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Cumulative Estimated Glucose Disposal Rate and Incident Stroke Risk in Middle-Aged and Older Chinese Adults With Prediabetes: A Prospective Cohort Study

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Cumulative eGDR and Incident Stroke in Prediabetes

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Cumulative Estimated Glucose Disposal Rate and Incident Stroke Risk in Middle-Aged and Older Chinese Adults With Prediabetes: A Prospective Cohort Study

Abstract

Background: Evidence regarding the association between long-term insulin resistance burden and stroke among individuals with prediabetes remains limited. We examined the prospective association between cumulative estimated glucose disposal rate (eGDR) and incident stroke among middle-aged and older Chinese adults with prediabetes.

Methods: This prospective cohort study included participants with prediabetes at the 2015 analytic baseline of the China Health and Retirement Longitudinal Study. Cumulative eGDR was calculated as the mean of eGDR measurements in 2011–2012 and 2015 multiplied by the 4-year exposure interval. Incident stroke was identified in 2018 and 2020, with event times assigned as 3 and 5 years, respectively. Associations were evaluated using Cox proportional hazards regression, restricted cubic splines, subgroup analyses, and sensitivity analyses.

Results: Among 2,593 participants, 204 (7.9%) developed incident stroke. The fully adjusted analysis included 2,573 participants and 202 events. Each 4-unit increment in cumulative eGDR was associated with a 17% lower stroke hazard (HR, 0.83; 95% CI, 0.77–0.90; $P < 0.001$). Compared with the lowest quartile, the adjusted HRs were 0.55 (95% CI, 0.37–0.81; $P = 0.003$) for the third quartile and 0.36 (95% CI, 0.23–0.58; $P < 0.001$) for the fourth quartile (P for trend < 0.001). Restricted cubic splines showed an inverse association without evidence of nonlinearity (P for overall association < 0.001; P for nonlinearity = 0.212). No statistically significant interactions were detected, and sensitivity analyses yielded generally consistent results.

Conclusions: Higher cumulative eGDR was associated with a lower hazard of incident stroke among Chinese adults with prediabetes. It may represent a marker of long-term insulin resistance burden, although its incremental predictive value and clinical utility require further investigation.

Keywords: estimated glucose disposal rate; insulin resistance; prediabetes; stroke; prospective cohort study

Introduction

Stroke remains the second leading cause of death and the third leading cause of death and disability combined worldwide, imposing substantial clinical, social, and economic burdens on public health systems [1, 2]. A substantial proportion of the global stroke burden occurs in China, where rapid population aging and the increasing prevalence of metabolic disorders have contributed to the continued rise in cerebrovascular disease [3]. Diabetes mellitus is a well-established risk factor for both ischemic and hemorrhagic stroke [2, 4]. However, accumulating evidence indicates that vascular risk begins to increase even during the prediabetic stage. Prediabetes, an intermediate metabolic state between normoglycemia and type 2 diabetes mellitus, is highly prevalent and is associated with increased risks of progression to diabetes and adverse cardiovascular outcomes [5]. Nevertheless, individuals with prediabetes represent a heterogeneous population, and identifying modifiable metabolic determinants of stroke risk may help improve early risk stratification and prevention in this high-risk group.

Insulin resistance is one of the earliest and most important metabolic abnormalities underlying prediabetes [6-8]. It has been implicated in the development of cerebrovascular disease through pathways involving endothelial dysfunction, impaired nitric oxide bioavailability, oxidative stress, chronic inflammation, dyslipidemia, elevated blood pressure, and a prothrombotic milieu [9]. Thus, insulin resistance may represent a mechanistically relevant marker for stroke risk assessment among individuals with prediabetes. Compared with the hyperinsulinemic-euglycemic clamp, the estimated glucose disposal rate (eGDR) has emerged as a practical surrogate marker of insulin resistance based on readily obtainable clinical parameters [10, 11]. Although previous studies have reported associations between eGDR and cardiovascular and cerebrovascular outcomes in various populations, including individuals with diabetes and those without diabetes, evidence specific to individuals with prediabetes remains limited [11-13].

To address this gap, we used data from the China Health and Retirement Longitudinal Study to investigate the prospective association between cumulative eGDR and incident stroke among middle-aged and older adults with prediabetes. We evaluated cumulative eGDR as both a continuous and categorical exposure, characterized its dose–response association with stroke, and examined the consistency of the association across clinically relevant subgroups and sensitivity analyses. We hypothesized that higher cumulative eGDR would be associated with a lower hazard of incident stroke.

Methods

2.1 Data source

Data for this study were derived from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative longitudinal cohort designed to assess the health, economic, and social circumstances of Chinese adults aged 45 years and older. The original CHARLS baseline cohort included 17,708 participants from 150 counties or districts and 450 villages or communities across 28 provinces in China [14]. Wave 1 was conducted in 2011–2012, followed by Wave 2 in 2013, Wave 3 in 2015, Wave 4 in 2018, and Wave 5 in 2020. Venous blood samples were collected at Waves 1 and 3. Detailed sampling procedures, physical examination protocols, and biochemical measurement methods have been described previously and are available on the CHARLS website (https://charls.pku.edu.cn/en/). CHARLS was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052–11015), and all participants provided written informed consent. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

2.2 Study design and study population

For this secondary analysis, Wave 3 (2015) was designated as the analytic baseline, and participants were followed prospectively through Wave 4 (2018) and Wave 5 (2020). Cumulative eGDR exposure over the 2011–2015 period was estimated using repeated measurements obtained at Wave 1 (2011–2012) and Wave 3 (2015). Participants who reported a physician-diagnosed stroke in 2011, 2013, or 2015 were excluded, ensuring that the exposure assessment preceded the ascertainment of incident stroke.

The Harmonized CHARLS file included 25,586 unique respondents who participated in at least one survey wave. Of these, 6,245 had the waist circumference, hypertension status, and HbA1c measurements required to calculate eGDR at both Wave 1 and Wave 3. Glycemic status was determined at the 2015 analytic baseline. Prediabetes was defined according to the 2024 American Diabetes Association criteria as a fasting plasma glucose concentration of 5.6–6.9 mmol/L or an HbA1c level of 5.7%–6.4% in the absence of diabetes [15]. Diabetes was defined as a fasting plasma glucose concentration of at least 7.0 mmol/L, an HbA1c level of at least 6.5%, a self-reported physician diagnosis of diabetes, or current use of glucose-lowering medication. Participants were not required to

meet the criteria for prediabetes at both eGDR measurement waves.

Of the 3,239 participants with prediabetes at the 2015 analytic baseline, we sequentially excluded those who reported a physician-diagnosed stroke in 2011, 2013, or 2015 and those with insufficient follow-up information to determine final incident stroke status. For time-to-event analyses, the wave at which stroke was first reported also had to be identifiable. One participant had a known final stroke status but an indeterminate first reporting wave because of missing intermediate-wave information; this participant was retained in analyses that did not require event-time information but excluded from Cox regression and Kaplan–Meier analyses. The overall outcome cohort comprised 2,593 participants, including 204 incident stroke cases. The time-to-event cohort comprised 2,592 participants, including 203 cases with an identifiable first reporting wave (**Figure 1**).

