Research Square

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Estimated Glucose Disposal Rate and Risk of Multiple Carotid Artery Plaques in High Stroke-Risk Individuals: A Community-Based Study

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Abstract

Aims

Carotid artery plaques are linked to elevated cardio-cerebrovascular disease risk. Insulin resistance is critical in the progression of carotid atherosclerosis. The estimated glucose disposal rate (eGDR) is a simple, cost-effective surrogate marker for insulin resistance. This study aim to investigate the association between eGDR and multiple carotid plaques in high stroke-risk individuals.

Methods

We retrospectively analyzed 1964 participants from a 2022–2023 cross-sectional survey in Shantou, China. Carotid artery plaques were assessed by Doppler ultrasonography. eGDR was calculated from waist circumference, hypertension, and HbA1c. A multivariable logistic regression model was applied to examine the association between eGDR and multiple carotid artery plaques, with adjustment for multiple confounding factors. Subgroup analyses were further performed to explore potential effect modifications across subgroups.

Results

The cohort median age was 63 years, and multiple carotid plaque prevalence was 37.6%. In Model 4, eGDR was inversely associated with multiple carotid plaques (β: -0.091, OR = 0.913, 95% CI: 0.854–0.976, $p < 0.05$). Subgroup analyses stratified by age, sex, BMI, hypertension, and diabetes status showed a robust and consistent association between eGDR and multiple carotid artery plaques across all subgroups (all p for interaction > 0.05).

Conclusion

eGDR is inversely associated with the risk of multiple carotid artery plaques in individuals at high risk of stroke. Assessment of eGDR may improve the early identification of individuals at high risk for multiple carotid artery plaques, thereby facilitating the implementation of proactive preventive strategies.

Introduction

Globally, ischaemic heart disease and stroke are the top two causes of death. As the world's largest developing country, China bears the world's highest burden of cardio-cerebrovascular diseases, which are leading causes of death and disability with a rapidly growing disease burden. Atherosclerosis is a primary risk factor for cardio-cerebrovascular diseases. Carotid atherosclerosis, characterized by intimal thickening, plaque formation, and stenosis, typically initiates in youth, remains asymptomatic for decades, and progresses silently to advanced stages(1). Although most atherosclerotic lesions are irreversible, lipid-rich soft plaques may be reversible. Carotid plaque presence is a well-established predictor of cardiovascular disease and ischaemic stroke(2–4). It has superior predictive value for atherosclerotic cardiovascular diseases compared with carotid intima-media thickness, a common marker of atherosclerosis severity(5–7). Therefore, identifying clinical predictors of carotid plaques is critical to reducing cardio-cerebrovascular morbidity and mortality.

Doppler ultrasonography is the preferred modality for evaluating carotid arteries in asymptomatic patients, with high sensitivity and specificity. However, routine screening is not recommended for asymptomatic individuals without atherosclerotic risk factors due to insufficient health economic evidence for large-scale screening(8–10). The ASA/AHA Stroke Council suggests that only highly selected patients may benefit, while general population screening for asymptomatic carotid stenosis is not cost-effective(11). Multiple studies recommend screening for those with multiple atherosclerotic risk factors, such as hypertension, dyslipidemia, family history of early atherosclerosis or ischemic stroke, and smoking(11–13). Accordingly, we enrolled high-risk patients with ≥ 3 risk factors or a history of stroke/coronary heart disease as study subjects.

Insulin resistance (IR) is a pathophysiological state characterized by reduced target-organ sensitivity to insulin, impairing glucose utilization. As a core mechanism in metabolic diseases, IR plays a key role in carotid plaque instability and subsequent cardio-cerebrovascular events(14). IR promotes atherosclerosis by inducing hemodynamic disorders and enhancing platelet function, thus increasing cardiovascular and stroke risk(15, 16). The homeostasis model assessment of insulin resistance (HOMA-IR), calculated from fasting glucose and insulin, is limited by the lack of routine insulin testing and potential interference from antidiabetic medications(17, 18). The hyperinsulinemic-euglycemic clamp, the gold standard for insulin sensitivity, is unsuitable for large-scale studies due to high cost and complexity(19).Therefore, alternative non-invasive detection methods, such as the estimated glucose disposal rate (eGDR), have attracted increasing attention. eGDR is a simple and non-invasive measure of IR derived from three clinically accessible variables: hypertension, waist circumference and glycated hemoglobin A1c (HbA1c)(20). With advantages of non-invasiveness, time efficiency and labor savings, eGDR is considered more suitable for clinical practice and large-scale epidemiological studies(21). Previous studies have indicated that lower eGDR is associated with an increased risk of stroke, cardiovascular diseases and retinopathy in specific populations(22–26). A study has suggested that decreased eGDR values are significantly correlated with a higher burden of subclinical coronary atherosclerosis in asymptomatic middle-aged Korean populations(27). However, the association between eGDR and carotid plaques remains poorly investigated.

This study aimed to analyze the epidemiological status of multiple carotid plaques in a high stroke-risk individuals in Shantou City, and investigate the association between eGDR and multiple carotid plaques.

