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Assessment of six insulin resistance surrogate indexes for predicting stroke incidence in Chinese middle-aged and elderly populations with abnormal glucose metabolism: a nationwide prospective cohort study

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Abstract

Background Estimate glucose disposal rate (eGDR), Chinese visceral adiposity index (CVAI), triglyceride-glucose (TyG), TyG-body mass index (TyG-BMI), metabolic score for insulin resistance (METS-IR), and atherogenic index of plasma (AIP) are considered surrogate indexes of insulin resistance (IR). There is a lack of studies comparing the predictive values of different IR surrogate indexes for stroke risk among individuals with abnormal glucose metabolism. This study aimed to investigate the relationships between six IR surrogate indexes and stroke risk in individuals with abnormal glucose metabolism, evaluate their predictive abilities for stroke risk.

Methods Data from the China Health and Retirement Longitudinal Study (CHARLS) were analysed in this study. Multivariate logistic regression models were applied to analyse the relationships of IR surrogate indexes with stroke risk. The dose-response relationships between IR surrogate indexes and stroke risk were explored using restricted cubic splines. The areas under the curve (AUCs) of IR surrogate indexes were calculated by receiver operating characteristic (ROC) analysis.

Results After adjusting for potential confounders, we observed that each standard deviation (SD) increase in eGDR was associated with a reduced risk of stroke, with an adjusted odds ratio (OR) of 0.746 [95% confidence interval (CI): 0.661–0.842]. In contrast, each SD increase in CVAI, TyG, TyG-BMI, METS-IR, and AIP were associated with an increased risk of stroke, with adjusted ORs (95% CIs) of 1.232 (1.106–1.373), 1.246 (1.050–1.479), 1.186 (1.022–1.376), 1.222 (1.069–1.396), and 1.193 (1.050–1.355), respectively. Dose-response analyses showed that eGDR, CVAI, TyG-BMI and

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METS-IR were linearly associated with stroke risk ($P_{nonlinear} \geq 0.05$), whereas TyG and AIP were nonlinearly associated with stroke risk ($P_{nonlinear} < 0.05$). According to ROC analysis, The AUC of eGDR for predicting stroke risk in the overall population with abnormal glucose metabolism (AUC: 0.612, 95% CI: 0.584–0.640) was significantly higher than that of other indexes.

Conclusion The six IR surrogate indexes were closely associated with high risk of stroke in individuals with abnormal glucose metabolism. The eGDR showed promising potential in predicting stroke risk in Chinese middle-aged and elderly populations with abnormal glucose metabolism.

Keywords Insulin resistance surrogate index, Stroke, Abnormal glucose metabolism, CHARLS

Introduction

Stroke represents a global public health challenge, with its high incidence and mortality rates imposing substantial burdens on societies and healthcare systems. According to Global Burden of Disease studies, stroke has become a major contributor to the global health burden [1, 2]. The prevalence and incidence of stroke remain notably high in China [3]. IR is widely recognised as an important risk factor for stroke [4, 5]. The risk of stroke is significantly increased in individuals with abnormal glucose metabolism. Studies have reported that prediabetes increases the risk of stroke [6], and individuals with diabetes have a two to four times higher risk of stroke compared to those without diabetes [7]. This heightened risk is likely related to the multiple metabolic abnormalities commonly seen in diabetes, including IR, hyperglycaemia, dyslipidaemia, and hypertension [8]. Therefore, effective preventive measures and management strategies, such as optimal glycaemic control, lipid and blood pressure management, for patients with abnormal glucose metabolism, especially those with diabetes, are essential to reduce stroke risk.

Although the hyperinsulinemic–euglycemic clamp is considered the gold standard for assessing IR [9], it is not suitable for clinical and epidemiological studies due to its complexity, invasiveness and high cost. As a result, various surrogate indexes of IR, such as eGDR, CVAI, TyG, TyG-BMI, METS-IR, and AIP, have received increasing attention. These indexes have been shown to be valuable in assessing IR and are strongly associated with the risk and prognosis of cardiovascular diseases [10–14].

Previous studies have explored the relationships between IR surrogate indexes and stroke risk. However, the utility of these indexes in predicting stroke risk remains controversial, influenced by factors such as race, region, sex and age. In individuals with abnormal glucose metabolism, the associations of eGDR, CVAI, TyG, TyG-BMI, METS-IR, and AIP with stroke risk remain unclear. Furthermore, there is a lack of studies comparing the predictive values of these IR surrogate indexes for stroke risk in individuals with abnormal glucose metabolism. Therefore, the aim of this study was to evaluate the associations between IR surrogate indexes and stroke risk, as well as the predictive values of these indexes for stroke risk in a Chinese middle-aged and elderly population with abnormal glucose metabolism, by analysing data from the CHARLS database.

Methods

Study design and population

The China Health and Retirement Longitudinal Study (CHARLS) is an ongoing nationally representative longitudinal survey designed to reflect the social, economic, and health status of middle-aged and elderly individuals aged 45 and older in China. The CHARLS cohort was established using a multistage probability sampling method, selecting participants from 150 counties (districts) and 450 villages (communities) across 28 provinces. The first survey of CHARLS was conducted in 2011, followed by four subsequent surveys in 2013, 2015, 2018, and 2020. The CHARLS project was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and all participants signed an informed consent form before participating in the study.

Our cohort study used data from the CHARLS surveys conducted in 2011, 2013, 2015, 2018, and 2020, with the 2011 survey serving as the baseline. A total of 17,707 participants from the 2011 baseline survey were included in this study. To refine the study, several exclusion criteria were applied. Participants were sequentially excluded based on the following steps: (1) participants with stroke or cancer at baseline; (2) participants aged under 45 years at baseline; (3) individuals without diabetes or prediabetes at baseline; (4) missing data on one of the six IR surrogate indexes at baseline; (5) incomplete information on socio-demographic, health-related, anthropometric, and other biomarkers at baseline; (6) missing stroke data at follow-up. Finally, a total of 4,598 participants were included in this study. The exclusion process is shown in Fig. 1.

