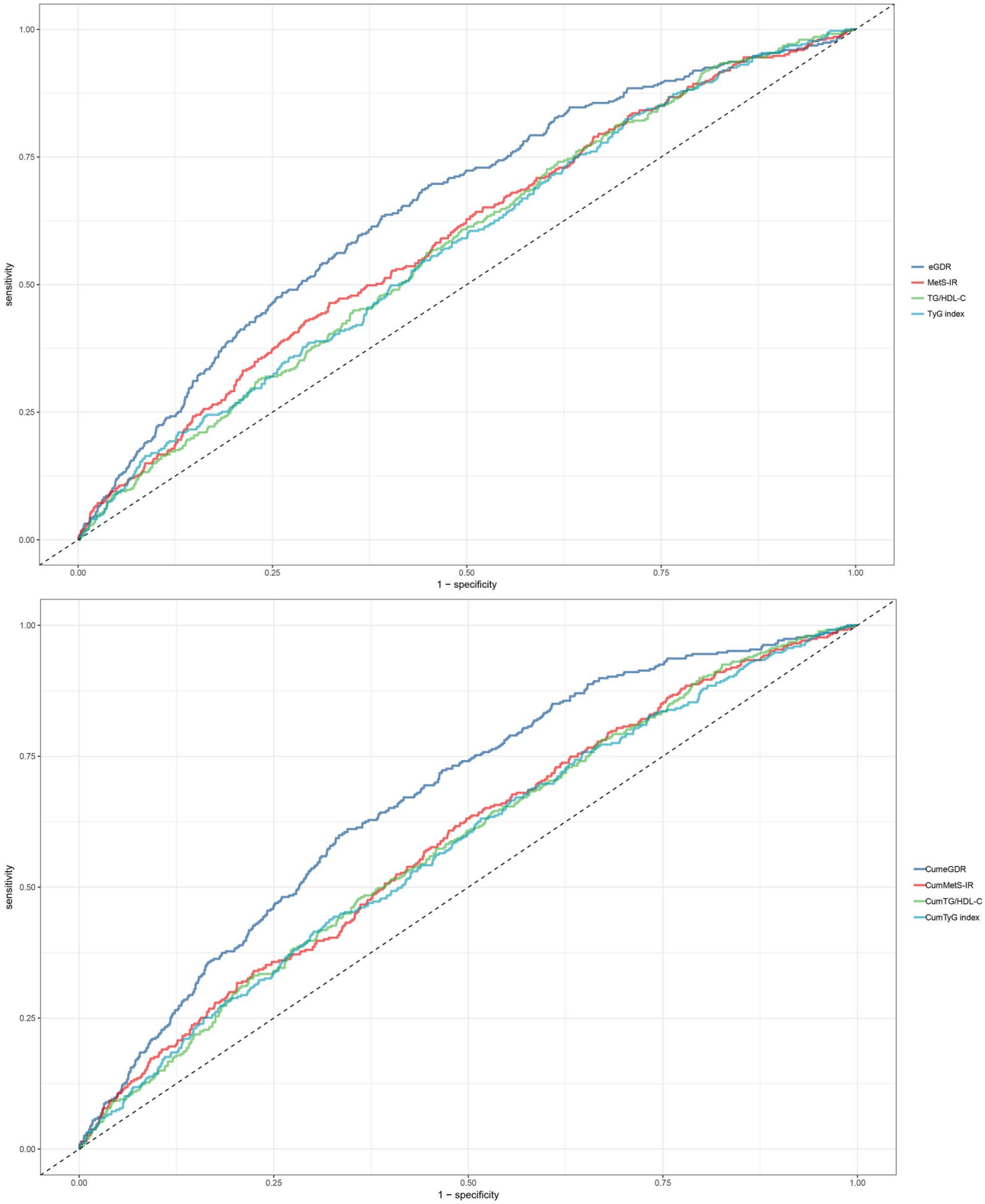


Fig. 3 ROC analysis curves of baseline IR surrogates and CumIR surrogates in predicting stroke. ROC: Receiver operating characteristic; IR: insulin resistance; CumIR: Cumulative insulin resistance; CumTyG: cumulative triglyceride-glucose; CumMetS-IR: cumulative metabolic score for insulin resistance; CumTG/HDL-C: cumulative triglyceride to high-density lipoprotein cholesterol; CumeGDR: cumulative estimated glucose disposal rate; CumIR: cumulative insulin resistance