2.3 Assessment of cumulative eGDR

The primary exposure was cumulative estimated glucose disposal rate (eGDR), a noninvasive surrogate measure of insulin resistance [16, 17]. At Wave 1 and Wave 3, eGDR was calculated as follows[17-19]: $eGDR$=21.158-($0.09\times WC$)-($3.407\times HTN$)-($0.551\times HbA1c$), where WC represents waist circumference in centimeters, HTN is a binary variable indicating hypertension status, with yes = 1 and no = 0, and HbA1c denotes glycated hemoglobin as a percentage. Waist circumference was measured at the level of the umbilicus, with participants standing upright, breathing normally. Hypertension was defined as self-reported physician-diagnosed hypertension, use of antihypertensive medication, mean systolic blood pressure ≥ 140 mmHg, or mean diastolic blood pressure ≥ 90 mmHg [20]. HbA1c was measured from whole blood samples using the boronate affinity high-performance liquid chromatography (HPLC) method. A higher eGDR value indicates greater insulin sensitivity, whereas a lower value reflects greater insulin resistance.

To characterize time-integrated eGDR exposure over the prespecified 4-year interval from Wave 1 to Wave 3, cumulative eGDR was calculated from the two repeated measurements using the trapezoidal method [17-19]: $cumulative\ eGDR=\frac{(eGDR_{wave1}+eGDR_{wave3})}{2}\times$ (2015-2011) $years$. Cumulative eGDR was expressed in $mg\cdot kg^{-1}\cdot min^{-1}\cdot$years. A 4-unit increment in cumulative eGDR was numerically equivalent to a 1-$mg\cdot kg^{-1}\cdot min^{-1}$ higher average eGDR over the exposure period. Cumulative eGDR was examined continuously per 4-unit increment and categorically by quartiles, with the lowest quartile serving as the reference group.

2.4 Outcome assessment

The primary outcome was incident stroke, ascertained at Wave 4 (2018) and Wave 5 (2020) using the standardized question, “Has a doctor ever told you that you had a stroke?” Among participants who did not report a physician-diagnosed stroke in 2011, 2013, or 2015, those who first reported such a diagnosis during follow-up were classified as having incident stroke. Because the exact date of stroke onset was unavailable, event time was assigned according to the wave at which stroke was first reported. Participants who first reported stroke in 2018 were assigned an event time of 3 years from the 2015 analytic baseline, whereas those who reported no stroke in 2018 but first reported stroke in 2020 were assigned an event time of 5 years. Participants who reported no stroke at either follow-up wave were censored at 5 years. Accordingly, the time-to-event analysis was based on the timing of the first reported physician diagnosis rather than the exact date of stroke onset. One participant had a known incident stroke status by the end of follow-up, but the wave of first stroke reporting could not be determined because stroke status at the intermediate follow-up wave was unavailable. This participant was included in analyses that did not require event-time information but was excluded from Cox regression and Kaplan–Meier analyses.

2.5 Covariates

Covariates were selected a priori based on previous studies and their potential roles as confounders of the association between cumulative eGDR and incident stroke. All covariates were assessed at the 2015 analytic baseline and included age, sex, residential area, educational level, marital status, smoking status, alcohol status, triglycerides (TG), blood urea nitrogen (BUN), serum creatinine, serum uric acid (UA), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BMI was not included as an adjustment covariate in the primary regression models but was examined as a stratification variable in subgroup analyses. Variables already incorporated into the eGDR formula (WC, HTN, HbA1c) were not re-entered as covariates in the regression models to avoid overadjustment, collinearity, and mathematical coupling with the exposure.

2.6 Statistical analysis

Continuous variables were presented as means with standard deviations (SDs), and categorical variables as frequencies with percentages. Baseline characteristics were compared across cumulative eGDR quartiles using Welch’s one-way analysis of variance for continuous variables and Pearson’s

chi-squared test for categorical variables.The association between cumulative eGDR and incident stroke was estimated using Cox proportional hazards regression models. Four progressively adjusted models were constructed: Model 1 was unadjusted (crude); Model 2 adjusted for age and sex; Model 3 further adjusted for residential area, educational level, marital status, smoking status, and alcohol drinking status; Model 4 (fully adjusted) was additionally adjusted for triglycerides, blood urea nitrogen, serum creatinine, serum uric acid, total cholesterol, HDL-C, and LDL-C. Cumulative eGDR was modeled both continuously, with HRs estimated per 4-unit increment, and categorically according to quartiles. A 4-unit increment was numerically equivalent to a 1-$mg \cdot kg^{-1} \cdot min^{-1}$ higher average eGDR over the 4-year exposure period. Linear trends were assessed by assigning participants the median value of their quartile and modeling this value continuously.

The proportional hazards assumption was evaluated using Schoenfeld residuals for cumulative eGDR and the global model, and tied event times were handled using the Efron approximation. Kaplan–Meier curves and log-rank tests were used to compare the cumulative probability of incident stroke across quartiles. Potential nonlinearity was examined using restricted cubic splines with four knots placed at the 5th, 35th, 65th, and 95th percentiles in the fully adjusted Cox model. The median cumulative eGDR was used as the reference. Wald tests were used to assess the overall association and nonlinearity.

Subgroup analyses were conducted according to age, sex, educational level, marital status, residential area, BMI, smoking status, and alcohol consumption status. Potential effect modification was assessed by including a multiplicative interaction term between cumulative eGDR and each subgroup variable in the corresponding model. P values for interaction were obtained using likelihood ratio tests comparing models with and without the corresponding interaction term.

Sensitivity analyses were performed by conducting a 3-year landmark analysis among participants who remained stroke-free through Wave 4 (2018), with incident stroke reported at Wave 5 (2020) as the outcome, repeating the analysis using logistic regression for incident stroke over the entire follow-up period without relying on assigned time-to-event information, and restricting the study population to participants with cumulative eGDR values within the 5th-95th and 1st-99th percentile ranges. The landmark and overall logistic regression analyses were estimated using logistic regression, whereas the percentile-restricted analyses were estimated using fully adjusted Cox proportional hazards models. Cox and logistic regression results are reported as HRs and ORs, respectively, with 95% CIs. Missing covariate data were handled using complete-case analysis. Consequently, the number of participants

included could vary slightly across models according to data availability. Participants with a known final stroke status but an indeterminate first reporting wave were eligible for logistic regression analyses but were excluded from Cox regression and Kaplan–Meier analyses because a valid event time could not be assigned. All statistical analyses were performed using R software, version 4.4.2. Two-sided P values <0.05 were considered statistically significant.