Data collection and measurement

During the baseline survey, interviewers collected socio-demographic (sex, age, education and marital status), health-related behaviours (smoking and alcohol

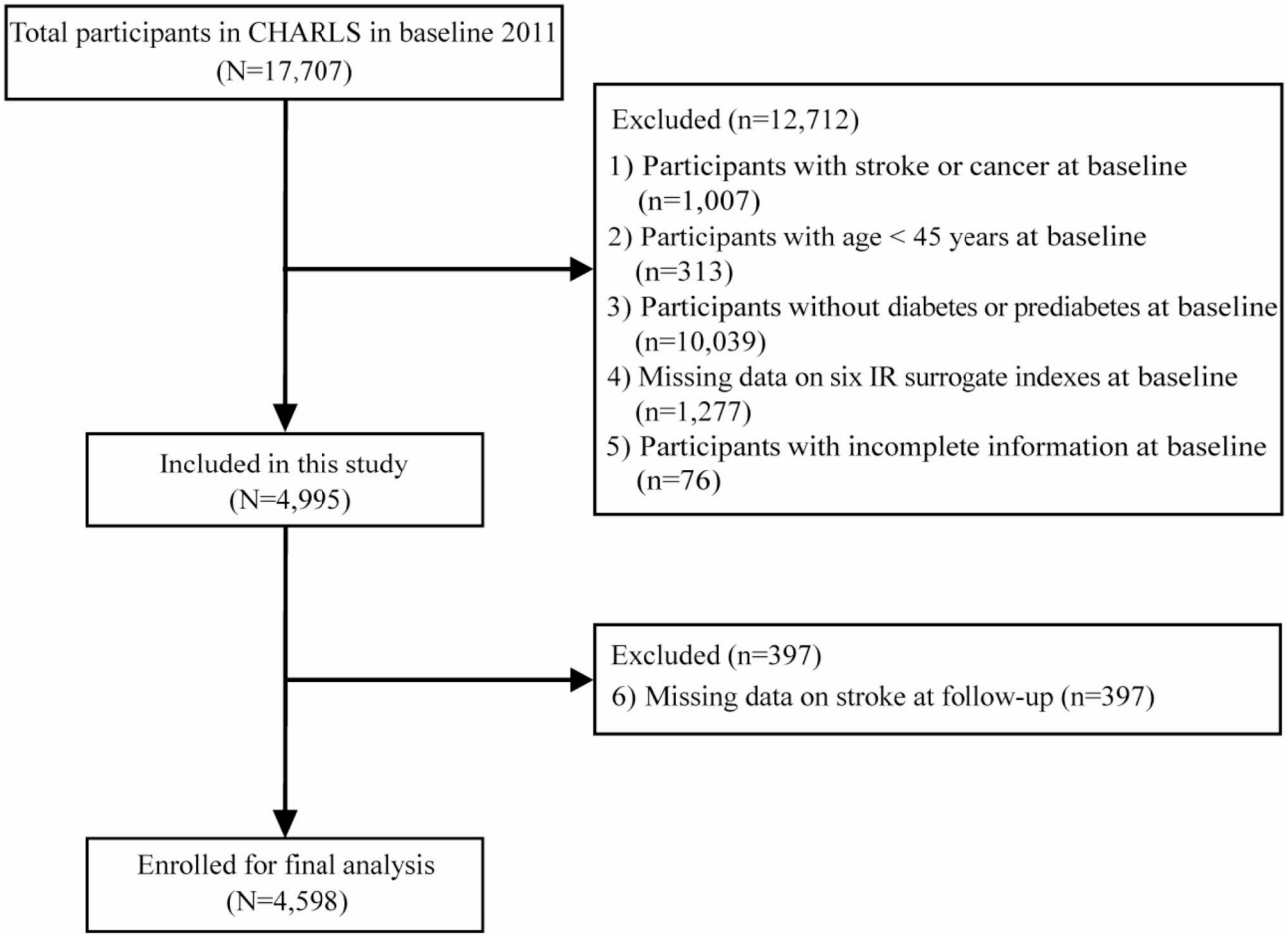

Fig. 1 Flowchart of participant selection

consumption) and medical history (diabetes, hypertension and heart disease) through questionnaires. Educational level was categorised as no formal education, primary school, middle school, high school or above. Marital status was categorised as married and other marital statuses (separated, divorced, widowed and never married). Smoking more than 100 cigarettes in a lifetime was defined as smoking. Smoking status was categorised into three groups: never smoker, former smoker and current smoker. Alcohol consumption was classified into three categories: never drinkers (those who never or rarely drink alcohol, consuming less than once a month), former drinkers (those who drank more than once a month but stopped in the past year), and current drinkers (those who drink more than once a month). Anthropometric data such as height, weight, waist circumference (WC), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by trained professionals. All participants provided venous blood samples after fasting for at least 8 h. Blood sample information included fasting plasma glucose (FPG), glycosylated hemoglobin A1c (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), serum creatinine (Scr), serum uric acid (SUA), blood urea nitrogen (BUN) and C-reactive protein (CRP).

eGDR, CVAI, TyG, TyG-BMI, METS-IR, and AIP were calculated using the following equations:

$BMI = weight_{kg} / height_{m}^{2}$

$eGDR = 21.158 - 0.09 \times WC_{cm} - 3.407 \times hypertension_{(yes = 1/no = 0)} - 0.551 \times HbA1c_{\%}$.

$CVAI\ (male) = -267.93 + 0.68 \times age_{years} + 0.03 \times BMI_{kg/m^2} + 4.00 \times WC_{cm} + 22.00 \times \log_{10}(TG_{mmol/L}) - 16.32 \times HDL\text{-}C_{mmol/L}$.

$CVAI\ (female) = -187.32 + 1.71 \times age_{years} + 4.23 \times BMI_{kg/m^2} + 1.12 \times WC_{cm} + 39.76 \times \log_{10}(TG_{mmol/L}) - 11.66 \times HDL\text{-}C_{mmol/L}$.

$TyG = \ln(TG_{mg/dl} \times FPG_{mg/dl} / 2)$.

$TyG\text{-}BMI = TyG \times BMI_{kg/m^2}$.

$METS\text{-}IR = \ln(2 \times FPG_{mg/dl} + TG_{mg/dl}) \times BMI_{kg/m^2} / \ln(HDL\text{-}C_{mg/dl})$.

$AIP = \log(TG_{mg/dl} / HDL\text{-}C_{mg/dl})$.

Definition

Prediabetes was defined as FPG levels between 100 and 125 mg/dL or HbA1c levels between 5.7% and 6.4%. Diabetes was defined as self-reported physician diagnosis, use of glucose-lowering medications, FPG ≥ 126 mg/dL or HbA1c ≥ 6.5% [15]. Prediabetes or diabetes was categorised as glucose metabolism disorders. Hypertension was defined as self-reported physician diagnosis, use of antihypertensive medications, or average SBP/DBP ≥ 140/90 mmHg [16].

The outcome of this study was stroke events. Participants who had no history of stroke at baseline but reported a stroke during follow-up were recorded as incident cases. Data on stroke events were obtained from the survey questionnaires conducted during each follow-up wave from 2013 to 2020. In accordance with previous studies [17, 18], stroke events were assessed using the following standardised questions: "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?"

Missing data processing

In our study, participants with incomplete IR surrogate index information (1,277, 20.12%), missing stroke follow-up data (397, 6.25%), or missing covariate data (e.g., baseline socio-demographic and health-related information) (76, 1.20%) were excluded. To assess potential selection bias, we compared the baseline characteristics of the excluded participants with those retained in the study (Additional file 1: Table S1).