Table 4 ROC analysis for IR surrogates and CumIR surrogates in predicting stroke

	AUC	95%CI low	95%CI upp	Best threshold	Specificity	Sensitivity
TyG index*	0.5761	0.5458	0.6063	8.2810	0.2957	0.8242
TG/HDL-C ratio*	0.5771	0.5474	0.6067	1.6682	0.3829	0.7406
MetS-IR*	0.5925	0.5619	0.6231	38.1325	0.6768	0.4640
eGDR	0.6541	0.6246	0.6835	9.5555	0.5493	0.6945
CumTyG index†	0.5772	0.5463	0.6081	26.5597	0.6784	0.4380
CumTG/HDL-C ratio†	0.5815	0.5511	0.6118	8.5673	0.6411	0.4784
CumMetS-IR†	0.5878	0.5571	0.6184	104.1542	0.5025	0.6311
CumeGDR	0.6706	0.6427	0.6984	23.7991	0.6553	0.6110

Abbreviations: ROC: receiver-operating characteristic curve; AUC: area under the ROC curve; CI: confidence interval; TyG: triglyceride-glucose; TG/HDL-C: triglyceride to high-density lipoprotein cholesterol; MetS-IR: metabolic score for insulin resistance; eGDR: estimated glucose disposal rate; CumTyG: cumulative triglyceride-glucose; CumMetS-IR: cumulative metabolic score for insulin resistance; CumTG/HDL-C: cumulative triglyceride to high-density lipoprotein cholesterol; CumeGDR: cumulative estimated glucose disposal rate; CumIR: cumulative insulin resistance

*$P < 0.05$ compared with eGDR (Delong test)

†$P < 0.05$ compared with CumeGDR (Delong test)

allowed us to identify CumeGDR as the most optimal surrogate for stroke risk assessment.

Regarding eGDR and its cumulative exposure being significantly superior to other IR surrogates in stroke risk assessment and event prediction, we attribute this advantage to eGDR's incorporation of metabolic components more closely linked to stroke. Compared to indices like the TyG index, TG/HDL-C ratio, and MetS-IR, the eGDR calculation incorporates more stable glycemic parameters such as HbA1c [44] and central obesity indicator WC, while additionally integrating hypertension– a critical risk factor for cerebrovascular and cardiovascular diseases [45]. From the perspective of stroke risk factors, blood pressure, blood glucose, and obesity all contribute significantly to stroke, whereas elevated cholesterol levels typically play a lesser role [46, 47]. Notably, in the context of blood glucose measurement, a single FPG measurement often exhibits high within-individual variability, making it a less-than-ideal indicator for reflecting chronic hyperglycemia; by contrast, HbA1c, as an integrated measure of blood glucose concentration, demonstrates superior temporal stability at the individual level [44, 48]. According to the study by Selvin et al., a multivariable model incorporating only FPG revealed associations similar to those observed for HbA1c-Stroke, yet the effect size of FPG was significantly smaller [46]. Regarding obesity assessment, prior research evidence confirms that central obesity contributes more substantially to stroke risk than general obesity [49, 50]. In the Atherosclerosis Risk in Communities study, Mozafar et al. employed targeted maximum likelihood estimation to compare the impacts of BMI and central obesity on stroke risk in individuals with and without diabetes. After adjusting for confounders, their findings revealed that the relative risk for stroke associated with BMI ranged from 1.04 to 1.11, whereas the relative risk associated with central obesity ranged from 1.10 to 1.15 [49]. Another study from Northeast China focusing on a middle-aged and elderly population reported comparable findings: they demonstrated that obesity assessed via BMI was associated with an odds ratio of 1.79 for stroke, while central obesity evaluated using WC showed an odds ratio of 1.94 [50]. Finally, compared to the TyG index, TG/HDL-C ratio, and MetS-IR, eGDR additionally incorporates hypertension as an evaluation factor, which may represent the most critical reason why eGDR significantly outperforms other IR surrogates in stroke risk assessment. As is well-established, hypertension represents the most important risk factor for stroke (far exceeding elevated LDL-C, hyperglycemia, and obesity in impact), and serves as the primary driver of the current and future increase in stroke-related disease burden [47, 51]. According to global stroke risk factor analysis data, approximately 39% of stroke events are attributable to hypertension [52]. In conclusion, we propose that the significant advantage of eGDR and its cumulative exposure in stroke risk assessment over other IR surrogates may primarily stem from the fact that the components of eGDR play a more critical role in promoting stroke risk. Furthermore, when multiple metabolic factors co-accumulate, the risk of stroke incidence is further elevated [47, 51, 53].