Results

3.1 Participant characteristics

A total of 2,593 participants with prediabetes were included in the final analytic cohort. Their mean age was 62.08 ± 8.67 years, and 1,494 participants (57.6%) were women. The mean cumulative eGDR was 36.13 ± 7.73 $mg \cdot kg^{-1} \cdot min^{-1} \cdot$years. During up to 5 years of follow-up, 204 participants (7.9%) reported incident stroke, whereas 2,389 remained free of stroke. Participants who reported incident stroke were older and had lower cumulative eGDR values than those who remained stroke-free. They also had higher levels of serum creatinine and uric acid and were more likely to be unmarried (**Table 1**). Baseline characteristics according to quartiles of cumulative eGDR are presented in **Table 2**. Participants in the highest cumulative eGDR quartile were younger and had lower levels of triglycerides, uric acid, total cholesterol, and LDL-C, as well as higher HDL-C levels, than those in the lowest quartile.

3.2 Association between continuous cumulative eGDR and incident stroke

The inverse association persisted across progressively adjusted models (**Table 3**). In the fully adjusted model, each 4-unit increment in cumulative eGDR was associated with a 17% lower hazard of incident stroke (HR, 0.83; 95% CI, 0.77–0.90; P < 0.001). The proportional hazards assumption was not violated for cumulative eGDR (P = 0.461) or for the fully adjusted model globally (P = 0.437). Overall, higher cumulative eGDR was consistently associated with a lower hazard of incident stroke among participants with prediabetes.

3.3 Association of cumulative eGDR quartiles with incident stroke

Kaplan–Meier curves showed significant differences in the estimated probability of incident stroke across cumulative eGDR quartiles (log-rank P < 0.001), with participants in the higher quartiles exhibiting lower stroke probabilities during follow-up (**Figure 2**). Consistent results were obtained from the Cox regression analyses (**Table 4** and **Figure 3**). In the fully adjusted model, compared with

Q1, the HRs for incident stroke were 0.81 (95% CI, 0.58-1.14; P = 0.229) for Q2, 0.55 (95% CI, 0.37-0.81; P = 0.003) for Q3, and 0.36 (95% CI, 0.23-0.58; P < 0.001) for Q4. The trend across quartiles was statistically significant (P for trend < 0.001).

3.4 Dose-response relationship between cumulative eGDR and incident stroke

Restricted cubic spline analysis based on the fully adjusted Cox model demonstrated a generally monotonic, approximately linear inverse association between cumulative eGDR and the hazard of incident stroke over the observed exposure range (**Figure 4**). The overall association was statistically significant (P for overall association < 0.001), whereas there was no evidence of departure from linearity (P for nonlinearity = 0.212). These findings were consistent with the inverse association observed when cumulative eGDR was modeled as a continuous linear variable.

3.5 Subgroup and sensitivity analyses

Subgroup analyses showed that the inverse association between cumulative eGDR and incident stroke was generally consistent across strata defined by age, sex, educational level, marital status, residential area, BMI, smoking status, and alcohol consumption status, with HRs per 4-unit increment ranging from 0.72 to 0.94 (**Table 5** and **Figure 5**). No interaction test reached statistical significance (all P for interaction > 0.05).

The primary findings remained generally consistent across sensitivity analyses (**Supplementary Table S1**). In the landmark analysis at 3 years, restricted to participants who remained free of stroke through 2018, each 4-unit increment in cumulative eGDR was associated with lower odds of incident stroke reported between 2018 and 2020 (OR, 0.86; 95% CI, 0.75-0.98; P = 0.025). Logistic regression evaluating incident stroke over the entire follow-up period yielded an OR of 0.82 (95% CI, 0.76-0.89; P < 0.001). The association also remained consistent after restricting the analyses to participants with cumulative eGDR values within the 5th–95th percentiles (HR, 0.85; 95% CI, 0.78-0.93; P < 0.001) and the 1st-99th percentiles (HR, 0.83; 95% CI, 0.77-0.90; P < 0.001).

Discussion

In this prospective cohort study of middle-aged and older Chinese adults with prediabetes, higher cumulative eGDR derived from repeated measurements was associated with a lower hazard of incident stroke. Each 4-unit increment in cumulative eGDR was associated with a 17% lower hazard after multivariable adjustment. The association was approximately linear and remained generally consistent

across prespecified subgroups and sensitivity analyses. These findings extend the evidence linking insulin resistance to cerebrovascular risk by focusing specifically on individuals with prediabetes and by incorporating repeated eGDR measurements over a 4-year exposure period.

Our findings are consistent with previous studies linking lower eGDR to adverse cardiovascular and cerebrovascular outcomes. Among adults with prediabetes, Huo et al. reported that each 1-unit increase in eGDR was associated with a 15% lower hazard of stroke (HR, 0.85; 95% CI, 0.82–0.89) [21]. Given that a 4-unit increment in cumulative eGDR corresponds to a 1-$mg \cdot kg^{-1} \cdot min^{-1}$ difference in average eGDR over the 4-year exposure period, the magnitude of our estimate was broadly comparable to that reported by Huo et al., although direct comparisons should be made cautiously because of differences in exposure assessment and study design. Other studies have similarly reported inverse associations of eGDR with stroke and cardiovascular outcomes across populations with different metabolic profiles, including individuals without diabetes [8, 22]. Collectively, these findings suggest that the adverse vascular consequences associated with insulin resistance may become apparent before the onset of overt diabetes. Emerging evidence further indicates that cumulative eGDR derived from repeated measurements may provide a more stable estimate of long-term insulin resistance burden than a single baseline measurement[12, 17, 23-25]. Most previous studies relied on a single eGDR measurement or included broader metabolic populations. In contrast, the present study focused specifically on individuals with prediabetes and integrated two eGDR measurements across a 4-year exposure period. Although this approach cannot characterize short-term fluctuations or detailed trajectories, it may better represent longer-term exposure than a single assessment.

Several mechanisms may help explain the observed association. Insulin resistance impairs vascular insulin signaling through the phosphatidylinositol 3-kinase/Akt/endothelial nitric oxide synthase pathway, thereby reducing nitric oxide bioavailability and endothelium-dependent vasodilation [26, 27]. Experimental evidence also links cerebrovascular insulin resistance to impaired Akt/eNOS signaling, increased reactive oxygen species generation, and reduced insulin-mediated cerebral vasodilation [28]. In parallel, insulin resistance promotes vascular inflammation, oxidative stress, dyslipidemia, and prothrombotic and proatherogenic changes [29-31]. Critically, these abnormalities may begin during prediabetes, before the development of overt diabetes [32]. Thus, lower cumulative eGDR may serve as a clinically accessible marker of the combined metabolic and vascular abnormalities associated with insulin resistance. Nevertheless, because eGDR is a composite surrogate

derived from glycemic status, central adiposity, and hypertension-related information, the observed association cannot be attributed exclusively to insulin resistance.

The consistency of the findings across multiple analyses supports the robustness of the observed inverse association between cumulative eGDR and incident stroke. The graded reduction in HRs across cumulative eGDR quartiles and the approximately linear spline pattern supported the continuous-exposure findings. The association for Q2 versus Q1 was not statistically significant, whereas lower hazards were evident in Q3 and Q4. This pattern should not necessarily be interpreted as a threshold effect, because categorizing a continuous exposure reduces information and statistical power. The association also remained generally consistent in the landmark, logistic, and percentile-restricted analyses. Taken together, these analyses reduce the likelihood that the main findings were driven by the choice of exposure parameterization, assigned event times, or extreme cumulative eGDR values, although they do not establish causality or demonstrate that increasing eGDR would reduce stroke risk.