Methods

Study Population and Data Collection

Between January 2022 and December 2023, one urban and one rural community in Shantou City were selected for screening. Participants were recruited by cluster sampling, with eligibility criteria: aged ≥ 45 years, residing in the community for ≥ 9 months annually, and a target population sampling coverage of ≥ 85%.

Trained staff from primary healthcare institutions collected sociodemographic, behavioral, medical history, and physical examination data. Age, sex, education, income, smoking, alcohol use, physical activity, medication, and family history were self-reported. Smoking and alcohol consumption were classified as ever or never users. Regular physical activity was defined as physical exercise > 3 times weekly,with each session lasting ≥ 30 minutes. A family history of stroke was defined as stroke in parents or siblings.

Physical examinations included body weight, height, and blood pressure measurements. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m²). Obesity was defined as BMI ≥

28 kg/m². Blood pressure was measured after 5 minutes of rest, and the mean of two readings taken 1 minute apart was used for analysis. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, or self-reported physician-diagnosed hypertension.

Venous blood samples were obtained for measurements of fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and homocysteine (Hcy). Diabetes mellitus was defined as FBG ≥ 7.0 mmol/L or self-reported physician-diagnosed diabetes. Dyslipidemia was defined as at least one of the following: TG ≥ 2.26 mmol/L, TC ≥ 6.22 mmol/L, HDL-C < 1.04 mmol/L, LDL-C ≥ 4.14 mmol/L, or self-reported physician-diagnosed dyslipidemia. Hyperhomocysteinemia was defined as plasma Hcy ≥ 15μmol/L.

Based on a previous study, individuals at high risk of stroke were defined as those aged > 45 years with ≥ 3 of the following risk factors: hypertension, atrial fibrillation or valvular heart disease, smoking, dyslipidemia, diabetes mellitus, physical inactivity, obesity, or family history of stroke. Participants with a history of stroke or transient ischemic attack were also classified as high stroke-risk individuals(28).

A total of 2297 participants underwent carotid ultrasonography. After excluding those with incomplete data, 1964 subjects were finally included.

Carotid Artery Ultrasound Screening Protocol

Carotid Artery Ultrasound Screening Protocol
Carotid artery ultrasonography was performed by qualified, standardized-trained sonographers. Examinations were conducted in the supine position using Logiq 9 (GE Healthcare), iU22 (Philips Healthcare), or S 2000 (Siemens Medical Solutions) with a 6–10 MHz linear array transducer. Atherosclerotic plaques were assessed in longitudinal and transverse planes for the common, internal, external carotid arteries, and carotid bulb.

Plaques were defined as: local intima-media thickness (IMT) ≥ 1.30 mm; thickness ≥ 0.50 mm greater than adjacent sites; 1.5 times the adjacent IMT; or color Doppler flow filling defect ≥ 10 mm². The mean bilateral IMT was used for analysis. All examiners were blinded to subjects' clinical data.

Calculation of eGDR

eGDR(mg/kg/min) = 21.158 −(0.09 × WC) − (3.407 × HT) − (0.551 × HbA1c)[WC = waist circumference (cm), HTN = hypertension (yes = 1/no = 0), and HbA1c = glycosylated hemoglobin (%)].

Statistics

All statistical analyses were performed using R software (Version 4.5.0).

The Shapiro-Wilk test (via the shapiro.test function) and the TableOne package in R were used to test the normality of continuous variables. All continuous variables showed a non-normal distribution and were therefore expressed as median (interquartile range) (Median [IQ1, IQ3]). The Mann-Whitney U test was used to analyze differences in continuous variables between independent groups. Categorical variables were described as case number and

percentage (n, %), and the chi-square test was adopted for intergroup comparison of categorical variables. Statistical significance was determined by a two-tailed $p < 0.05$.

The glm function was used to construct a multivariable logistic regression model for assessing the association between eGDR and multiple carotid plaques, with four models set up for analysis: Model 1 was unadjusted; Model 2 was adjusted for age and sex; Model 3 was adjusted for age, sex, smoking, alcohol consumption and waist-to-weight ratio on the basis of Model 2; Model 4 was further adjusted for low-density lipoprotein cholesterol, homocysteine and triglyceride-glucose index in addition to the variables adjusted in Model 3. All results were reported as odds ratios (ORs) with 95% confidence intervals (CIs), and a two-tailed $p < 0.05$ was considered statistically significant.

Subgroup analyses were conducted to evaluate the potential effects of age, sex, obesity status, glycated hemoglobin and blood pressure on the development of multiple carotid plaques, with eGDR stratified by quartiles. Participants were stratified according to the aforementioned variables, and the association between eGDR and multiple carotid plaques was assessed in each subgroup. Interaction terms were incorporated into the logistic regression models, which enabled us to determine whether the association between eGDR and the prevalence of multiple carotid plaques varied across subgroups with different demographic and clinical characteristics. All statistical tests were two-tailed, with a $p < 0.05$ regarded as statistically significant. The forestplot package was used to visualize the results with figures.