Our study has important implications for public health and clinical practice. First, given the significant pathogenic role of IR in stroke, we believe it is essential to incorporate IR assessments into stroke clinical practice, particularly for middle-aged and older populations [1, 7, 8]. Despite the availability of multiple methods for assessing IR [9–15], for primary prevention in the general population, IR surrogates remain the most suitable due to their simplicity, reproducibility, and wide applicability [16]. Based on our findings, we recommend eGDR as the optimal IR surrogate for stroke monitoring. From a data-driven perspective, CumeGDR incorporates both baseline eGDR values and longitudinal changes during follow-up. It not only preserves the predictive value

of eGDR for stroke risk assessment but also provides more risk warnings and predictive information compared to baseline eGDR alone. Therefore, theoretically, maintaining lower CumeGDR levels during follow-up may help control stroke risk. From another perspective, for the middle-aged and elderly populations in China, whether undergoing single or multiple health assessments, focusing on eGDR and CumeGDR can provide effective prediction and risk evaluation for future stroke events. Considering the significant advantages of eGDR and CumeGDR in stroke assessment—along with their simplicity, convenience, and cost-effectiveness—they are highly suitable for widespread use. Based on our findings, we recommend a baseline eGDR threshold of 9.5555 for individuals undergoing single-time health checks. For those who undergo annual checks, we recommend maintaining eGDR below 9.5555 and limiting the cumulative exposure to eGDR over three years to 23.7991. For the control of eGDR and its cumulative exposure levels, we believe that appropriate lifestyle interventions and the application of medications may be significantly helpful [2, 54–56]. This is because lifestyle interventions and drug treatments significantly improve metabolism, which may lead to a reduction in eGDR and its cumulative exposure levels and thus lower the risk of stroke. When an individual exceeds the threshold for eGDR and its cumulative exposure, implementing the following clinical actions may be beneficial: (1) Healthy Diet: Adopt a balanced diet emphasizing vegetables, fruits, whole grains, and low-fat dairy products while reducing intake of saturated fats, trans fats, cholesterol, and salt. Avoid sugary beverages and processed foods, and stay adequately hydrated by drinking moderate amounts of water [57, 58]. (2) Moderate Exercise: Engage in activities such as brisk walking, jogging, swimming, or cycling, combined with strength training to enhance muscle strength [2, 59]. (3) Smoking Cessation and Alcohol Moderation: Quitting smoking and limiting alcohol consumption significantly improve metabolic parameters and are among the critical measures for stroke prevention [2, 60]. (4) Management of blood pressure, blood glucose, lipids, and weight: these indicators can be controlled through a combination of lifestyle modifications and pharmacotherapy interventions [2, 54–56]. However, whether lifestyle interventions or drug therapies (e.g., hypoglycemic, antihypertensive, or statin medications) are suitable for specific CumeGDR thresholds cannot be determined in the current study. This issue still requires further interventional research for validation. In addition to its direct application in stroke prevention, the comparative findings of the current study can also serve as a valuable reference and guide for future related research. Furthermore, these findings offer valuable resources for future model development and outcome validation across other ethnic populations.