This study has several strengths. Its prospective design preserved the temporal ordering between the exposure assessment period and subsequent stroke ascertainment. The analysis focused specifically on individuals with prediabetes, a metabolically heterogeneous population at elevated risk of progression to diabetes and vascular disease. In addition, repeated eGDR measurements provided a time-integrated proxy for insulin resistance-related metabolic burden over the preceding 4 years.

Several limitations should also be considered. First, the observational design precludes causal inference, and residual confounding cannot be excluded. Second, stroke was identified through self-reported physician diagnosis; therefore, outcome misclassification and under-ascertainment were possible, and stroke subtypes could not be examined separately. Third, exact stroke-onset dates were unavailable, and event times were assigned according to the wave of first reporting. Although analyses not requiring assigned event times yielded generally consistent results, some imprecision in the time-to-event estimates remains possible. Fourth, eGDR is a surrogate measure of insulin resistance, and the observed association may partly reflect its components, including hypertension, central adiposity, and glycemic status. Fifth, cumulative eGDR was derived from only two measurements and could not capture shorter-term fluctuations or more complex longitudinal patterns. Sixth, competing-risk analyses could not be performed because sufficiently detailed mortality information was unavailable. Finally, requiring eGDR measurements at both waves and using complete-case analyses may have introduced selection bias, and the findings may not be generalizable beyond middle-aged and older

Chinese adults with prediabetes.

Conclusion

Among middle-aged and older Chinese adults with prediabetes, higher cumulative eGDR derived from repeated measurements was associated with a lower hazard of incident stroke. The association was approximately linear and remained generally consistent across subgroup and sensitivity analyses. Cumulative eGDR may serve as a marker of longer-term insulin resistance burden associated with stroke, but its incremental predictive value and clinical utility require further evaluation.

Declarations

Ethics approval and consent to participate: The China Health and Retirement Longitudinal Study (CHARLS) was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052–11015), and written informed consent was obtained from all participants. The present study was a secondary analysis of de-identified CHARLS data.

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Availability of data and materials: The datasets analyzed in this study are available from the CHARLS repository at https://charls.pku.edu.cn/en/ after registration and approval in accordance with the CHARLS data-use policy.

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Table 1. Baseline characteristics of participants according to incident stroke status

Characteristic	Overall (N = 2,593)	No incident stroke (N = 2,389)	Incident stroke (N = 204)	p value
Age (years)	62.08 ± 8.67	61.86 ± 8.69	64.62 ± 7.99	<0.001
Sex				0.551
Female	1,494 (57.6%)	1,381 (57.8%)	113 (55.4%)	
Male	1,099 (42.4%)	1,008 (42.2%)	91 (44.6%)	
Education				>0.999
Middle school or below	2,381 (91.8%)	2,194 (91.8%)	187 (91.7%)	
High school or above	212 (8.2%)	195 (8.2%)	17 (8.3%)	
Marital status				0.030
Unmarried	337 (13.0%)	300 (12.6%)	37 (18.1%)	
Married/partnered	2,256 (87.0%)	2,089 (87.4%)	167 (81.9%)	
Residence				0.878
Urban	794 (30.6%)	733 (30.7%)	61 (29.9%)	
Rural	1,799 (69.4%)	1,656 (69.3%)	143 (70.1%)	
Smoking				0.904
No	1,915 (73.9%)	1,763 (73.9%)	152 (74.5%)	
Yes	676 (26.1%)	624 (26.1%)	52 (25.5%)	
Drinking				0.940
No	1,753 (67.7%)	1,614 (67.6%)	139 (68.1%)	
Yes	838 (32.3%)	773 (32.4%)	65 (31.9%)	
Cumulative eGDR	36.13 ± 7.73	36.40 ± 7.70	32.91 ± 7.39	<0.001
eGDR in 2011	9.41 ± 2.06	9.47 ± 2.05	8.70 ± 2.08	<0.001
eGDR in 2015	8.66 ± 2.12	8.73 ± 2.12	7.76 ± 1.91	<0.001
Triglycerides (mg/dl)	139.36 ± 87.16	138.50 ± 86.83	149.33 ± 90.58	0.102
Blood Urea Nitrogen (BUN) (mg/dl)	15.75 ± 4.47	15.72 ± 4.45	16.05 ± 4.66	0.333
Creatinine (mg/dl)	0.80 ± 0.22	0.79 ± 0.22	0.85 ± 0.25	0.003
Uric Acid (mg/dl)	4.89 ± 1.36	4.87 ± 1.35	5.16 ± 1.46	0.006
Total Cholesterol (mg/dl)	188.90 ± 36.02	188.66 ± 35.77	191.68 ± 38.73	0.285
HDL Cholesterol (mg/dl)	52.45 ± 12.08	52.54 ± 11.97	51.41 ± 13.26	0.241
LDL Cholesterol (mg/dl)	106.18 ± 29.01	106.00 ± 28.78	108.31 ± 31.57	0.314

Data are presented as mean ± SD or n (%). P values were calculated using Welch's two-sample t test for continuous

variables and Pearson's chi-squared test for categorical variables. All characteristics were assessed at the 2015 analytic baseline unless otherwise indicated. Cumulative eGDR was calculated as the mean of eGDR measured at Wave 1 (2011-2012) and Wave 3 (2015), multiplied by the prespecified 4-year exposure interval. eGDR, estimated glucose disposal rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

Table 2. Baseline characteristics of participants according to cumulative eGDR quartiles

Characteristic	Overall (N = 2,593)	Q1 (N = 649)	Q2 (N = 648)	Q3 (N = 648)	Q4 (N = 648)	p value
Age (years)	62.08 ± 8.67	63.38 ± 8.81	62.92 ± 9.06	60.74 ± 8.16	61.27 ± 8.35	<0.001
Sex						0.618
Female	1,494 (57.6%)	386 (59.5%)	371 (57.3%)	375 (57.9%)	362 (55.9%)	
Male	1,099 (42.4%)	263 (40.5%)	277 (42.7%)	273 (42.1%)	286 (44.1%)	
Education						0.373
Middle school or below	2,381 (91.8%)	596 (91.8%)	605 (93.4%)	589 (90.9%)	591 (91.2%)	
High school or above	212 (8.2%)	53 (8.2%)	43 (6.6%)	59 (9.1%)	57 (8.8%)	
Marital status						0.030
Unmarried	337 (13.0%)	95 (14.6%)	99 (15.3%)	72 (11.1%)	71 (11.0%)	
Married/partnered	2,256 (87.0%)	554 (85.4%)	549 (84.7%)	576 (88.9%)	577 (89.0%)	
Residence						0.015

