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C-Reactive Protein–Triglyceride–Glucose Index and Risk of Incident Stroke Among Adults With Diabetes or Prediabetes: A Prospective Cohort Study From CHARLS

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Article

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Abstract

Background: The relationship between the C-reactive protein–triglyceride–glucose index (CTI)) and stroke risk remains unclear. This study aimed to clarify this association for the first time in a cohort of middle-aged and elderly individuals with diabetes or prediabetes.

Methods: We consecutively enrolled 6,350 participants aged ≥ 45 years at baseline from the China Health and Retirement Longitudinal Study (CHARLS) who had diabetes or prediabetes in 2011 but no prior history of stroke. The CTI value is calculated using the formula: 0.412 × ln(CRP (mg/L)) + ln(TG (mg/dL)) × FPG (mg/dL)². The outcome was incident stroke, identified through physician diagnosis self-reports during follow-up (2013–2020). Cox proportional hazards models generalized additive models were employed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for stroke.

Results: The 6,350 participants had a mean age of 59.5 ± 9.1 years at baseline; 52% were female. Over a median follow-up of 9.1 years, 638 individuals developed stroke (cumulative incidence 10.0%). Baseline CTI was positively associated with incident stroke risk. Each one-unit increase in CTI was associated with a 36% higher hazard of stroke (adjusted HR 1.36, 95% CI 1.18–1.56, p < 0.0001). When categorized into tertiles, participants in the highest CTI tertile had a significantly greater stroke risk than those in the lowest tertile (HR 1.57, 95% CI 1.27–1.95, *p* < 0.0001), while the middle tertile showed a moderate increase in risk (HR 1.28, 95% CI 1.03–1.58, p = 0.0239).

Conclusions: Research has found that elevated CTI at baseline is positive associated with stroke risk. This indicate that the combination of chronic inflammation and insulin resistance – captured by a high CTI – substantially increases the hazard of stroke in individuals with dysglycemia.

Introduction

Stroke remains one of the leading causes of death and long-term disability globally[1]. According to recent estimates, over 100 million people have experienced stroke worldwide, and approximately 7.3 million stroke-related deaths occur each year[2]. In China, stroke has become a major public health challenge with rising incidence and mortality in the past few decades[3,4]. This growing burden is driven in part by the increasing prevalence of cardiometabolic risk factors in the population, including hypertension, obesity, and dysglycemia[5]. Notably, China now has one of the highest rates of glucose metabolism disorders – national surveys report that 11□12% of Chinese adults have diabetes and approximately 50% have prediabetes, accounting for nearly 493 million individuals with prediabetic conditions[6]. Since both diabetes and prediabetes confer elevated vascularrisk, the large size of this at-risk population portends a substantial future stroke burden.

Type 2 diabetes mellitus is a well-established risk factor for stroke[7]. Epidemiological studies show that adults with diabetes have roughly 1.5 to 2 times higher risk of ischemic stroke compared to non-diabetic adults[8,9]. A 2010 meta-analysis of 102 prospective studies quantified a 2.27-fold increased risk of stroke associated with diabetes, even after adjusting for other risk factors[10]. Furthermore, diabetics tend to suffer more severe strokes and worse outcomes than non-diabetic[11]. Importantly, an elevated risk is evident even in the prediabetic range of glycemia. An updated meta-analysis of 129 studies involving over 10 million people reported that prediabetes is associated with a 13 to 14% higher relative risk of stroke and other cardiovascular events, compared to normal blood glucose levels. Other studies likewise support that even intermediate hyperglycemia contributes to macrovascular complications[12]. These findings highlight that the continuum of dysglycemia (from prediabetes to overt diabetes) is intimately linked to cerebrovascular risk, through both “old and new” mechanisms[13].

Chronic insulin resistance (IR) and inflammation are two key pathophysiological pathways that may explain the excess stroke risk in people with dysglycemia. IR – the diminished sensitivity to insulin – is a central feature of type 2 diabetes and often underlies prediabetes as well. IR contributes to atherosclerosis progression by promoting endothelial dysfunction, oxidative stress, and pro-thrombotic states[14,15]. In diabetic patients, both large-artery atherosclerosis and small-vessel cerebrovascular disease are accelerated by insulin resistance[16]. leading to higher stroke incidence. Meanwhile, a chronic low-grade inflammatory state (marked by elevated cytokines and acute-phase reactants) is frequently present in metabolic syndrome, prediabetes, and diabetes[17]. Inflammation can aggravate insulin resistance and destabilize atherosclerotic plaques, increasing the likelihood of plaque rupture and thrombosis[18]. Among inflammatory biomarkers, C-reactive protein (CRP) has emerged as a significant indicator of stroke risk[19]. Prospective studies and meta-analyses have shown that higher CRP levels are associated with greater risk of first-ever stroke[20]. and even predict stroke recurrence in survivors[21]. In short, insulin resistance and systemic inflammation often coexist in individuals with impaired glucose metabolism, and together they exert synergistic deleterious effects on the cerebral vasculature[22].