Study strengths and limitations

The strengths of this study include the following: (1) This study evaluated for the first time the association between CumTG/HDL-C ratio and stroke. (2) In terms of innovation, this study systematically analyze the effects of various CumIR surrogates on stroke, providing crucial research data for primary stroke prevention. (3) From a clinical perspective, this study provides both baseline and cumulative exposure data, which intuitively illustrates the importance of controlling cumulative IR exposure and offers significant threshold recommendations. This provides a direct and easily understandable approach for primary stroke prevention in middle-aged and elderly populations. (4) In terms of result robustness, the study performed six different sensitivity analyses, with highly consistent findings.

Similarly, there are certain limitations of the current study that need to be reported: (1) As the data in this study were based on the CHARLS registry questionnaire, where stroke diagnoses relied on self-reported information from participants and medical diagnoses, there may be recall bias, potentially leading to misclassification of some participants [61]. However, according to the latest evidence from repeated checks in the Health and Retirement Study, Glymour et al. suggested that misreporting of stroke is typically non-systematic, and the potential for misclassification bias is minimal [62]. (2) While the incidence of stroke increases with age, the increasing trend of stroke in younger populations also requires attention [1, 63]. The current study's findings are applicable only to middle-aged and elderly populations, and future research should further explore the role of CumIR surrogates in younger populations. (3) Although the CHARLS study is prospective, observational studies do not involve active intervention protocols for the study population [64]; therefore, this study cannot assess the impact of interventions on improving stroke risk associated with CumIR surrogates. (4) It is unavoidable that a large proportion of participants with missing blood parameters were excluded from the analysis, which led to a relative reduction in sample size. (5) Stroke is a multifactorial, complex disease, and although the current analysis accounted for many confounding factors, there may still be unmeasured or unconsidered confounders [65].

Conclusions

In this national cohort study, we found that, compared to CumTyG index, CumTG/HDL-C ratio, and CumMetS-IR, cumulative exposure to eGDR offers significant advantages in stroke risk assessment and prediction in middle-aged and elderly populations. From a primary prevention perspective, we recommend incorporating eGDR as an IR surrogate for stroke monitoring.

Abbreviations

CHARLS	China Health and Retirement Longitudinal Study
CI	Confidence intervals
CumIR	Cumulative exposure to IR
eGDR	Estimated glucose disposal rate
HRs	Hazard ratios
IR	Insulin resistance
MetS-IR	Metabolic score for insulin resistance
ROC	Receiver operating characteristic
TG/HDL-C	Triglyceride to high-density lipoprotein cholesterol
TyG	Triglyceride-glucose

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
YZ and WW: Conceptualization, project administration, supervision, and YZ and DZ-H: methodology, writing-original draft preparation. XH-L, GT-S, HH-Y, WW: writing-reviewing and editing. YZ: Software. DZ-H, WW: formal analysis and validation. YZ and GT-S: data curation. All authors read and approved the final manuscript.

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Data availability
The data used in this study were provided by the CHARLS research team; all research data can be downloaded from the official CHARLS website (http://charls.pku.edu.cn/en).

Declarations

Ethics approval and consent to participate
All participants in the CHARLS study provided written informed consent before participation, and subsequent surveys, physical measurements, blood collection, and follow-up were carried out after approval. The implementation of CHARLS was authorized by the Ethics Committee of Peking University (No. 00001052–11015), and all research data were de-identified.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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