Characteristic	Overall (N = 2,593)	Q1 (N = 649)	Q2 (N = 648)	Q3 (N = 648)	Q4 (N = 648)	p value
Urban	794 (30.6%)	222 (34.2%)	210 (32.4%)	190 (29.3%)	172 (26.5%)	
Rural	1,799 (69.4%)	427 (65.8%)	438 (67.6%)	458 (70.7%)	476 (73.5%)	
Smoking						<0.001
No	1,915 (73.9%)	513 (79.0%)	478 (73.8%)	485 (75.1%)	439 (67.7%)	
Yes	676 (26.1%)	136 (21.0%)	170 (26.2%)	161 (24.9%)	209 (32.3%)	
Drinking						0.010
No	1,753 (67.7%)	470 (72.6%)	438 (67.6%)	428 (66.0%)	417 (64.4%)	
Yes	838 (32.3%)	177 (27.4%)	210 (32.4%)	220 (34.0%)	231 (35.6%)	
eGDR in 2011	9.41 ± 2.06	6.65 ± 0.84	9.03 ± 1.45	10.43 ± 0.73	11.53 ± 0.57	<0.001
eGDR in 2015	8.66 ± 2.12	6.05 ± 0.79	7.79 ± 1.41	9.80 ± 0.80	11.00 ± 0.64	<0.001
Triglycerides (mg/dl)	139.36 ± 87.16	165.69 ± 97.01	141.04 ± 84.73	138.65 ± 86.77	111.91 ± 69.57	<0.001
Blood Urea Nitrogen (BUN) (mg/dl)	15.75 ± 4.47	15.89 ± 4.48	15.93 ± 4.40	15.49 ± 4.35	15.69 ± 4.62	0.250

Characteristic	Overall (N = 2,593)	Q1 (N = 649)	Q2 (N = 648)	Q3 (N = 648)	Q4 (N = 648)	p value
Creatinine (mg/dl)	0.80 ± 0.22	0.81 ± 0.23	0.80 ± 0.23	0.80 ± 0.23	0.78 ± 0.19	0.077
Uric Acid (mg/dl)	4.89 ± 1.36	5.32 ± 1.39	4.94 ± 1.38	4.81 ± 1.35	4.51 ± 1.20	<0.001
Total Cholesterol (mg/dl)	188.90 ± 36.02	192.16 ± 39.59	190.45 ± 35.85	189.32 ± 33.30	183.66 ± 34.52	<0.001
HDL Cholesterol (mg/dl)	52.45 ± 12.08	49.87 ± 10.36	52.59 ± 12.56	51.70 ± 11.40	55.65 ± 13.10	<0.001
LDL Cholesterol (mg/dl)	106.18 ± 29.01	107.83 ± 32.66	107.05 ± 26.68	107.16 ± 28.12	102.67 ± 27.98	0.004

Data are presented as mean ± SD or n (%). P values were calculated using Welch's one-way analysis of variance for continuous variables and Pearson's chi-squared test for categorical variables. Q1 through Q4 represent increasing quartiles of cumulative eGDR. The quartile ranges were ≤29.233 $mg \cdot kg^{-1} \cdot min^{-1} \cdot$years for Q1, >29.233 to ≤37.616 $mg \cdot kg^{-1} \cdot min^{-1} \cdot$years for Q2, >37.616 to ≤42.723 $mg \cdot kg^{-1} \cdot min^{-1} \cdot$years for Q3, and >42.723 $mg \cdot kg^{-1} \cdot min^{-1} \cdot$years for Q4. All characteristics were assessed at the 2015 analytic baseline unless otherwise indicated. Cumulative eGDR was calculated as the mean of eGDR measured at Wave 1 (2011–2012) and Wave 3 (2015), multiplied by the prespecified 4-year exposure interval. eGDR, estimated glucose disposal rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Q, quartile; SD, standard deviation.

Table 3. Association between continuous cumulative eGDR and incident stroke

Model	HR (95% CI)	P value
Model 1	0.81 (0.75–0.87)	<0.001
Model 2	0.82 (0.76–0.88)	<0.001
Model 3	0.82 (0.76–0.88)	<0.001
Model 4	0.83 (0.77–0.90)	<0.001

HRs and 95% CIs are reported per 4-unit increment in cumulative eGDR. A 4-unit increment in cumulative eGDR corresponds numerically to a 1-mg·kg-1·min-1 difference in average eGDR over the 4-year exposure period. Model 1 was unadjusted. Model 2 was adjusted for age and sex. Model 3 was additionally adjusted for place of residence, educational level, marital status, smoking status, and alcohol consumption status. Model 4 was further adjusted for triglycerides, blood urea nitrogen, serum creatinine, serum uric acid, total cholesterol, HDL-C, and LDL-C. Waist circumference, hypertension status, and HbA1c were not entered separately because they are components of the eGDR formula. BMI, body mass index; CI, confidence interval; eGDR, estimated glucose disposal rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

Table 4. Association between cumulative eGDR quartiles and incident stroke.

Model	Quartile	HR (95% CI)	P value
Model 1	Q1	Reference	-
	Q2	0.77 (0.55–1.08)	0.130
	Q3	0.48 (0.33–0.71)	<0.001
	Q4	0.31 (0.19–0.48)	<0.001
Model 2	Q1	Reference	-
	Q2	0.78 (0.56–1.10)	0.155
	Q3	0.52 (0.35–0.77)	<0.001
	Q4	0.32 (0.21–0.51)	<0.001
Model 3	Q1	Reference	-
	Q2	0.78 (0.56–1.09)	0.152
	Q3	0.52 (0.35–0.77)	<0.001
	Q4	0.32 (0.20–0.51)	<0.001
Model 4	Q1	Reference	-
	Q2	0.81 (0.58–1.14)	0.229
	Q3	0.55 (0.37–0.81)	0.003
	Q4	0.36 (0.23–0.58)	<0.001

HRs and 95% CIs were estimated using Cox proportional hazards regression models, with Q1, the lowest cumulative eGDR quartile, serving as the reference group. Linear trends were evaluated by assigning each participant the median cumulative eGDR value of the corresponding quartile and entering this value as a continuous term in the model. In the fully adjusted model, the P value for trend was <0.001. Model 1 was unadjusted. Model 2 was adjusted for age and sex. Model 3 was additionally adjusted for place of residence, educational level, marital status, smoking status, and alcohol consumption status. Model 4 was further adjusted for triglycerides, blood urea nitrogen, serum creatinine, serum uric acid, total cholesterol, HDL-C, and LDL-C. Waist circumference, hypertension status, and HbA1c were not entered separately because they are components of the eGDR formula. BMI was not included in the primary adjustment models. BMI, body mass index; CI, confidence interval; eGDR, estimated glucose disposal rate; HbA1c, glycated hemoglobin; HDL-C, high-density

lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Q, quartile.