Results

A total of 5749 residents were enrolled between January 2022 and December 2023. Based on risk factor screening, 2297 were identified as high stroke-risk individuals and underwent carotid artery ultrasonography. After excluding 333 residents with incomplete data, 1964 subjects were finally included in the study. The participant screening flowchart is shown in Fig. 1. Among them, the prevalence of multiple carotid plaques was 37.6%

The characteristics of the study subjects are summarized in Table 1. A total of 1964 participants were enrolled, of whom 738 were diagnosed with multiple carotid plaques. The mean age was 63 years, including 1072 males (54.6%) and 892 females (45.4%). Participants with multiple carotid plaques were significantly older than those without (68 vs. 59 years, $p < 0.001$). The overall mean eGDR was 7.27. As shown in Table 1, participants with multiple carotid plaques had lower eGDR values compared with the non-multiple plaque group (7.12 vs. 7.33, $p < 0.001$). The multiple carotid plaque group also included a higher proportion of females, individuals with lower educational level and lower income, and non-diabetic participants. Moreover, this group had a higher prevalence of hypertension and higher systolic blood pressure, as well as higher levels of homocysteine, fasting plasma glucose, and HbA1c. No statistically significant differences were observed between the two groups regarding smoking, alcohol consumption, blood lipid profile, height, waist circumference, diastolic blood pressure, or heart rate.

Table 1
Demographic and baseline characteristics of no multiple carotid plaques group and matched comparators of multiple carotid plaques group

N	level	Total	No Multiple Carotid Plaques Group	Multiple Carotid Plaques Group	*P*
		1964	**1226**	**738**	
eGDR		7.27 [6.44, 8.26]	7.33 [6.55, 8.51]	7.12 [6.31, 8.01]	**< 0.001**
Multiple carotid plaque (%)	No	1226 (62.4)	1226 (100.0)	0 (0.0)	**< 0.001**
	Yes	738 (37.6)	0 (0.0)	738 (100.0)	
Marital (%)	Single	16 (0.8)	8 (0.7)	8 (1.1)	**0.001**
	Married	1759 (89.6)	1124 (91.7)	635 (86.0)	
	widowed	184 (9.4)	91 (7.4)	93 (12.6)	
	divorced	5 (0.3)	3 (0.2)	2 (0.3)	
Educational level (%)	Primary school or below	1237 (63.0)	725 (59.1)	512 (69.4)	**< 0.001**
	Junior high school	468 (23.8)	324 (26.4)	144 (19.5)	
	Senior high school	198 (10.1)	128 (10.4)	70 (9.5)	
	College or higher	61 (3.1)	49 (4.0)	12(1.6)	
Annual income (%)	< 5000 RMB	709 (36.1)	399 (32.5)	310 (42.0)	**< 0.001**
	5000-10000RMB	349 (17.8)	206 (16.8)	143 (19.4)	
	10000-20000RMB	441 (22.5)	282 (23.0)	159 (21.5)	
	>20000RMB	465 (23.7)	339 (27.7)	126 (17.1)	
gender (%)	female	892 (45.4)	515 (42.0)	377 (51.1)	**< 0.001**
	male	1072 (54.6)	711 (58.0)	361 (48.9)	
age (year)		63.00 [56.00, 69.00]	59.00 [54.00, 66.00]	68.00 [62.00, 72.00]	**< 0.001**
height (cm)		159.00 [154.00, 165.00]	159.00 [154.00, 166.00]	159.00 [153.00, 165.00]	0.058
weight (kg)		62.00 [55.00, 70.00]	63.00 [56.00, 70.00]	61.00 [54.00, 68.00]	**< 0.001**

N	level	Total	No Multiple Carotid Plaques Group	Multiple Carotid Plaques Group	*P*
		1964	**1226**	**738**	
waist (cm)		81.00 [75.00, 86.00]	81.00 [75.00, 87.00]	80.00 [75.00, 86.00]	0.44
BMI		24.46 [22.14, 27.04]	24.61 [22.21, 27.24]	24.09 [22.02, 26.61]	**0.001**
smoking (%)	No	1282 (65.3)	813 (66.3)	469 (63.6)	0.221
	Yes	682 (34.7)	413 (33.7)	269 (36.4)	
drinking (%)	No	1575 (80.2)	975 (79.5)	600 (81.3)	0.371
	Yes	326 (16.6)	214 (17.5)	112 (15.2)	
	Sometimes	63 (3.2)	37 (3.0)	26 (3.5)	
Regular exercise(%)	No	953 (48.5)	622 (50.7)	331 (44.9)	**0.012**
	Yes	1011 (51.5)	604 (49.3)	407 (55.1)	
hypertension (%)	No	350 (17.8)	268 (21.9)	82 (11.1)	**< 0.001**
	Yes	1614 (82.2)	958 (78.1)	656 (88.9)	
SBP (mmHg)		145.00 [133.00, 159.00]	142.00 [131.00, 157.00]	149.00 [138.00, 163.00]	**< 0.001**
DBP (mmHg)		89.00 [83.00, 97.00]	89.00 [83.00, 97.00]	89.00 [83.00, 97.00]	0.637
HR (bpm)		82.00 [75.00, 90.00]	81.00 [75.00, 90.00]	83.00 [75.00, 91.00]	0.127
Dyslipidemia (%)	No	589 (30.0)	359 (29.3)	230 (31.2)	0.388
	Yes	1375 (70.0)	867 (70.7)	508 (68.8)	
TG (mmol/L)		1.55 [1.12, 2.15]	1.58 [1.13, 2.17]	1.48 [1.10, 2.10]	0.053
TC(mmol/L)		4.90 [4.06, 5.92]	4.87 [4.05, 5.93]	4.94 [4.07, 5.91]	0.381
LDL-C (mmol/L)		2.96 [2.28, 3.83]	2.92 [2.29, 3.79]	3.03 [2.25, 3.86]	0.255
HDL-C (mmol/L)		1.12 [0.94, 1.39]	1.11 [0.94, 1.35]	1.15 [0.94, 1.43]	**0.041**
Hcy (ummol/L)		10.80 [7.80, 14.30]	10.30 [7.70, 13.70]	11.60 [8.12, 14.80]	**< 0.001**