Statistical analysis

Continuous variables were presented as means and standard deviations, and categorical variables were expressed as numbers and percentages. The independent t-test, Mann-Whitney U test, or chi-square test were employed for comparisons between groups. Correlations between surrogate indexes of IR and stroke risk were assessed using logistic regression analysis. To allow direct comparisons of OR values, the six IR surrogate indexes were converted into Z-scores. Three logistic models were used in this study. Model 1 was not adjusted for any variables. Model 2 was adjusted for sex, age, education level, marital status, smoking status, alcohol consumption, BMI, and WC. Model 3 was adjusted for sex, age, education level, marital status, smoking status, alcohol consumption, BMI, WC, TC, HDL-C, LDL-C, Scr, SUA, BUN, CRP, hypertension, and heart diseases. For all IR surrogate indexes, variables already included in the equations were not adjusted for in the regression models. We assessed potential multicollinearity among variables in each model using the variance inflation factor (VIF). The VIF values for all variables in each model were below 10 and no significant multicollinearity problems were detected. In addition, we explored the dose-response relationships of the IR surrogate indexes with stroke risk using restricted cubic splines. The abilities of these indexes to predict stroke risk were evaluated using ROC curves. The AUC, optimal cutoff value, sensitivity, specificity, and Youden's index (sensitivity + specificity-1) were calculated for each index to predict stroke risk. We also used DeLong's test to detect differences in the AUCs of different IR surrogate indexes. $P < 0.05$ indicated statistical significance. All statistical analyses in this study were performed using EmpowerStats (version 4.2) and R (version 4.4.1).

Results

Baseline characteristics of study participants

A total of 4,598 participants were enrolled in the study, including 2,069 males and 2,529 females, with mean ages of 59.90 and 59.06 years, respectively. General clinical and biochemical characteristics of stroke and non-stroke participants were described according to sex (Table 1). 199 males (9.62%) and 230 females (9.09%) were diagnosed with stroke, with a significantly higher proportion of males suffering from stroke. Compared to non-stroke males, stroke-affected males were older and had higher proportions of hypertension and heart disease. Stroke-affected males exhibited higher levels of SBP, DBP, BMI, WC, TC, TG, LDL-C, Scr, SUA, CRP, HbA1c, CVAI, TyG, TyG-BMI, METS-IR, and AIP, and lower levels of eGDR ($P < 0.05$). Similarly, compared to non-stroke females, stroke-affected females were older and had higher proportions of hypertension, heart disease and alcohol consumption. Stroke-affected females also showed higher levels of SBP, DBP, WC, TG, Scr, CRP, FPG, HbA1c, CVAI, TyG, TyG-BMI, METS-IR, and AIP, and lower levels of HDL-C and eGDR ($P < 0.05$). Additionally, we compared the baseline characteristics of participants excluded due to missing data (e.g., incomplete IR surrogate index information, missing stroke follow-up data, and missing covariate data) with those retained in the study (Additional file 1: Table S1). The results revealed some differences between the excluded and retained groups in terms of SUA and CRP levels, while the differences in most other baseline characteristics were minimal. Therefore, we believe that the exclusion of participants due to missing data is unlikely to result in significant selection bias overall.

Table 1 Baseline characteristics of the study participants with and without stroke by sex

Variable	Male			Female		
	Non-Stroke	Stroke	*P* value	Non-Stroke	Stroke	*P* value
Number	1870	199		2299	230	
Age (years)	59.71 ± 8.90	61.74 ± 8.45	0.001	58.87 ± 9.20	60.96 ± 8.43	< 0.001
Education level, n (%)			0.169			0.498
Below primary school	256 (13.69%)	33 (16.58%)		1032 (44.89%)	107 (46.52%)	
Primary school	880 (47.06%)	96 (48.24%)		800 (34.80%)	81 (35.22%)	
Middle school	528 (28.24%)	43 (21.61%)		343 (14.92%)	35 (15.22%)	
High school or above	206 (11.02%)	27 (13.57%)		124 (5.39%)	7 (3.04%)	
Marital status, n (%)			0.194			0.911
Married	189 (10.11%)	26 (13.07%)		413 (17.96%)	42 (18.26%)	
Others	1681 (89.89%)	173 (86.93%)		1886 (82.04%)	188 (81.74%)	
Smoking status, n (%)			0.181			0.528
Never	490 (26.20%)	43 (21.61%)		2123 (92.34%)	209 (90.87%)	
Former	314 (16.79%)	42 (21.11%)		53 (2.31%)	8 (3.48%)	
Current	1066 (57.01%)	114 (57.29%)		123 (5.35%)	13 (5.65%)	
Alcohol consumption, n (%)			0.277			0.044
Never	563 (30.11%)	56 (28.14%)		1923 (83.65%)	178 (77.39%)	
Former	219 (11.71%)	31 (15.58%)		108 (4.70%)	17 (7.39%)	
Current	1088 (58.18%)	112 (56.28%)		268 (11.66%)	35 (15.22%)	
Hypertension, n (%)	763 (40.80%)	122 (61.31%)	< 0.001	1011 (43.98%)	134 (58.26%)	< 0.001
Heart diseases, n (%)	244 (13.05%)	38 (19.10%)	0.018	382 (16.62%)	64 (27.83%)	< 0.001
SBP (mmHg)	130.63 ± 19.46	141.07 ± 23.24	< 0.001	131.57 ± 21.67	138.02 ± 24.53	< 0.001
DBP (mmHg)	76.31 ± 11.90	80.72 ± 13.22	< 0.001	75.91 ± 11.44	77.63 ± 11.50	0.024
BMI (kg/m^2)	23.25 ± 3.49	24.27 ± 3.91	< 0.001	24.42 ± 3.92	24.93 ± 4.20	0.065
WC (cm)	85.72 ± 9.74	88.52 ± 9.60	< 0.001	85.75 ± 12.67	87.61 ± 12.55	0.011
TC (mg/dl)	192.90 ± 38.59	200.99 ± 40.68	0.005	203.69 ± 39.62	206.45 ± 38.27	0.312
TG (mg/dl)	138.16 ± 116.63	149.71 ± 101.88	< 0.001	149.73 ± 108.51	166.65 ± 113.90	0.007
HDL-C (mg/dl)	50.83 ± 17.14	48.66 ± 16.07	0.088	50.54 ± 14.47	48.40 ± 13.17	0.032
LDL-C (mg/dl)	114.17 ± 35.63	121.21 ± 39.06	0.009	123.81 ± 37.18	125.00 ± 37.05	0.645
Scr (mg/dl)	0.88 ± 0.20	0.91 ± 0.17	0.022	0.69 ± 0.15	0.71 ± 0.14	0.030
SUA (mg/dl)	4.99 ± 1.27	5.20 ± 1.36	0.019	4.09 ± 1.07	4.03 ± 1.05	0.398
BUN (mg/dl)	16.69 ± 4.59	16.92 ± 4.41	0.500	15.19 ± 4.31	14.95 ± 4.03	0.411
CRP (mg/L)	2.87 ± 8.35	3.78 ± 10.96	0.031	2.66 ± 6.68	3.31 ± 9.69	0.012
FPG (mg/dl)	121.49 ± 39.54	125.58 ± 51.83	0.179	120.37 ± 38.27	130.51 ± 56.08	< 0.001
HbA1c (%)	5.40 ± 0.87	5.55 ± 1.02	0.031	5.48 ± 0.96	5.70 ± 1.25	< 0.001
eGDR	9.08 ± 2.17	8.05 ± 2.21	< 0.001	8.93 ± 2.34	8.15 ± 2.32	< 0.001
CVAI	97.02 ± 44.50	111.74 ± 43.34	< 0.001	103.62 ± 35.61	113.89 ± 35.93	< 0.001
TyG	8.79 ± 0.69	8.93 ± 0.70	0.003	8.91 ± 0.64	9.07 ± 0.71	< 0.001
TyG-BMI	205.11 ± 39.26	217.38 ± 42.10	< 0.001	218.08 ± 41.24	226.52 ± 44.36	0.003
METS-IR	35.91 ± 8.26	38.20 ± 9.03	< 0.001	37.73 ± 8.32	39.41 ± 9.10	0.004
AIP	0.37 ± 0.36	0.44 ± 0.34	0.003	0.42 ± 0.34	0.48 ± 0.33	0.006