Table 5. Subgroup analyses of the association between cumulative eGDR and incident stroke

Subgroup	Level	N	Events	HR (95% CI)	P value	P for interaction
Age	<60 years	1,018	55	0.77 (0.66–0.88)	<0.001	0.585
	≥60 years	1,555	147	0.85 (0.78–0.93)	<0.001	0.585
Sex	Female	1,480	111	0.83 (0.75–0.92)	<0.001	0.906
	Male	1,093	91	0.85 (0.76–0.95)	0.004	0.906
Education	Middle school or below	2,361	185	0.84 (0.78–0.91)	<0.001	0.291
	High school or above	212	17	0.72 (0.55–0.95)	0.022	0.291
Marital status	Unmarried	330	36	0.94 (0.78–1.15)	0.561	0.180
	Married/partnered	2,243	166	0.81 (0.75–0.88)	<0.001	0.180
Residence	Urban	786	60	0.81 (0.71–0.93)	0.003	0.656
	Rural	1,787	142	0.84 (0.76–0.91)	<0.001	0.656
BMI	<24 kg/m^2	1,425	108	0.77 (0.69–0.86)	<0.001	0.107
	≥24 kg/m^2	1,137	91	0.85 (0.76–0.96)	0.008	0.107
Smoking	No	1,900	151	0.83 (0.76–0.90)	<0.001	0.902
	Yes	673	51	0.83 (0.71–0.97)	0.016	0.902
Drinking	No	1,739	137	0.80 (0.73–0.87)	<0.001	0.184

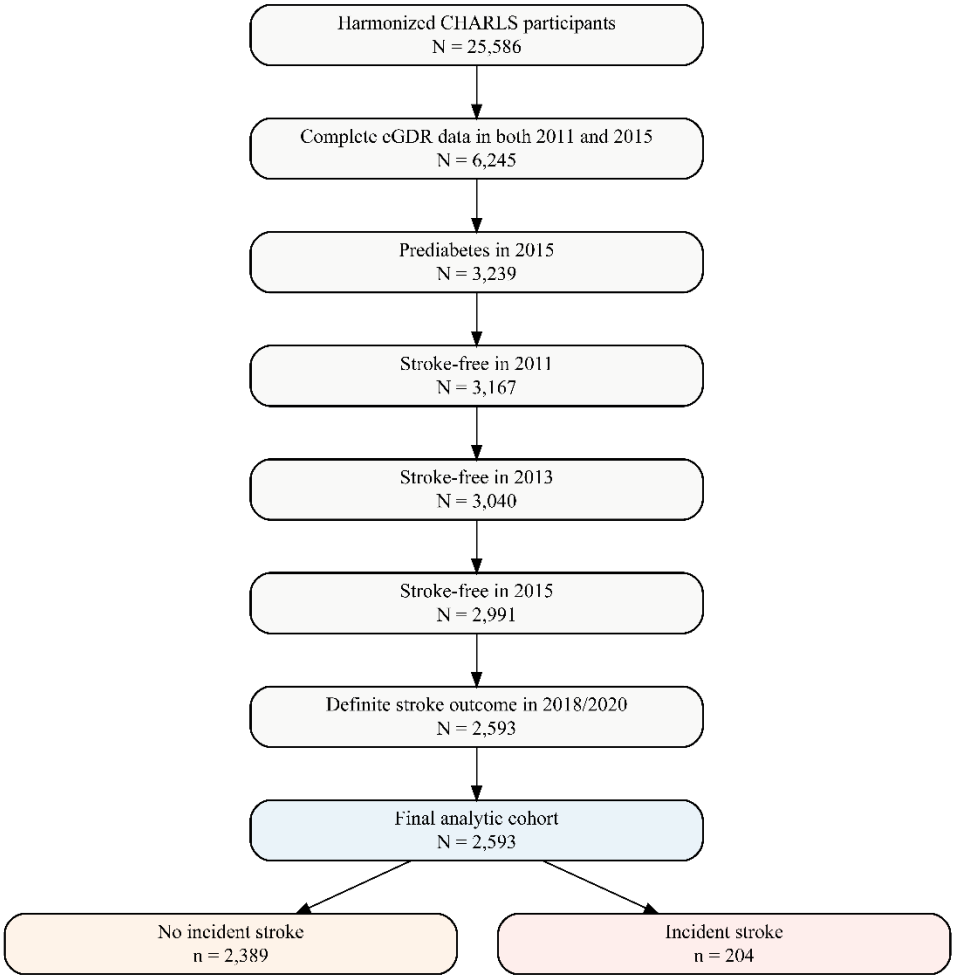
Subgroup	Level	N	Events	HR (95% CI)	P value	P for interaction
	Yes	834	65	0.88 (0.77–1.01)	0.061	0.184

HRs and 95% CIs are reported per 4-unit increment in cumulative eGDR. A 4-unit increment in cumulative eGDR corresponds numerically to a 1-$mg \cdot kg^{-1} \cdot min^{-1}$ difference in average eGDR over the 4-year exposure period. Within-stratum estimates were obtained from Cox proportional hazards regression models adjusted for age, sex, place of residence, educational level, marital status, smoking status, alcohol consumption status, triglycerides, blood urea nitrogen, serum creatinine, serum uric acid, total cholesterol, HDL-C, and LDL-C, except for the variable used to define the corresponding subgroup. BMI, body mass index; CI, confidence interval; eGDR, estimated glucose disposal rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

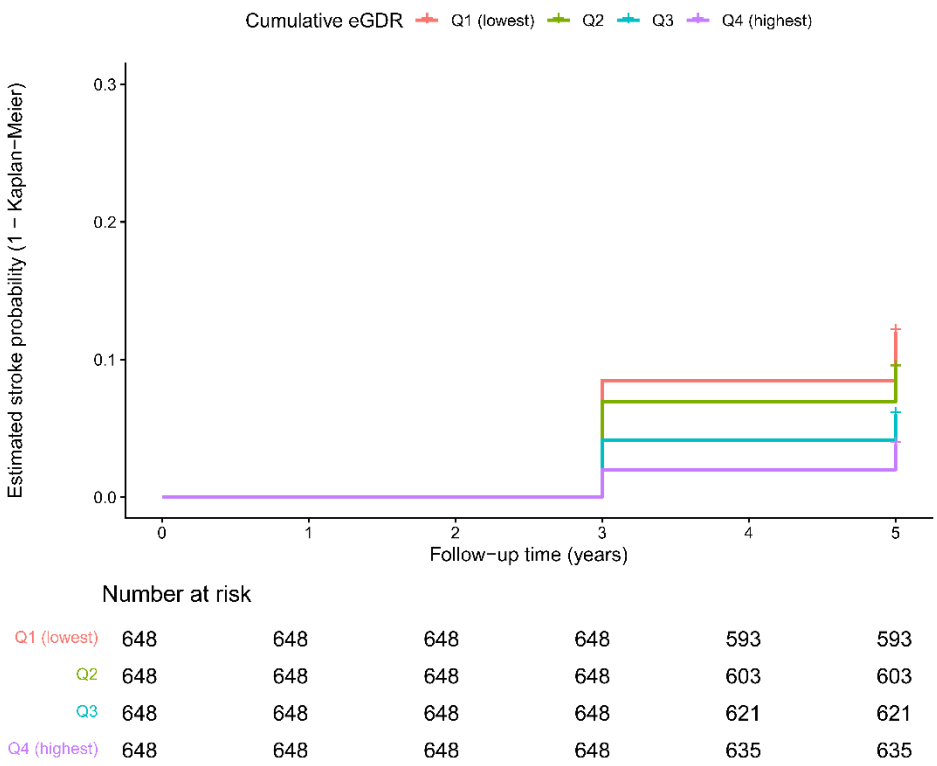
Supplementary Table S1. Sensitivity analyses of the association between cumulative eGDR and incident stroke