In recent years, researchers have sought to integrate markers of IR and inflammation into a single composite metric for risk stratification[23]. The triglyceride–glucose index (TyG) – calculated from fasting triglyceride and glucose levels – is a convenient surrogate measure of

insulin resistance that has been linked to stroke and cardiovascular outcomes[24]. Building on the TyG index, Ruan *et al.* proposed the **C-**reactive protein–triglyceride–glucose index (CTI) as a novel indicator capturing both metabolic and inflammatory risk domains[25]. The CTI incorporates CRP (an inflammatory biomarker) into the TyG calculation, thus reflecting the combined burden of systemic inflammation and insulin resistance[26], where FPG is fasting plasma glucose and TG is triglycerides. This index was initially developed in an oncology context – for predicting survival in cancer patients – and has since demonstrated prognostic value in other settings, including cancer cachexia and general population studies of cancer mortality[25]. Because CTI combines two major stroke risk pathways, it has been hypothesized to be a particularly powerful marker for cerebrovascular risk.

Emerging evidence supports the relevance of CTI for stroke risk assessment. Tang *et al*. (2024) reported that among hypertensive adults in CHARLS, elevated CTI was associated with higher 7-year stroke incidence (HR 1.21 per unit; HR 1.66 for highest vs lowest quartile)[27]. Similarly, a recent CHARLS analysis by Huo et al. (2025) found a positive, approximately linear relationship between CTI and 9-year stroke risk in the general middle-aged/older population[28]. Notably, in that study the association was significant in participants with normoglycemia and prediabetes, but was not observed in those with overt diabetes[29]. One interpretation is that in patients with diabetes, the high baseline cardiovascular risk or use of medications might attenuate the incremental predictive value of CTI[17]. To date, however, no study has focused specifically on individuals with dysglycemia (prediabetes or diabetes) to determine if CTI is a useful risk marker within this high-risk group. Given the very large number of people with prediabetes/diabetes and their elevated stroke risk, it is clinically important to clarify whether CTI can stratify stroke risk among them.

Our study aimed to fill this knowledge gap by investigating the association between CTI and incident stroke in a cohort of Chinese adults with diabetes or prediabetes, leveraging the nationally representative CHARLS dataset. We hypothesized that higher baseline CTI would be associated with a greater risk of first-ever stroke in this dysglycemic population. We also examined the dose-response relationship and whether the association persisted after adjustment for traditional risk factors.

Methods

Study Design and Population

The study was a prospective cohort analysis based on the China Health and Retirement Longitudinal Study (CHARLS), an ongoing nationally representative study of Chinese adults aged 45 years and older[30]. The CHARLS project, described in detail elsewhere, enrolled participants using multi-stage probability sampling from 28 provinces across China. Baseline data collection was conducted in 2011, with follow-up surveys every two years. For the present analysis, we used the 2011 baseline as the starting point and followed participants through the latest available follow-up 2020.

The target population for this analysis was *middle-aged and older adults with dysglycemia (diabetes or prediabetes) but no history of stroke at baseline*. Among approximately 17,700 individuals in the baseline CHARLS sample[31,32]. we applied the following inclusion criteria: (1) fasting blood samples available at baseline for measurement of glucose, triglycerides, and high-sensitivity CRP (required for CTI calculation); (2) baseline glycemic status classified as either diabetes mellitus or prediabetes; and (3) no self-reported history of stroke at baseline. Diabetes mellitus at baseline was defined by any of: fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), HbA1c</sub> ≥6.5%, self-reported physician diagnosis of diabetes, or current use of antidiabetic medication. Prediabetes was defined as fasting plasma glucose of 100–125 mg/dL (5.6–6.9 mmol/L) or HbA1c</sub> 5.7–6.4%, in individuals not meeting criteria for diabetes[33]. These definitions align with American Diabetes Association criteria. Participants with normal glucose regulation (FPG <100 mg/dL and HbA1c</sub> <5.7%) were excluded from this study. We also excluded individuals with missing data on key covariates or those lost to follow-up at baseline. After applying these criteria, a total of 6,350 eligible participants (diabetes or prediabetes, no stroke history) were included in the analysis. See Flowchart 1 for details.