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; SUA, serum uric acid; BUN, blood urea nitrogen; CRP, C-reactive protein; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c; eGDR, estimated glucose disposal rate; CVAI, Chinese visceral adiposity index; TyG, triglyceride-glucose; TyG-BMI, TyG-body mass index; METS-IR, metabolic score for insulin resistance; AIP, atherogenic index of plasma

Data are presented as mean ± standard deviation or number (%)

Associations and dose-response relationships between IR surrogate indexes and stroke risk

The associations between IR surrogate indexes and stroke risk in participants with abnormal glucose metabolism are shown in Table 2. The results indicated that in both Model 1 and Model 2, eGDR was negatively associated with stroke risk, whereas other IR surrogate indexes (CVAI, TyG, TyG-BMI, METS-IR, and AIP) were positively associated with stroke risk. This associations between the IR surrogate indexes and stroke risk remained significant after adjusting for all confounders (Model 3). A per-SD increase in eGDR corresponded to adjusted OR (95% CI) of 0.746 (0.661–0.842). A per-SD increase in CVAI, TyG, TyG-BMI, METS-IR, and AIP

Table 2 Multivariate regression analysis of the associations between six IR surrogate indexes and stroke risk

Variable	Model 1		Model 2		Model 3	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
eGDR	0.677 (0.612, 0.748)	< 0.001	0.716 (0.636, 0.807)	< 0.001	0.746 (0.661, 0.842)	< 0.001
CVAI	1.353 (1.226, 1.494)	< 0.001	1.356 (1.227, 1.499)	< 0.001	1.232 (1.106, 1.373)	< 0.001
TyG	1.236 (1.125, 1.357)	< 0.001	1.207 (1.093, 1.334)	< 0.001	1.246 (1.050, 1.479)	0.012
TyG-BMI	1.256 (1.144, 1.379)	< 0.001	1.295 (1.141, 1.469)	< 0.001	1.186 (1.022, 1.376)	0.025
METS-IR	1.238 (1.128, 1.359)	< 0.001	1.252 (1.106, 1.417)	< 0.001	1.222 (1.069, 1.396)	0.003
AIP	1.204 (1.094, 1.325)	< 0.001	1.172 (1.057, 1.300)	0.003	1.193 (1.050, 1.355)	0.007

Model 1 was unadjusted.

Model 2 was adjusted for sex, age, education level, marital status, smoking status, alcohol consumption, BMI, and WC.

Model 3 was adjusted for Model 2 + TC, HDL-C, LDL-C, Scr, SUA, BUN, CRP, hypertension, and heart diseases.

OR, odds ratio; CI, confidence interval; eGDR, estimated glucose disposal rate; CVAI, Chinese visceral adiposity index; TyG, triglyceride-glucose; TyG-BMI, TyG-body mass index; METS-IR, metabolic score for insulin resistance; AIP, atherogenic index of plasma; WC, waist circumference; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; SUA, serum uric acid; BUN, blood urea nitrogen; CRP, C-reactive protein.

ORs are presented as per 1 SD increase in the IR surrogate indexes for stroke risk.

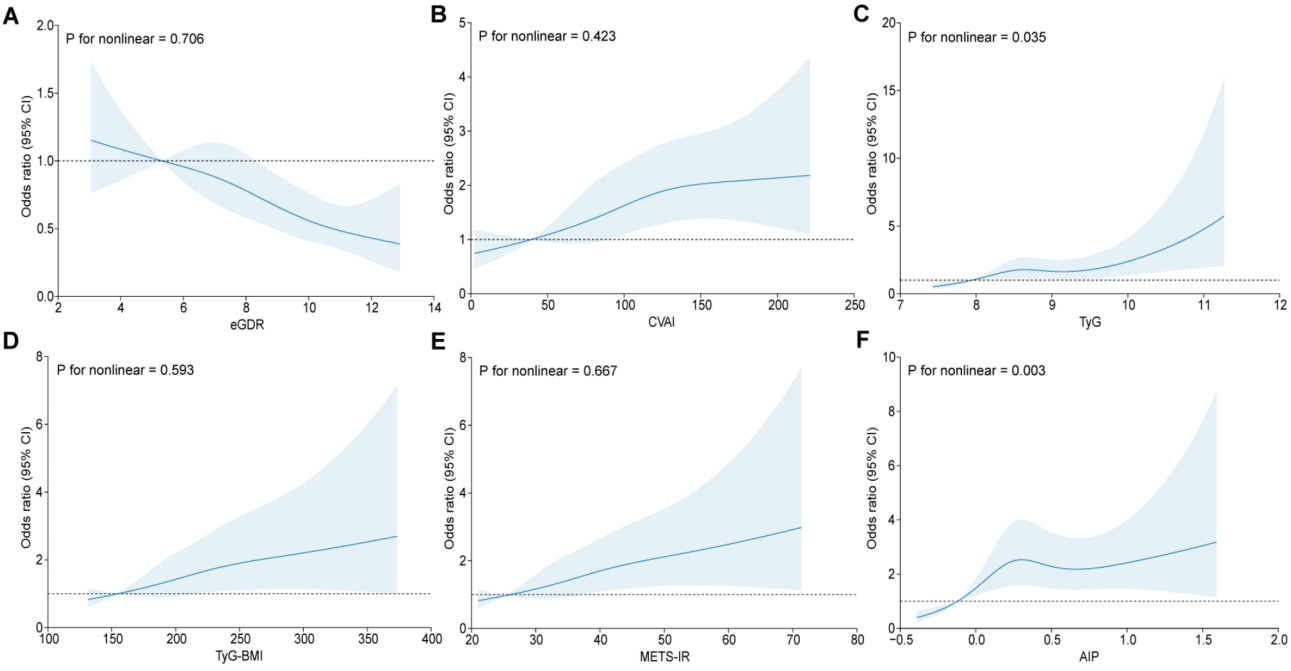

Fig. 2 Dose-response relationships between IR surrogate indexes and stroke risk. We adjusted the model fully for sex, age, education level, marital status, smoking status, alcohol consumption, BMI, WC, TC, HDL-C, LDL-C, Scr, SUA, BUN, CRP, hypertension, and heart diseases. CI, confidence interval; eGDR, estimated glucose disposal rate; CVAI, Chinese visceral adiposity index; TyG, triglyceride-glucose; TyG-BMI, TyG-body mass index; METS-IR, metabolic score for insulin resistance; AIP, atherogenic index of plasma; WC, waist circumference; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; SUA, serum uric acid; BUN, blood urea nitrogen; CRP, C-reactive protein.

corresponded to adjusted ORs (95% CIs) of 1.232 (1.106–1.373), 1.246 (1.050–1.479), 1.186 (1.022–1.376), 1.222 (1.069–1.396), and 1.193 (1.050–1.355), respectively.