Sensitivity analysis	N	Events	Measure	Effect (95% CI)	P value
2018 landmark analysis	2,434	63	OR	0.86 (0.75-0.98)	0.025
Overall follow-up logistic regression	2,574	203	OR	0.82 (0.76-0.89)	<0.001
Restricted to the 5^{th}-95^{th} percentiles of cumulative eGDR	2,313	180	HR	0.85 (0.78-0.93)	<0.001
Restricted to the 1^{st}-99^{th} percentiles of cumulative eGDR	2,521	198	HR	0.83 (0.77-0.90)	<0.001

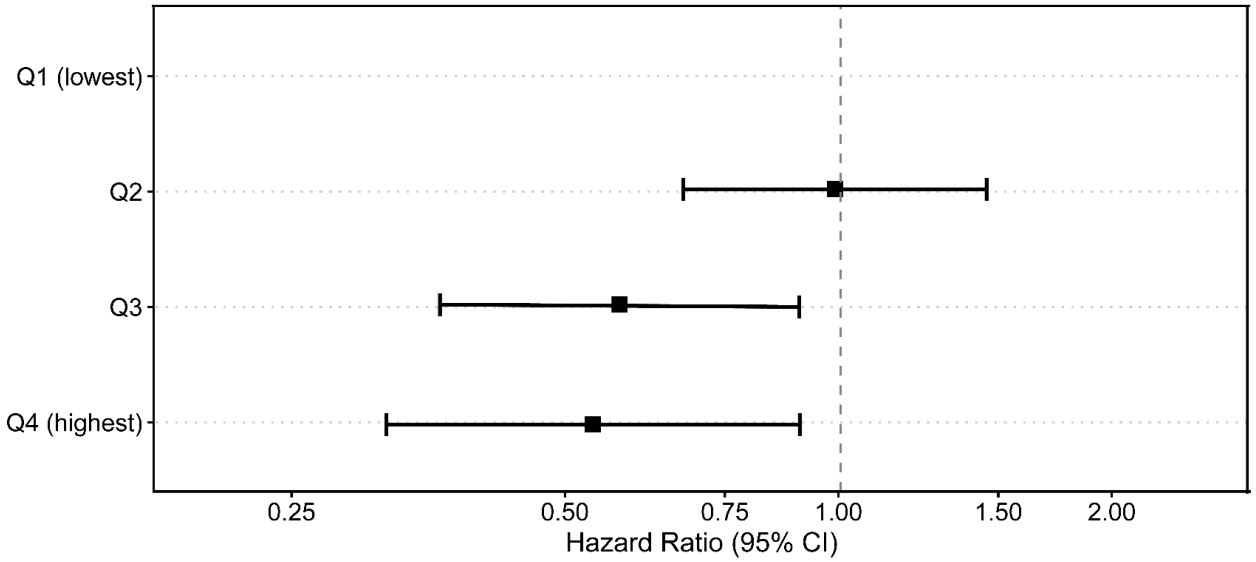
All effect estimates are reported per 4-unit increment in cumulative eGDR. A 4-unit increment in cumulative eGDR corresponds numerically to a 1-$mg \cdot kg^{-1} \cdot min^{-1}$ difference in average eGDR over the 4-year exposure period. The 3-year landmark analysis was restricted to participants who remained free of stroke through Wave 4 (2018) and used logistic regression to evaluate incident stroke first reported between 2018 and 2020. The overall follow-up logistic regression analysis evaluated incident stroke by the end of follow-up without relying on assigned time-to-event information. The percentile-restricted analyses were performed using fully adjusted Cox proportional hazards models after excluding participants with cumulative eGDR values outside the indicated ranges. All models were adjusted for age, sex, place of residence, educational level, marital status, smoking status, alcohol consumption status, triglycerides, blood urea nitrogen, serum creatinine, serum uric acid, total cholesterol, HDL-C, and LDL-C. Analyses were based on complete data for all variables included in the corresponding model. CI, confidence interval; eGDR, estimated glucose disposal rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.



■ **Figure 1. Flowchart of participant selection.** Participants with prediabetes at the 2015 analytic baseline were identified from the Harmonized China Health and Retirement Longitudinal Study dataset. Cumulative eGDR was calculated using eGDR measurements obtained at Wave 1 (2011–2012) and Wave 3 (2015). Participants who reported a physician-diagnosed stroke in 2011, 2013, or 2015 or had insufficient follow-up information to determine final incident stroke status were excluded. The overall outcome cohort included 2,593 participants, of whom 204 reported incident stroke. CHARLS, China Health and Retirement Longitudinal Study; eGDR, estimated glucose disposal rate.



■ **Figure 2. Kaplan–Meier estimates of the cumulative probability of incident stroke according to cumulative eGDR quartiles.** Curves show the estimated cumulative probability of incident stroke across increasing quartiles of cumulative eGDR, with Q1 representing the lowest quartile and Q4 the highest. Numbers at risk are shown below the plot. Differences among quartiles were evaluated using the log-rank test. eGDR, estimated glucose disposal rate; Q, quartile.



■ **Figure 3. Association between cumulative eGDR quartiles and incident stroke.** HRs and 95% CIs are shown for increasing quartiles of cumulative eGDR, with Q1, the lowest quartile, serving as the reference group. Estimates were obtained from the fully adjusted Cox proportional hazards model, which included age, sex, place of residence, educational level, marital status, smoking status, alcohol consumption status, triglycerides, blood urea nitrogen, serum creatinine, serum uric acid, total cholesterol, HDL-C, and LDL-C. CI, confidence interval; eGDR, estimated glucose disposal rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Q, quartile.