N	level	Total	No Multiple Carotid Plaques Group	Multiple Carotid Plaques Group	*P*
		1964	**1226**	**738**	
Diabetes (%)	No	1398 (71.2)	920 (75.0)	478 (64.8)	**< 0.001**
	Yes	566 (28.8)	306 (25.0)	260 (35.2)	
Fpg (mmol/L)		5.30 [4.70, 6.40]	5.20 [4.70, 6.10]	5.50 [4.80, 7.00]	**< 0.001**
HbA1c (%)		5.90 [5.50, 6.60]	5.90 [5.50, 6.50]	6.00 [5.50, 6.80]	**0.004**
Tyg_index		8.84 [8.46, 9.21]	8.83 [8.46, 9.20]	8.85 [8.46, 9.25]	0.6

Table 2 summarizes the logistic regression analyses exploring the association between eGDR and the prevalence of multiple carotid plaques. In the crude model (Model 1), eGDR was significantly and inversely associated with multiple carotid plaques (β: -0.127, OR = 0.881, 95% CI: 0.836–0.927, $p < 0.001$). This association remained significant after adjustment for confounders in Models 2–4. Model 2 was adjusted for age and sex; Model 3 was further adjusted for smoking, alcohol consumption, and waist-to-weight ratio; Model 4 was additionally adjusted for low-density lipoprotein cholesterol, homocysteine, and triglyceride-glucose(TyG) index. In the fully adjusted Model 4, each 1-unit increase in eGDR was associated with an OR of 0.913 (95% CI: 0.854–0.976, $p = 0.008$) for multiple carotid plaques, indicating that higher eGDR was linked to a lower prevalence, corresponding to an 8.7% risk reduction.

Table 2
Association between eGDR and multiple carotid artery plaques among study participants

Model 1	β	SE	OR	95%CI	p value
	-0.127	**0.026**	**0.881**	**[0.836,0.927]**	**<0.001**
Model 2	-0.079	0.029	0.924	[0.872,0.978]	0.007
Model 3	-0.095	0.032	0.909	[0.854,0.967]	0.003
Model 4	-0.091	0.034	0.913	[0.854,0.976]	0.008
Model 1: unadjusted;					
Model 2: adjusted age and sex;					
Model 3: adjusted age,sex,smoking,drinkin and WWI;					
Model 4: adjusted age,sex,smoking,drinkin,WWI,LDL,Hcy and Tyg index.					

The robustness of the association between eGDR and multiple carotid plaques was evaluated by subgroup analyses (Table 3, Fig. 2). Subgroups were stratified by age, sex, BMI, hypertension, and diabetes status according to previous studies. The results revealed no significant interaction across most subgroups (all *p* for interaction >

0.05), indicating a consistent association between eGDR and multiple carotid plaques in subgroups stratified by age, sex, obesity, SBP > 160 mmHg, and diabetes. In some subgroup analyses, increasing eGDR was accompanied by a decreasing trend in the prevalence of multiple carotid plaques.

Table 3
Multivariate regression analysis of the association between eGDR and multiple carotid artery plaques in different population subgroups

Variables	Subgroups	Group	Event	Total	Event/total%	aOR (95% CI)	P value	P for interaction
age_group	Interaction							0.783
	age < 65	Q1	73	260	28.08	Ref		
	age < 65	Q2	60	248	24.19	0.67 (0.43–1.03)	0.069	
	age < 65	Q3	72	279	25.81	0.86 (0.55–1.33)	0.497	
	age < 65	Q4	49	306	16.01	0.56 (0.35–0.89)	0.015	
	age ≥ 65	Q1	138	232	59.48	Ref		
	age ≥ 65	Q2	128	242	52.89	0.72 (0.49–1.05)	0.091	
	age ≥ 65	Q3	121	213	56.81	0.89 (0.59–1.35)	0.589	
	age ≥ 65	Q4	97	184	52.72	0.73 (0.47–1.13)	0.160	
sex	Interaction							0.215
	female	Q1	106	224	47.32	Ref		
	female	Q2	95	230	41.30	0.65 (0.42–0.99)	0.045	
	female	Q3	98	200	49.00	1.11 (0.70–1.78)	0.647	
	female	Q4	78	238	32.77	0.60 (0.38–0.95)	0.030	
	male	Q1	105	268	39.18	Ref		
	male	Q2	93	260	35.77	0.74 (0.50–1.10)	0.135	
	male	Q3	95	292	32.53	0.70 (0.47–1.06)	0.090	