We analysed the dose-response relationships between six IR surrogate indexes and stroke risk using the RCS. As shown in Fig. 2, after adjusting for confounding factors, eGDR was linearly and negatively associated with stroke risk ($P_{\text{nonlinear}} > 0.05$, Fig. 2A). CVAI, TyG-BMI, and METS-IR were linearly and positively associated with stroke risk ($P_{\text{nonlinear}} > 0.05$, Fig. 2B, D, and E). TyG and AIP were nonlinearly and positively associated with stroke risk ($P_{\text{nonlinear}} < 0.05$, Fig. 2C, F). The results from the RCS analysis were generally consistent with those from the multivariate regression analysis.

Subgroup analyses to determine the associations between IR surrogate indexes and stroke risk

To further explore the relationships between six IR surrogate indexes and stroke risk in participants with abnormal glucose metabolism, subgroup analyses were performed by sex and age. As shown in Fig. 3, we found that the associations between IR surrogate indexes and stroke

Subgroup	OR (95% CI)	P value	P for interaction
eGDR			
Sex			0.1120
Male	0.694 (0.576, 0.835)	<0.0001	
Female	0.791 (0.673, 0.930)	0.0046	
Age			0.0191
<60	0.626 (0.522, 0.752)	<0.0001	
≥60	0.841 (0.717, 0.986)	0.0330	
CVAI			
Sex			0.8325
Male	1.232 (1.067, 1.423)	0.0045	
Female	1.299 (1.094, 1.543)	0.0028	
Age			0.0334
<60	1.362 (1.149, 1.615)	0.0004	
≥60	1.125 (0.972, 1.302)	0.1155	
TyG			
Sex			0.6929
Male	1.179 (0.921, 1.509)	0.1904	
Female	1.314 (1.031, 1.675)	0.0273	
Age			0.4750
<60	1.139 (0.880, 1.474)	0.3223	
≥60	1.358 (1.073, 1.718)	0.0109	
TyG−BMI			
Sex			0.3763
Male	1.280 (0.975, 1.680)	0.0750	
Female	1.162 (0.966, 1.399)	0.1119	
Age			0.8821
<60	0.980 (0.749, 1.283)	0.8848	
≥60	1.261 (1.052, 1.513)	0.0124	
METS−IR			
Sex			0.5920
Male	1.244 (0.986, 1.570)	0.0655	
Female	1.230 (1.037, 1.459)	0.0177	
Age			0.5240
<60	1.110 (0.896, 1.375)	0.3386	
≥60	1.277 (1.071, 1.521)	0.0064	
AIP			
Sex			0.9413
Male	1.170 (0.974, 1.406)	0.0928	
Female	1.224 (1.020, 1.470)	0.0299	
Age			0.8065
<60	1.143 (0.941, 1.389)	0.1785	
≥60	1.246 (1.050, 1.477)	0.0117	

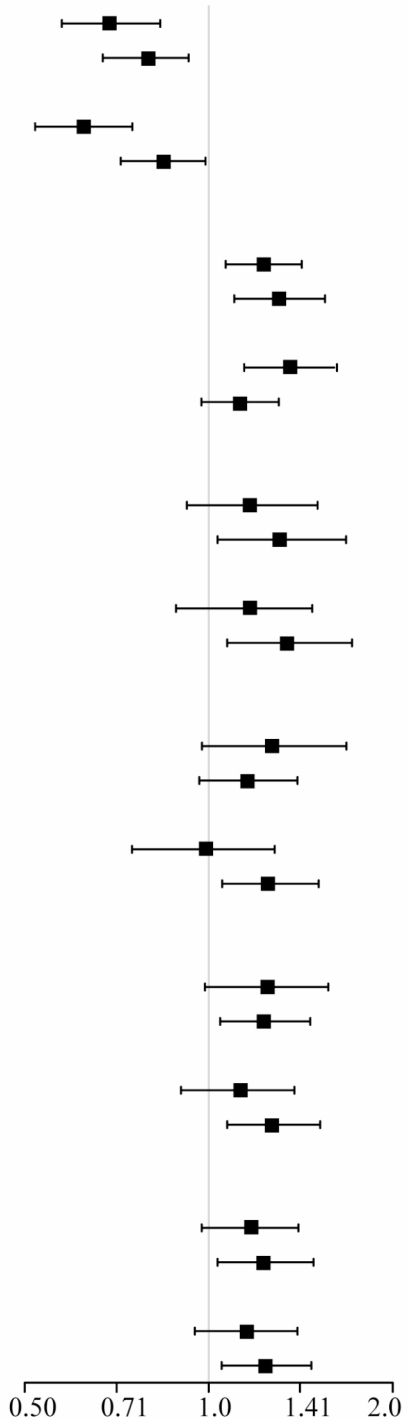

Fig. 3 Subgroup analyses of the associations between IR surrogate indexes and stroke risk. Each subgroup was adjusted for sex, age, education level, marital status, smoking status, alcohol consumption, BMI, WC, TC, HDL-C, LDL-C, Scr, SUA, BUN, CRP, hypertension, and heart diseases, except for stratification variables. ORs are presented as per 1 SD increase in the IR surrogate indexes for stroke risk. OR, odds ratio; CI, confidence interval; eGDR, estimated glucose disposal rate; CVAI, Chinese visceral adiposity index; TyG, triglyceride-glucose; TyG-BMI, TyG-body mass index; METS-IR, metabolic score for insulin resistance; AIP, atherogenic index of plasma; WC, waist circumference; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; SUA, serum uric acid; BUN, blood urea nitrogen; CRP, C-reactive protein.

risk varied by sex and age. eGDR was significantly associated with stroke risk across both sex and age groups, with stronger associations observed in males and middle-aged participants (under 60 years). The significant associations of other IR surrogate indexes with stroke risk were predominantly observed in females and older participants (over 60 years). Additionally, significant interactions were found between eGDR (P for interaction = 0.0191) and CVAI (P for interaction = 0.0334) with age.