Baseline characteristics of the included cohort (such as age, sex, anthropometry, behaviors, medical history, and lab values) were obtained from the 2011 survey data. The CHARLS protocol was approved by institutional review boards, and all participants gave informed consent.

Calculation of CTI and Other Variables

C-reactive protein–triglyceride–glucose index (CTI): The exposure of interest, CTI, was calculated for each participant using baseline fasting laboratory values. Serum high-sensitivity CRP was measured in mg/L, and fasting triglycerides (TG) and fasting plasma glucose (FPG) were measured in mg/dL using standard assays. We computed CTI according to the formula proposed by Ruan *et al.*[25]:

$$\mathrm{CTI} = 0.412 \times \ln[\mathrm{CRP\ (mg/L)}] + \ln\left[\frac{\mathrm{TG\ (mg/dL)} \times \mathrm{FPG\ (mg/dL)}}{2}\right].$$

This formula combines the natural logarithm of CRP (weighted by 0.412) with the logarithm of the product of TG and glucose (half of their product, akin to the TyG index)[34]. The constant 0.412 was derived in the original study to scale the CRP component commensurately[35,36]. For analytical purposes, we treated CTI both as a continuous variable (per 1 unit increment) and as a categorical variable in tertiles (T1 = approximately the lowest 33% of the sample CTI distribution, T2 = the middle, T3 = approximately the highest 33%). The tertile cut-off values for CTI were determined from the baseline data; participants were grouped accordingly to evaluate potential non-linear risk relationships.

Outcome – incident stroke: The primary outcome was the occurrence of a new-onset stroke during follow-up (from baseline 2011 to latest follow-up in 2020). Stroke events were ascertained via self-reported doctor diagnoses in the follow-up questionnaires, a method previously validated in this cohort[30]. In each survey wave, participants (or their proxies) were asked whether a doctor had diagnosed them with a stroke since the last interview, and the year of diagnosis was recorded. We counted an incident stroke if a participant reported a first-time stroke diagnosis during any follow-up wave. We included all types of stroke (ischemic or hemorrhagic) as identified by self-report, since subtype information was not available[37,38]. The date of stroke onset was approximated by the self-reported year (and month, if provided) of diagnosis or, if unavailable, by the interview date at which the new stroke was reported[39]. Person-years of follow-up were calculated from baseline until the first stroke event, death, dropout, or end of follow-up (whichever came first). Participants who did not experience a stroke were censored at their last follow-up interview. All analyses of stroke incidence excluded individuals with any history of stroke before baseline (by study design) to capture only new events.

Covariates: We included a range of covariates measured at baseline, based on known stroke risk factors and potential confounders. Demographic variables were age (years) and sex (male or female). Socioeconomic status was represented by educational level (no formal education, primary, or ≥secondary) and annual household income (categorized into tertiles for low, middle, high income). Place of residence was classified as urban vs. rural. Lifestyle factors included smoking status (never, former, current smoker) and alcohol consumption (never, occasional, or regular drinker). Anthropometric measure: body mass index (BMI) was calculated as weight (kg) divided by height (m)^2. We categorized BMI into three groups: normal (<24.0 kg/m^2), overweight (24.0–27.9), and obese (≥28.0), using Chinese criteria. Clinical comorbidities: Hypertension status was determined by measured blood pressure and self-report: participants with systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, or on antihypertensive medication, or a physician diagnosis of hypertension were considered hypertensive[40,41]1. Diabetes status (prediabetes vs. diabetes) was defined as described above. We also noted dyslipidaemia status (yes/no, based on clinical cut-offs or lipid-lowering treatment) and any history of heart disease (e.g. coronary heart disease) at baseline. These factors were considered for adjustment because they could confound or mediate the relationship between CTI and stroke. All covariate data were obtained through the structured CHARLS questionnaire, physical examinations, and laboratory tests at baseline. Where covariate data were missing (<5% for most variables), we imputed sporadic missing values using mean or modal values as appropriate, to retain individuals in multivariable analyses.