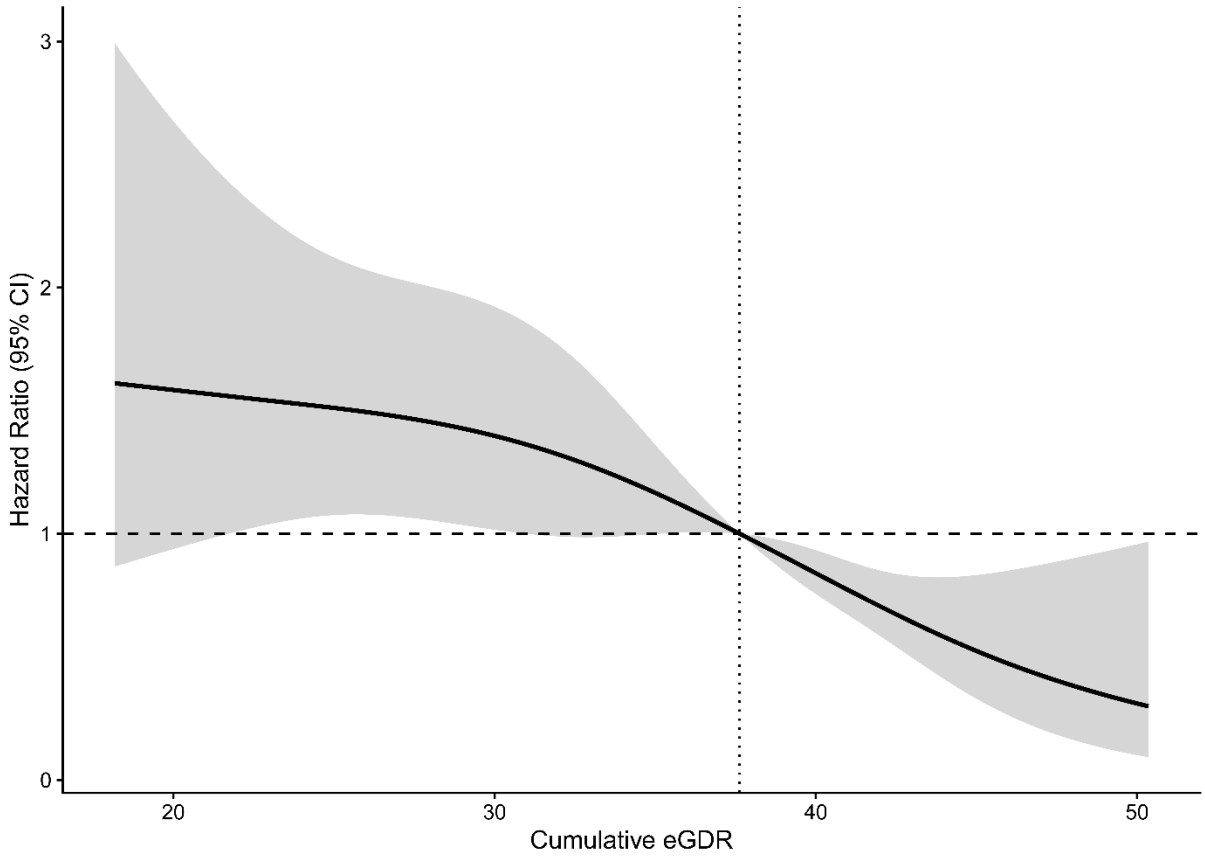
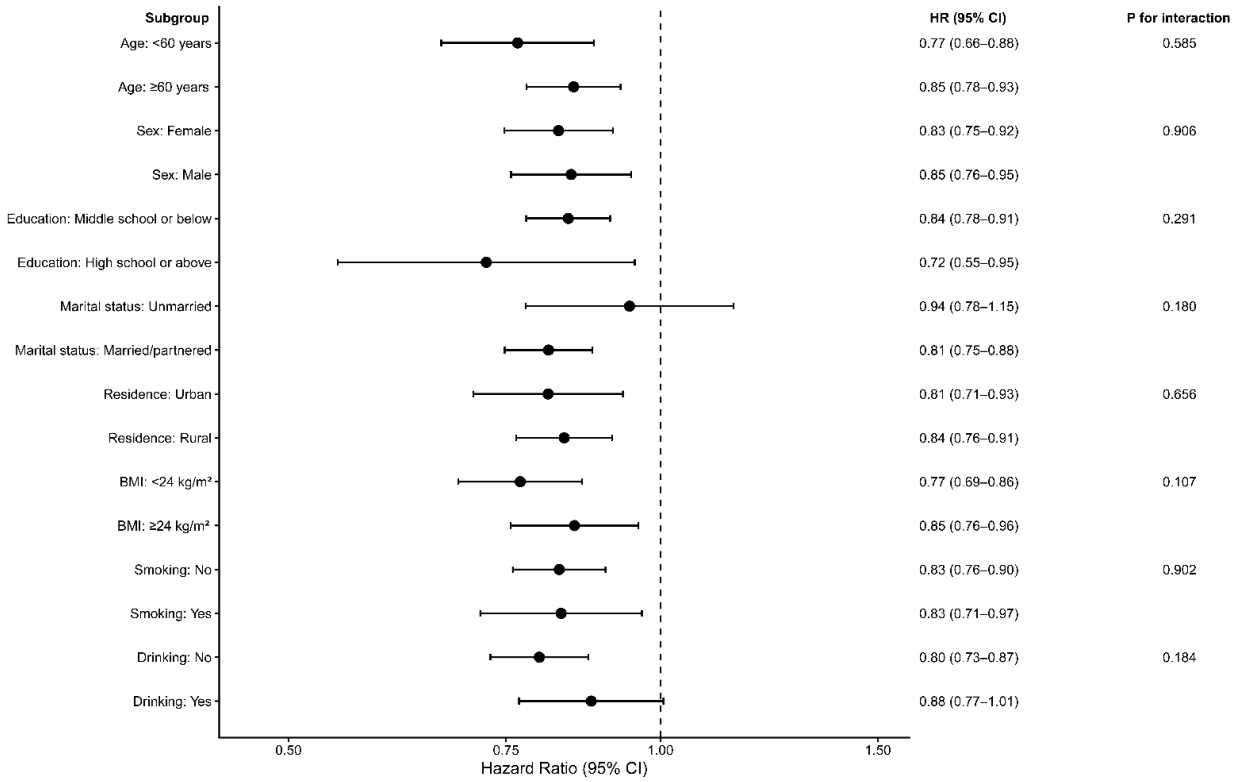


Figure 4. Dose–response association between cumulative eGDR and incident stroke. Restricted cubic spline analysis was performed using the fully adjusted Cox proportional hazards model, with four knots placed at the 5th, 35th, 65th, and 95th percentiles of the cumulative eGDR distribution. The median cumulative eGDR value was used as the reference. The solid line represents the estimated HR, and the shaded area represents the 95% CI. The model was adjusted for age, sex, place of residence, educational level, marital status, smoking status, alcohol consumption status, triglycerides, blood urea nitrogen, serum creatinine, serum uric acid, total cholesterol, HDL-C, and LDL-C. CI, confidence interval; eGDR, estimated glucose disposal rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.



■ **Figure 5. Subgroup analyses of the association between cumulative eGDR and incident stroke.** HRs and 95% CIs are reported per 4-unit increment in cumulative eGDR across subgroups defined by age, sex, educational level, marital status, place of residence, BMI, smoking status, and alcohol consumption status. A 4-unit increment in cumulative eGDR corresponds numerically to a 1-mg·kg^{-1}·min^{-1} difference in average eGDR over the 4-year exposure period. Within-stratum estimates were obtained from Cox proportional hazards regression models adjusted for age, sex, place of residence, educational level, marital status, smoking status, alcohol consumption status, triglycerides, blood urea nitrogen, serum creatinine, serum uric acid, total cholesterol, HDL-C, and LDL-C, except for the variable used to define the corresponding subgroup. BMI was used as a stratification variable but was not included as an adjustment covariate. BMI, body mass index; CI, confidence interval; eGDR, estimated glucose disposal rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

Supplementary Files

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- SupplementaryTableS1.docx