Predictive performance of IR surrogate indexes for stroke risk in the overall population and in different sex groups

Table 3; Fig. 4 present the predictive abilities of IR surrogate indexes for stroke risk in the overall population, as well as in male and female subgroups. Among the overall population with abnormal glucose metabolism, eGDR demonstrated superior predictive ability for stroke risk compared to other IR surrogate indexes, with the highest AUC value (AUC: 0.612, 95% CI: 0.584–0.640), followed by CVAI (AUC: 0.588, 95% CI: 0.560–0.616). The predictive performances of different IR surrogate indexes for stroke risk were further compared in different sex groups. In males, eGDR showed significantly better predictive ability for stroke risk compared to other IR surrogate indexes ($P < 0.05$). In females, eGDR outperformed TyG-BMI and METS-IR in predicting stroke risk ($P < 0.05$). For other indexes, no significant differences were observed in their predictive performance for stroke risk between sex groups.

Predictive performance of IR surrogate indexes for stroke risk in different sex and age groups

Table 4; Fig. 4 show the predictive abilities of IR surrogate indexes for stroke risk at different ages for males and females. We found that eGDR had the highest AUC values in middle-aged males, older males, and middle-aged females, with AUCs of 0.669 (95% CI: 0.610–0.729), 0.598 (95% CI: 0.542–0.654), and 0.622 (95% CI: 0.566–0.677), respectively. We compared the predictive abilities of different IR surrogate indexes for stroke risk in different sex and age groups. Among middle-aged males and females, eGDR demonstrated better predictive ability for stroke risk compared to TyG and AIP ($P < 0.05$). In middle-aged males, CVAI showed superior predictive performance for stroke risk compared to TyG, TyG-BMI, METS-IR, and AIP ($P < 0.05$). In different sex and age groups, the majority of IR surrogate indexes did not show significant statistical differences in their predictive abilities for stroke risk. Across different sex and age groups, the AUC values of all six IR surrogate indexes for predicting stroke risk exceeded 0.5, indicating their predictive values for stroke risk in populations with abnormal glucose metabolism.

Discussion

Stroke is recognised as a major public health problem with serious consequences for individuals and society. IR is a critical risk factor for stroke. Developing a rapid and easy-to-use test for early identification and intervention of stroke is crucial. In this study, we evaluated the predictive abilities of six IR surrogate indexes for stroke risk in Chinese middle-aged and elderly populations with abnormal glucose metabolism. Our results revealed

Table 3 ROC curves of IR surrogate indexes and stroke risk in different sex groups

Group	Variable	AUC (95% CI)	*P* value	*P* for comparison	Optimal cutoff value	Sensitivity	Specificity	Youden index
All	eGDR	0.612(0.584, 0.640)	< 0.001	Reference	8.759	0.627	0.558	0.185
	CVAI	0.588(0.560, 0.616)	< 0.001	0.040	116.312	0.490	0.658	0.148
	TyG	0.560(0.533, 0.588)	< 0.001	0.002	8.577	0.737	0.375	0.112
	TyG-BMI	0.568(0.539, 0.596)	< 0.001	< 0.001	198.203	0.711	0.406	0.117
	METS-IR	0.564(0.536, 0.592)	< 0.001	< 0.001	35.777	0.611	0.503	0.114
	AIP	0.556(0.529, 0.583)	< 0.001	< 0.001	0.325	0.660	0.455	0.115
Male	eGDR	0.632(0.591, 0.673)	< 0.001	Reference	8.669	0.648	0.582	0.230
	CVAI	0.597(0.556, 0.637)	< 0.001	0.036	113.652	0.528	0.651	0.178
	TyG	0.564(0.524, 0.604)	0.003	0.007	8.616	0.678	0.456	0.135
	TyG-BMI	0.585(0.544, 0.626)	< 0.001	0.011	211.450	0.558	0.618	0.176
	METS-IR	0.576(0.535, 0.617)	< 0.001	0.004	38.062	0.472	0.666	0.139
	AIP	0.563(0.524, 0.602)	0.003	0.004	0.324	0.633	0.498	0.131
Female	eGDR	0.596(0.558, 0.634)	< 0.001	Reference	8.430	0.591	0.565	0.156
	CVAI	0.579(0.541, 0.617)	< 0.001	0.320	114.503	0.491	0.636	0.127
	TyG	0.561(0.522, 0.599)	0.002	0.125	8.786	0.635	0.466	0.101
	TyG-BMI	0.559(0.519, 0.598)	0.003	0.040	236.113	0.409	0.700	0.109
	METS-IR	0.557(0.518, 0.596)	0.004	0.036	35.777	0.648	0.452	0.100
	AIP	0.552(0.515, 0.589)	0.010	0.057	0.213	0.817	0.293	0.110

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; eGDR, estimated glucose disposal rate; CVAI, Chinese visceral adiposity index; TyG, triglyceride-glucose; TyG-BMI, TyG-body mass index; METS-IR, metabolic score for insulin resistance; AIP, atherogenic index of plasma.