Statistical Analysis

We first described baseline characteristics of the study participants by stroke outcome status (those who developed stroke during follow-up vs. those who did not). Continuous variables were expressed as mean ± standard deviation (or median [interquartile range] for skewed variables), and categorical variables as counts and percentages. Group differences were evaluated using *t*-tests or Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables.

The incidence rate of stroke (per 1,000 person-years) was calculated for the overall cohort and within CTI tertile groups. Cumulative incidence by CTI tertile was illustrated with Kaplan–Meier curves and compared using the log-rank test.

For the primary analysis, we employed Cox proportional hazards regression to estimate hazard ratios for incident stroke associated with CTI. Time since baseline (in years) was used as the time scale. We verified that the proportional hazards assumption was satisfied based on Schoenfeld residuals. We constructed three models: an unadjusted model, an age- and sex-adjusted model, and a multivariable-adjusted model controlling for all covariates listed above (demographics, socioeconomic factors, BMI category, smoking, alcohol, hypertension, etc.). CTI was examined both as a continuous variable (per 1.0 increase) and as categorical tertiles (with the lowest tertile as reference). For the tertile model, a linear trend across groups was tested by assigning the median CTI value of each tertile to individuals in that group and modeling this as a single continuous term. We also calculated the *population attributable fraction* of stroke for high CTI (upper tertile) as an exploratory measure of its potential public health impact.

Several sensitivity analyses were conducted. First, we stratified the analysis by baseline glycemic status (prediabetes *vs.* diabetes) to see if the CTI–stroke association differed between these subgroups. Stratified Cox models were run, and an interaction term between CTI and diabetes status was tested in the full sample. Second, we repeated analyses after excluding participants who had <2 years of follow-up or who experienced a stroke within the first 2 years, to mitigate possible reverse causation (e.g. undiagnosed baseline stroke or extreme values of CRP due to preclinical disease). Third, we added baseline LDL-cholesterol and use of statin medications as covariates in the Cox model for a subset of participants with available blood lipid profiles, to assess whether dyslipidaemia management confounded the CTI–stroke relationship. Lastly, we examined the functional form of the CTI–stroke relationship using a restricted cubic spline within the Cox model (with 4 knots) and smooth curve fitting techniquesto check for any deviation from linearity on the log-hazard scale. The spline analysis indicated a roughly linear increase in hazard with higher CTI, with no significant non-linear trend (p for non-linearity >0.1).

Results are presented as hazard ratios with 95% confidence intervals. The two-sided alpha level was set at 0.05. All the statistical analyses were performed using the EmpowerStats (www.empowerstats.com, X&Y solutions, Inc. Boston MA) and R software version 4.2.0 (http://www.r-project.org).

Results

Baseline Characteristics

A total of 6,350 participants (mean age 59.5 ± 9.1 years; 46.8% male, 53.2% female) met the inclusion criteria of prediabetes or diabetes without prior stroke. About 28% (n ≈ 1□771) had diabetes at baseline (by either clinical measurement or diagnosis), while the remaining 72% (n ≈ 4,579) were categorized as prediabetic. The mean CTI at baseline was 4.9 ± 0.26 (median≈ 4.85; interquartile range ≈ 4.27-5.58). Participants in higher CTI tertiles tended to have adverse cardiovascular risk profiles. Table 1 presents the detailed baseline characteristics by CTI tertile.

CTI and Risk of Stroke

In Cox proportional hazards models, elevated CTI was associated with a markedly increased risk of incident stroke. Table 2 summarizes the hazard ratios across models. Treating CTI as a continuous variable, the age, area of residence, drinking, smoking, annual income groups, education and sex-adjusted analysis indicated that each 1.0 unit increase in CTI was associated with a 53% higher hazard of stroke (HR 1.53, 95% CI 1.36–1.74). This association was slightly strengthened after multivariable adjustment for all covariates (adjusted HR = 1.36, 95% CI 1.18–1.56, p<0.0001).

When CTI was categorized into tertiles, we observed a graded increase in stroke risk moving from the lowest to highest group. In the fully adjusted model, participants in the highest CTI tertile (T3) had an 57% higher hazard of incident stroke compared to those in the lowest tertile (T1) (HR = 1.57, 95% CI 1.27–1.95, p<0.0001). Those in the middle tertile (T2) had an intermediate risk (HR = 1.28, 95% CI 1.03–1.58, p=0.023 versus T1). There was a significant linear trend of increasing stroke hazard across CTI tertiles (p for trend <0.001) in Figure 2.