Variables	Subgroups	Group	Event	Total	Event/total%	aOR (95% CI)	P value	P for interaction
	male	Q4	68	252	26.98	0.63 (0.40–0.98)	0.043	
bmi_group	Interaction							0.229
	0	Q1	146	305	47.87	Ref		
	0	Q2	151	390	38.72	0.58 (0.41–0.82)	0.002	
	0	Q3	180	445	40.45	0.76 (0.54–1.08)	0.122	
	0	Q4	140	449	31.18	0.55 (0.38–0.79)	0.001	
	1	Q1	65	187	34.76	Ref		
	1	Q2	37	100	37.00	1.03 (0.56–1.87)	0.929	
	1	Q3	13	47	27.66	0.93 (0.38–2.21)	0.874	
	1	Q4	6	41	14.63	0.42 (0.13–1.18)	0.121	
HblAc_group	Interaction							0.118
	HblAc < 6.5	Q1	69	166	41.57	Ref		
	HblAc < 6.5	Q2	129	363	35.54	0.61 (0.40–0.95)	0.028	
	HblAc < 6.5	Q3	171	428	39.95	0.90 (0.57–1.41)	0.638	
	HblAc < 6.5	Q4	131	421	31.12	0.64 (0.40–1.02)	0.061	
	HblAc ≥ 6.5	Q1	142	326	43.56	Ref		
	HblAc ≥ 6.5	Q2	59	127	46.46	1.00 (0.62–1.59)	0.992	
	HblAc ≥ 6.5	Q3	22	64	34.38	0.68 (0.35–	0.241	

Variables	Subgroups	Group	Event	Total	Event/total%	aOR (95% CI)	P value	P for interaction
						1.28)		
	HblAc ≥ 6.5	Q4	15	69	21.74	0.47 (0.23–0.91)	0.030	
hypertension_group	Interaction							0.328
	SBP < 160	Q1	143	346	41.33	Ref		
	SBP < 160	Q2	125	344	36.34	0.64 (0.45–0.90)	0.012	
	SBP < 160	Q3	133	356	37.36	0.81 (0.57–1.16)	0.256	
	SBP < 160	Q4	120	444	27.03	0.57 (0.39–0.81)	0.002	
	SBP ≥ 160	Q1	68	146	46.58	Ref		
	SBP ≥ 160	Q2	63	146	43.15	0.86 (0.51–1.43)	0.552	
	SBP ≥ 160	Q3	60	136	44.12	0.97 (0.55–1.71)	0.921	
	SBP ≥ 160	Q4	26	46	56.52	1.25 (0.56–2.78)	0.586	

Discussion

This study investigated the association between eGDR and the development of multiple carotid plaques in individuals aged ≥ 45 years at high stroke risk. Our findings revealed that lower eGDR levels were associated with an increased risk of multiple carotid plaque formation in this high-risk population. This association remained consistent after adjustment for multiple potential confounders, including age, sex, BMI, hypertension, and diabetes mellitus. Additionally, subgroup analyses demonstrated that the inverse relationship between eGDR and multiple carotid plaques was not modified by age, sex, BMI, hypertension, or diabetes status. Thus, our primary findings may be reasonably extrapolated to these subpopulations.Our results suggest that eGDR, a metric derived from traditional risk factors, may facilitate the early identification of individuals at high cardio-cerebrovascular disease risk, allowing for targeted early interventions. Furthermore, this simple, convenient, and low-cost tool is readily applicable in regions with limited medical resources and may have improved clinical utility for individuals with limited health literacy.

With the increasing prevalence of hypertension, diabetes, obesity, and other conditions, the incidence of cardio-cerebrovascular diseases has risen annually. Identifying atherosclerotic vascular alterations and early detection of

carotid plaques can help evaluate cardio-cerebrovascular disease risk and guide timely intervention. However, due to the low prevalence of carotid stenosis, many authorities do not recommend universal screening in the general population(9, 10, 29, 30). Several studies have suggested screening individuals with multiple atherosclerotic risk factors, including hypertension, dyslipidemia, family history of atherosclerosis or ischemic stroke before age 60, and smoking(8, 12, 31, 32). Nevertheless, the size of this at-risk population remains extremely large, leading to high costs for comprehensive community screening. In the present study, we found that eGDR can serve as a predictor for the prevalence of multiple carotid plaques in individuals at high stroke risk, allowing improved identification and intervention of high-risk subjects. Given its non-invasiveness, time efficiency, and labor savings, eGDR is more suitable for large-scale screening in real-world settings, with important implications for clinical practice.