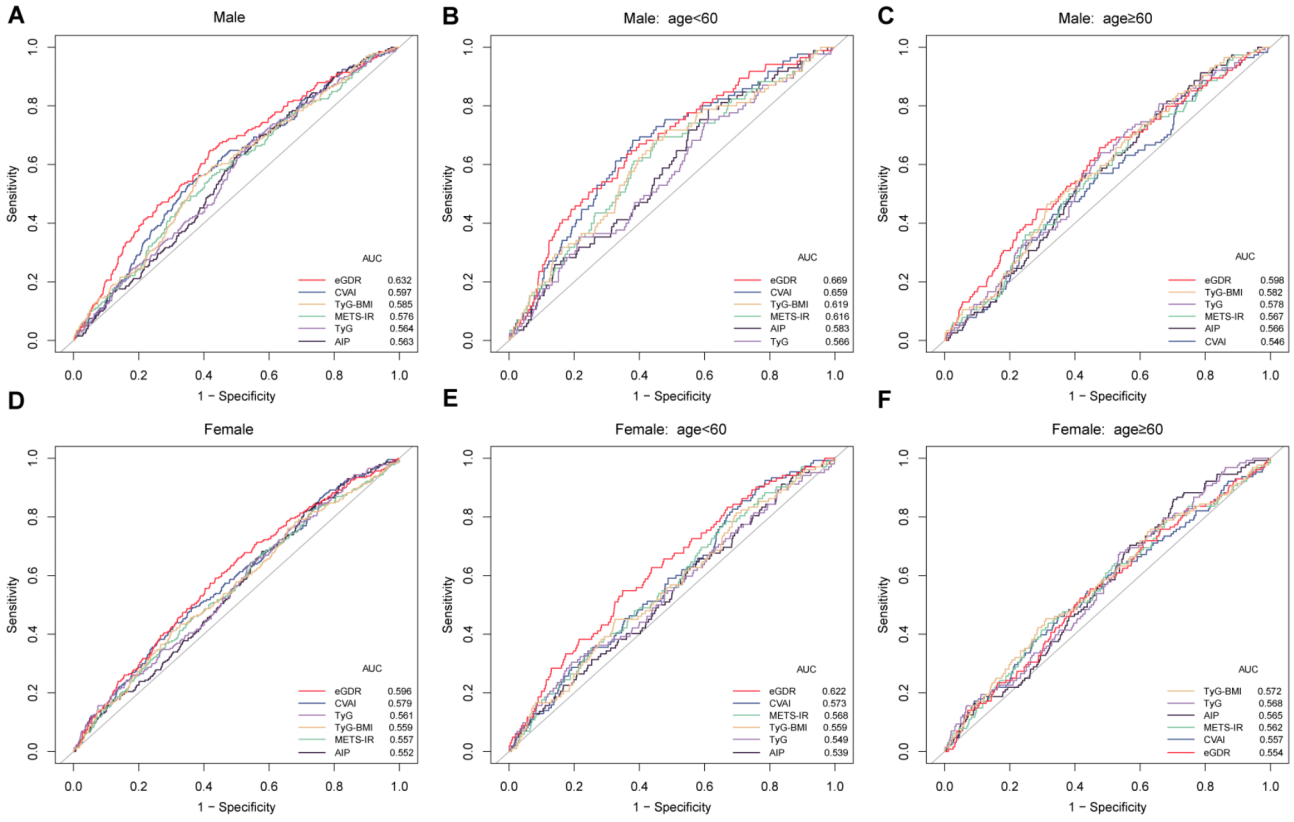

Fig. 4 The ROC curves of IR surrogates and stroke risk in different sex and age groups. ROC, receiver operating characteristic; AUC, area under the curve; eGDR, estimated glucose disposal rate; CVAI, Chinese visceral adiposity index; TyG, triglyceride-glucose; TyG-BMI, TyG-body mass index; METS-IR, metabolic score for insulin resistance; AIP, atherogenic index of plasma.

statistically significant relationships between the six IR surrogate indexes and stroke risk after adjusting for confounders. These indexes all provided predictive values for stroke risk in the Chinese middle-aged and elderly population with abnormal glucose metabolism. eGDR demonstrated significant potential in predicting stroke risk in populations with abnormal glucose metabolism.

IR is typically characterised by hyperglycaemia, dyslipidaemia, hypertension and obesity [19]. Surrogate indexes of IR (eGDR, CVAI, TyG, TyG-BMI, METS-IR and AIP) derived from different combinations of these characteristics may better reflect the degree of IR in different ways. The eGDR, calculated based on WC, hypertension, and HbA1c, was first developed by Williams et al. for patients with type 1 diabetes [20]. The index is validated by the hyperinsulinemic-euglycemic clamp technique and provides a good reflection of insulin sensitivity. eGDR has shown good potential for application in epidemiological studies of patients with type 1 diabetes [21–23]. In addition, the value of eGDR in type 2 diabetes is gaining attention. A review and meta-analysis showed that among patients with type 1 diabetes mellitus with a median follow-up period of 10 years, each 1-unit increase in the eGDR index was associated with a 17% reduction in the hazard ratio for cardiovascular disease [24]. A study conducted in populations with diabetes demonstrated that lower eGDR levels were associated with an increased risk of stroke and mortality [25]. Our study found a significant negative correlation between eGDR and the occurrence of stroke in individuals with abnormal glucose metabolism. CVAI, a reliable index of visceral fat distribution in the Chinese population, has been widely used to assess the risk of cardiovascular and metabolic diseases [11, 26, 27]. Studies have shown that CVAI outperforms traditional obesity indexes in predicting stroke risk and is considered a valuable index of abdominal obesity for identifying individuals at high risk of stroke [28, 29]. This enhanced predictive ability may be attributed to its comprehensive nature, integrating factors such as sex, age, BMI, WC, and lipid levels. In this study, we found that CVAI performed well in predicting stroke risk in the overall population with abnormal glucose metabolism, second only to eGDR. The TyG index, based on TG and FPG, has been widely used to predict diabetes and cardiovascular disease [30–32]. The association between obesity and IR has been well established [33, 34]. Some studies suggest that TyG-BMI is superior to TyG in predicting IR [35]. By integrating the TyG index

Table 4 ROC curves of IR surrogates and stroke risk at different ages for males and females

Group	Variable	AUC (95% CI)	*P* value	*P* for comparison	Optimal cutoff value	Sensitivity	Specificity	Youden index
Male								
< 60	eGDR	0.669(0.610, 0.729)	< 0.001	Reference	8.638	0.635	0.639	0.274
	CVAI	0.659(0.600, 0.719)	< 0.001	0.678	108.804	0.682	0.621	0.303
	TyG	0.566(0.503, 0.630)	0.043	0.011	8.590	0.753	0.391	0.144
	TyG-BMI	0.619(0.556, 0.682)	< 0.001	0.081	211.450	0.682	0.557	0.240
	METS-IR	0.616(0.553, 0.678)	< 0.001	0.071	36.632	0.694	0.544	0.238
	AIP	0.583(0.522, 0.643)	0.011	0.022	0.262	0.788	0.389	0.177
≥ 60	eGDR	0.598(0.542, 0.654)	0.001	Reference	8.674	0.658	0.525	0.183
	CVAI	0.546(0.492, 0.601)	0.107	0.018	112.803	0.465	0.644	0.108
	TyG	0.578(0.526, 0.630)	0.007	0.530	8.628	0.640	0.521	0.162
	TyG-BMI	0.582(0.530, 0.635)	0.004	0.505	211.680	0.465	0.686	0.151
	METS-IR	0.567(0.513, 0.620)	0.020	0.207	31.768	0.702	0.429	0.131
	AIP	0.566(0.515, 0.617)	0.021	0.303	0.143	0.807	0.330	0.137
Female								
< 60	eGDR	0.622(0.566, 0.677)	< 0.001	Reference	8.414	0.549	0.651	0.200
	CVAI	0.573(0.518, 0.627)	0.014	0.057	73.675	0.853	0.286	0.139
	TyG	0.549(0.489, 0.610)	0.096	0.030	9.442	0.304	0.808	0.112
	TyG-BMI	0.559(0.501, 0.616)	0.048	0.024	236.457	0.451	0.675	0.126
	METS-IR	0.568(0.512, 0.625)	0.022	0.057	34.205	0.784	0.336	0.120
	AIP	0.539(0.481, 0.597)	0.190	0.016	0.092	0.912	0.164	0.076
≥ 60	eGDR	0.554(0.501, 0.607)	0.047	Reference	7.640	0.555	0.553	0.108
	CVAI	0.557(0.503, 0.611)	0.036	0.891	129.977	0.461	0.653	0.114
	TyG	0.568(0.518, 0.619)	0.012	0.648	8.786	0.680	0.462	0.142
	TyG-BMI	0.572(0.518, 0.626)	0.008	0.442	229.412	0.453	0.690	0.143
	METS-IR	0.562(0.509, 0.616)	0.021	0.721	35.219	0.641	0.479	0.120
	AIP	0.565(0.516, 0.614)	0.016	0.721	0.206	0.859	0.298	0.157

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; eGDR, estimated glucose disposal rate; CVAI, Chinese visceral adiposity index; TyG, triglyceride-glucose; TyG-BMI, TyG-body mass index; METS-IR, metabolic score for insulin resistance; AIP, atherogenic index of plasma.

and BMI, TyG-BMI likely provides a more comprehensive perspective for assessing IR. METS-IR and AIP have also been identified as strong independent predictors of adverse cardiovascular and cerebrovascular events, closely associated with stroke risk [36–39].