IR is a key mechanism underlying the increased risk of cardio-cerebrovascular diseases. Initially developed to evaluate IR in patients with type 1 diabetes mellitus (T1DM), eGDR has been shown to achieve accuracy comparable to the hyperinsulinemic-euglycemic clamp. Although originally designed for T1DM patients, eGDR has been widely investigated and applied in non-diabetic individuals and across diverse ethnic populations. eGDR demonstrates strong predictive value for the incidence of cardio-cerebrovascular diseases. A recent study reported that eGDR is associated with elevated cardiovascular disease risk in the general population independent of diabetes status, and may be more sensitive for predicting cardiovascular disease in non-diabetic individuals(33, 34). A study in a multi-ethnic atherosclerotic cohort revealed a linear inverse association between eGDR levels and the risk of atherosclerotic cardiovascular disease events(23). Multiple studies have confirmed a linear relationship between eGDR and stroke incidence, with lower eGDR significantly increasing the risk of stroke and mortality(26, 35, 36). eGDR is also closely linked to thrombolytic prognosis in acute cerebral infarction and may serve as a valuable indicator for prognostic evaluation(37). The predictive ability of eGDR for cardio-cerebrovascular diseases may be partially explained by its formula components: waist circumference, hypertension status, and HbA1c, all of which are established risk factors for atherosclerosis and cardio-cerebrovascular diseases. Furthermore, eGDR has been shown to outperform the TyG index in predicting cardiovascular disease incidence in the elderly(33). The superior performance of eGDR has been attributed to its integration of clinical and laboratory data, allowing a more comprehensive assessment of IR(33). Given the invasiveness and high cost of conventional IR assessment methods, eGDR is more suitable for large-scale screening in real-world settings. Unlike HOMA-IR and the TyG index, eGDR does not require fasting blood samples or insulin measurements, but instead uses routine clinical parameters (waist circumference, hypertension status, and HbA1c), rendering it particularly convenient for large-scale studies and metabolic evaluations.

Although numerous studies have confirmed an association between eGDR and cardio-cerebrovascular disease risk, the optimal timing for initiating interventions in these high-risk populations remains poorly defined. Atherosclerotic lesions progress gradually and are generally irreversible; however, early lipid-rich soft plaques may be reversible, and identification of the subclinical disease stage may offer therapeutic potential(1). Our study demonstrated an inverse association between eGDR and the risk of multiple carotid plaque formation. Early screening for multiple carotid plaques and risk assessment in this high-risk population may facilitate more informed decisions regarding the timing of intervention. IR fosters a pro-atherosclerotic microenvironment by disrupting lipid metabolism, promoting inflammation, and impairing vascular function(38). Previous studies have reported that reduced eGDR is significantly associated with a greater burden of subclinical coronary atherosclerosis in asymptomatic middle-aged Korean individuals(27). Two studies in T1DM patients also found an inverse relationship between eGDR and preclinical carotid atherosclerotic plaques(39, 40). However, evidence

regarding the association between eGDR and carotid plaque risk in the general population is lacking. Our study is the first to demonstrate a significant correlation between eGDR and multiple carotid plaque formation. Furthermore, subgroup analyses showed that this inverse association was not modified by age, sex, BMI, hypertension, or diabetes, supporting the broad clinical applicability of eGDR.These findings provide guidance for the early identification of individuals at high risk of multiple carotid plaques, offer effective monitoring and preventive strategies for the clinical management of cardio-cerebrovascular diseases in high-risk populations, and enable self-assessment among healthy individuals.

In subgroup analyses, the risk of multiple carotid plaque formation exhibited an overall decreasing trend with increasing eGDR levels. However, an anomalous rise in plaque risk was observed in the eGDR Q3 subgroup across all strata except for males, obese individuals, and those with HbA1c ≥ 6.5%. Furthermore, an increasing trend was present in both the Q3 and Q4 subgroups within the SBP ≥ 160 mmHg stratum. We hypothesize that this phenomenon is mainly attributable to the multifactorial nature of carotid plaque risk, which involves several unadjusted confounders in the present study; these factors may obscure health risk predictions for certain individuals in real-world settings. Therefore, despite the inverse association between eGDR and multiple carotid plaque risk, unexplained residual carotid plaque risk may still exist in some individuals.

Limitations

When interpreting our findings, the limitations of the present study must be acknowledged. First, this was a cross-sectional study without follow-up data; thus, our results only demonstrate an association between eGDR and multiple carotid plaques, and cannot establish a causal relationship between the variables and outcomes. A prospective cohort study is warranted to confirm their longitudinal relationship. Second, participants were recruited from only one region in southeastern China and were predominantly of Han ethnicity. Therefore, the external validity of our findings may be limited, and caution should be exercised when extrapolating the results to other geographic regions or populations with different demographic characteristics. To confirm the generalizability of our findings and improve external validity, future studies should focus on validation in multicenter prospective cohorts with more diverse populations. Third, residual confounding remains a concern despite adjustment for multiple covariates and performance of sensitivity analyses. Information on medication use and dietary factors was unavailable in this study, and failure to adjust for these key factors may have influenced the results; thus, further prospective studies incorporating medication data are needed to optimize risk prediction. Finally, the use of self-reported, non-clinically verified data may introduce potential recall bias, particularly for comorbidities and lifestyle factors related to eGDR.

Conclusions

This study found that lower eGDR levels were associated with an increased risk of multiple carotid plaque formation in individuals aged ≥ 45 years at high stroke risk. Assessment using eGDR may facilitate the early identification and intervention of patients at high cardio-cerebrovascular disease risk. In regions with limited medical resources, it provides a cost-effective and readily available approach for evaluating carotid plaque formation risk in large populations, particularly for individuals with limited capacity to access, process and understand health information and services.

Abbreviations

Abbreviation Full Name

ASA American Stroke Association

AHA American Heart Association

BMI Body Mass Index

CI Confidence Interval

DBP Diastolic Blood Pressure

eGDR estimated Glucose Disposal Rate

FBG Fasting Blood Glucose

HbA1c Glycated Hemoglobin A1c

HDL-C High-Density Lipoprotein Cholesterol

Hcy Homocysteine

HOMA-IR Homeostasis Model Assessment of Insulin Resistance

HTN Hypertension

IMT Intima-Media Thickness

IR Insulin Resistance

LDL-C Low-Density Lipoprotein Cholesterol

OR Odds Ratio

SBP Systolic Blood Pressure

TC Total Cholesterol

TG Triglycerides

TyG Triglyceride-Glucose

WC Waist Circumference

Declarations

Ethical Approval:

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Shantou Central Hospital (Approval No. [2026] Scientific Research 029; Date: April 7, 2026). This retrospective study was approved by the institutional review board with a waiver of informed consent.

Consent for publication:

Not applicable.

Conflict of interest statement:

The authors have no conflicts of interest to declare.

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Author Contribution

HS Zhou and H Lin were responsible for the coordination, supervision, and overall guidance of the research project. They bear final responsibility for the submission and publication of the findings. DN Li, YY Xie, YT Huang, and T Fang contributed to the design of the study. DN Li, YY Xie, YT Huang, and T Fang, FY Ye , J Lin , H Rui, and HX Wu were involved in data screening and collection. DN Li conducted the statistical analysis. YY Xie wrote the initial draft of the manuscript. YT Huang critically reviewed and revised the manuscript.HS Zhou and H Lin are joint corresponding authors and share equal responsibility for this work. DN Li, YY Xie, YT Huang contribute equally to this work and are co-first authors of this manuscript.

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Data Availability

The data generated and analysed during the current study are not publicly available due to patient privacy and ethical restrictions, but are available from the corresponding author on reasonable request.