We explored the dose-response relationships between the IR surrogate indexes and stroke risk using RCS. Previous studies have shown a linear negative correlation between eGDR and stroke risk [40]. Our study, based on individuals with diabetes and prediabetes, also revealed a similar negative linear correlation. This was attributed to the fact that the eGDR calculation formula utilised negative WC, hypertension and HbA1c values. Most other IR surrogate indexes demonstrated linear positive correlations with stroke risk, which is consistent with previous research [41, 42]. For TyG, our study was similar to a study based on Chinese populations, which reported a nonlinear positive correlation between TyG and stroke risk [43]. A study assessing stroke incidence in the general population of rural China, found a linear positive correlation between AIP and stroke risk [44]. In contrast, our study observed a nonlinear positive correlation between AIP and stroke risk. This differences may be attributed to the heterogeneity of the study population, the complexity of the disease, the settings of the RCS curve parameters, and the models used for analysis. Considering the nonlinear dose-response relationships between these IR surrogates and stroke risk, it is recommended that clinical stroke risk assessment should be based on the characteristics of different populations and the specific thresholds of IR surrogates for more precise risk assessment.

In the subgroup analysis, we found significant associations between eGDR and stroke risk across different sex and age groups. Additionally, a significant interaction between eGDR and age on risk of stroke was observed. Specifically, the association between eGDR and stroke risk was more pronounced in the middle-aged population. This finding is consistent with a study that evaluated the relationship between eGDR and cardiovascular disease risk in individuals with diabetes and prediabetes in the United States, which found a more significant association between eGDR and cardiovascular disease in those under 60 years old [45]. Another study assessing the relationship between eGDR and atherosclerotic cardiovascular disease risk in the general population also observed a significant interaction between eGDR and age on stroke risk [10]. However, studies by Kong et al. and Le et al. did not find a significant impact of age on the association

between eGDR and stroke risk [46, 47]. We also observed a significant interaction between CVAI and age on stroke risk, which aligns with previous research findings [48–50]. Furthermore, significant associations between other IR surrogate indexes and stroke risk were primarily observed in female and elderly participants. The heterogeneity of the study population and differences in data partitioning may partially explain the discrepancies in results. Therefore, future studies should consider these factors to further explore the role of IR surrogate indexes in different populations and to gain deeper insights into the potential impact of age on stroke risk.

In this study, we found that, among the overall population with abnormal glucose metabolism and within different sex groups, eGDR exhibited the highest AUC value compared to other IR surrogate indexes, demonstrating better performance in predicting stroke risk. After stratifying by sex and age, we observed that in middle-aged males and females, the predictive ability of eGDR for stroke risk was not significantly different from that of other IR surrogate indexes, such as CVAI and METS-IR. However, in elderly male and female groups, the predictive abilities of the six IR surrogate indexes for stroke risk were generally similar. Additionally, we found that eGDR appeared to predict stroke risk more effectively in middle-aged males than in other populations. Differences in fat distribution, hormone levels, and metabolic changes between males and females, as well as variations in metabolic function between middle-aged and elderly individuals, may influence the performances of IR surrogate indexes in predicting stroke risk. Therefore, when conducting stroke risk assessments, it is crucial not only to consider the overall effectiveness of these indexes but also to account for their performance differences across different sex and age groups, in order to facilitate personalised health management and risk prediction.

Our study utilised data from the nationally representative CHARLS dataset, and the prospective cohort design enhanced the causal inference of our findings. Additionally, this study evaluated the predictive values of six IR surrogate indexes for stroke risk in middle-aged and elderly individuals with abnormal glucose metabolism in China, providing new insights for early identification and prevention of stroke risk. Furthermore, we controlled potential confounders as much as possible during the analysis and conducted subgroup analyses to ensure the reliability and robustness of our results.

However, there are several limitations in this study. First, a major limitation is the lack of time-to-event analysis. Without considering time as a factor, we were unable to assess its impact on the relationships between IR surrogate indexes and stroke risk. Therefore, future studies should consider incorporating time-to-event analysis to more comprehensively evaluate the impact of IR surrogate indexes on stroke risk. Second, the stroke data relied on self-reporting from participants, which may lead to an underestimation of actual prevalence. Medical histories such as diabetes mellitus and hypertension also partially relied on self-reported data. Moreover, although we adjusted for and controlled the known major confounders, the influence of unknown factors (such as genetics, diet, physical activity, and environmental changes) on the results cannot be excluded. Finally, this study focused on middle-aged and elderly individuals with abnormal glucose metabolism in China, and whether the findings can be generalised to populations in other countries requires further investigation and validation.

Conclusion

In conclusion, our findings indicated that the six IR surrogate indexes were strongly associated with stroke occurrence in Chinese middle-aged and elderly populations with abnormal glucose metabolism. Among these indexes, eGDR showed considerable potential in assessing stroke risk in populations with abnormal glucose metabolism. However, its application should be tailored to account for the specific characteristics of different sex and age groups. Furthermore, our study has several limitations, such as the reliance on self-reported data. Therefore, future studies should further explore and validate these findings to provide a basis for early stroke prediction and personalised intervention.

Abbreviations

eGDR	Estimated glucose disposal rate
CVAI	Chinese visceral adiposity index
TyG	Triglyceride-glucose
TyG-BMI	TyG-body mass index
METS-IR	Metabolic score for insulin resistance
AIP	Atherogenic index of plasma
IR	Insulin resistance
CHARLS	China Health and Retirement Longitudinal Study
AUC	Area under the curve
ROC	Receiver operating characteristic
SD	Standard deviation
OR	Odds ratio
CI	Confidence interval
WC	Waist circumference
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
FPG	Fasting plasma glucose
HbA1c	Glycosylated hemoglobin A1c
TC	Total cholesterol
TG	Triglyceride
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
Scr	Serum creatinine
SUA	Serum uric acid
BUN	Blood urea nitrogen
CRP	C-reactive protein
VIF	Variance inflation factor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02618-7 .

Supplementary Material 1

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Author contributions
LJ contributed to the study design, statistical analysis, and drafting of the manuscript. TZ, WS, YZ, and YT participated in the study design and data collection. FR, ZX, LL, and XF performed the statistical analysis. DL, AC, and QW contributed to the editing and review of the manuscript. All authors made critical revision of the manuscript for important intellectual content and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study protocol was reviewed and approved by the Ethical Review Committee of Peking University (IRB00001052-11015), and all participants provided written informed consent at the time of participation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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