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Figures

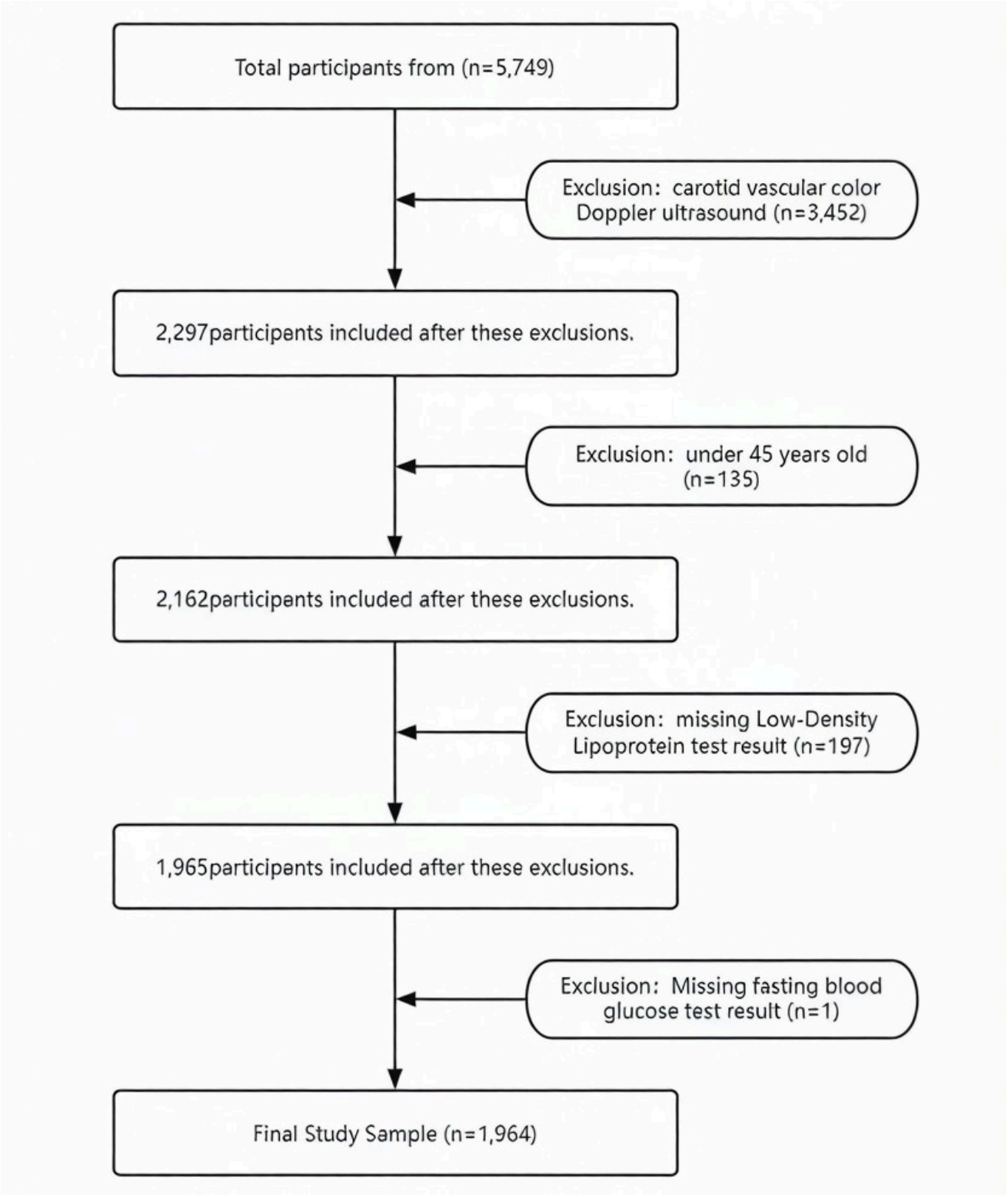


Figure 1

Flowchart of participant selection.

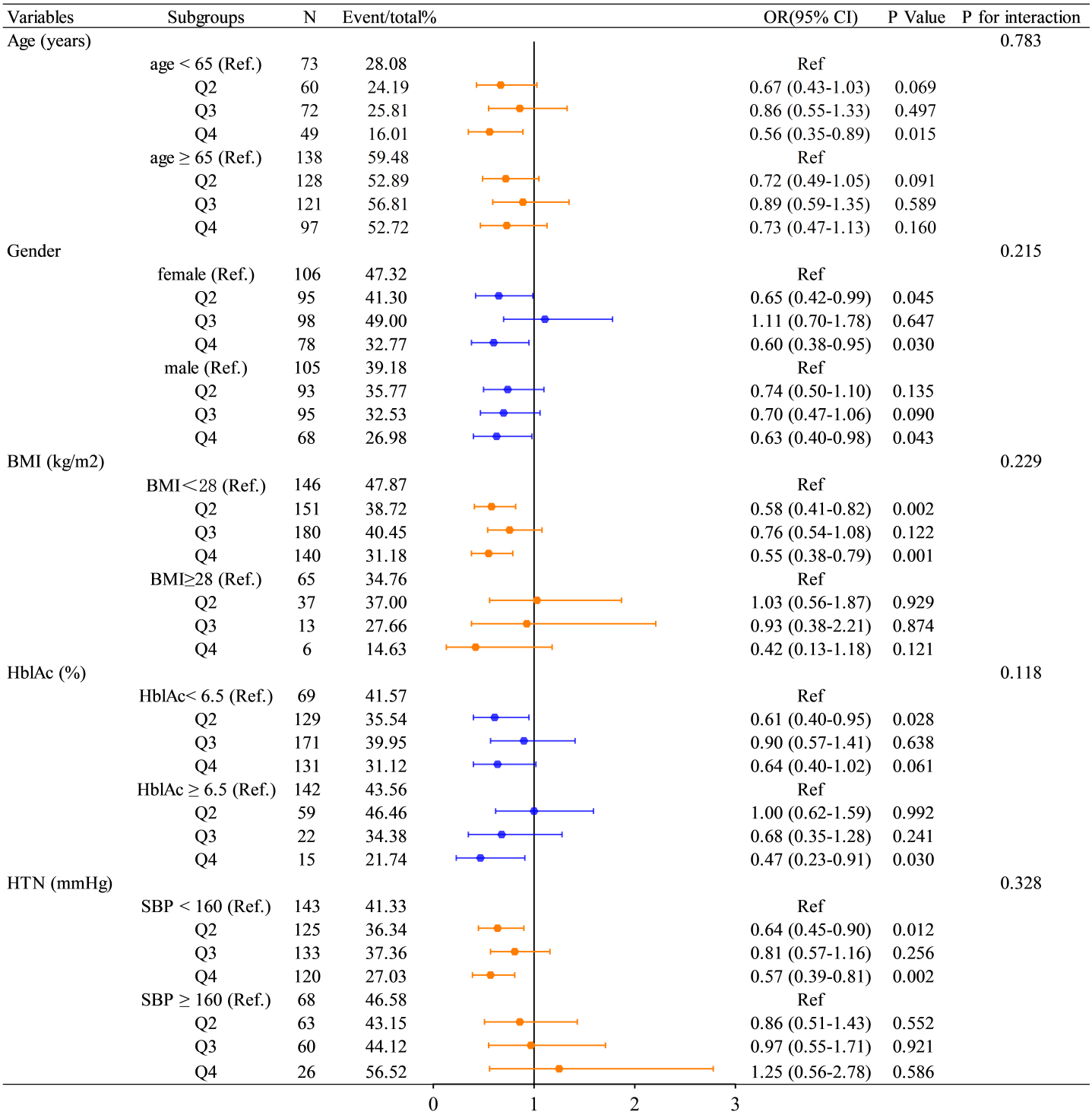


Figure 2

Subgroup analysis. Forest plot of the association between eGDR and multiple carotid plaques in different population subgroups. (HTN: Hypertension)