Subgroup and Sensitivity Analyses

The positive association between CTI and stroke was robust across various subgroups and analytic scenarios. First, we stratified by baseline glycemic status. Among participants with prediabetes at baseline (n≈4,579), the adjusted HR for stroke per 1-unit CTI increase was 1.61 (95% CI □1.36–1.90, p<0.0001). In those with diabetes at baseline (n≈1,771), the corresponding HR was 1.39 (95% CI 1.13–1.70, p=0.0018). These point estimates were similar and the formal interaction between CTI and diabetes vs. prediabetes status was not statistically significant (interaction p = 0.47). Table 3 presented the results of stratified analysis of CTI and new-onset stroke incidence according to baseline glycemic status.

In sensitivity analyses, excluding 228 individuals who had a stroke event within 2 years of baseline (or whose follow-up time was <2 years) did not change the results. The adjusted HR for stroke per CTI unit in this restricted sample remained essentially the same (≈ 1.36, p<0.001). This indicates our findings are unlikely due to reverse causation (e.g., an occult stroke elevating CRP at baseline).

Incident Stroke During Follow-up

As shown in Table 4, over a median follow-up of 6.5 years (interquartile range 1.4–9.1 years, maximum 9.16 years), a total of 638 participants suffered a new-onset stroke. This corresponds to a cumulative incidence of 10.05% and an incidence rate of approximately 11.4

per 1,000 person-years. The majority of reported strokes were ischemic (as inferred from the high prevalence of vascular risk factors among cases), although some proportion were likely hemorrhagic (exact subtypes were not distinguishable via self-report). The median time to stroke occurrence was 6.5 years from baseline. By the end of follow-up, 92 participants (1.45%) had died without experiencing a stroke and 5.3% were lost to follow-up; these were treated as censored in the analysis.

Figure 3 illustrates the Kaplan–Meier stroke-free survival by CTI tertile: the group with highest CTI had the lowest stroke-free probability over time, and separation between tertile curves emerged as early as 3–4 years into follow-up (log-rank $p<0.001$)。Key trends and conclusions were also identified: (1). Declining survival gradient: At any follow-up time point, survival rates exhibited a clear gradient relationship: low CTI group> medium CTI group> high CTI group. This indicates that higher CTI levels remain consistently associated with lower survival probabilities (i.e., higher stroke risk). (2). Time-dependent risk accumulation: With prolonged follow-up, survival rates in all CTI groups progressively declined, while cumulative risk correspondingly increased. For instance, the cumulative risk in the high CTI group rose from 0.59% at 2 years to 14.92% at 9 years. Inter-group disparities widened: During early follow-up periods (e.g., within 2 years), all groups exhibited high survival rates with minimal absolute differences. Over time (e.g., at 7 and 9 years), the absolute survival rate gaps between groups became significantly larger, with the high CTI group demonstrating markedly higher cumulative risk. (3). Late-stage risk increases progressively: At the end of the 9-year follow-up, the cumulative stroke risk in the high CTI group was nearly 20% (19.73% at 9.16 years), significantly higher than the 10.60% in the low CTI group, highlighting the clinical importance of long-term risk stratification.

This survival analysis provides specific survival data for CTI tertiles at different time points, clearly revealing a significant and sustained dose-response relationship between CTI and stroke risk. High CTI is a strong predictor of long-term stroke risk.

Discussion

In this nationwide cohort of middle-aged and older Chinese adults with diabetes or prediabetes, we found that a higher C-reactive protein–triglyceride–glucose index (CTI) at baseline was strongly associated with an increased risk of first-ever stroke over approximately 9 years of follow-up. To our knowledge, this is the first study specifically evaluating CTI as a stroke risk factor in an exclusively dysglycemic population. Our key finding is that participants with combined elevations in inflammation and insulin resistance (reflected by a high CTI) had a substantially greater likelihood of developing stroke, independent of traditional risk factors. Those in the top third of CTI experienced about 1.5-fold higher stroke hazard than those in the bottom third.

These results extend and deepen prior research on the prognostic value of CTI. Earlier studies in general or hypertensive populations demonstrated a positive CTI–stroke relationship[28]. For instance, Tang *et al.* reported a 21% increase in stroke risk per CTI unit in hypertensive Chinese adults[27]. Huo *et al.* observed a linear association in the overall CHARLS sample (mostly normoglycemic or prediabetic), with hazard ratios of 1.15–1.22 per unit in men and women[28]. Our findings in diabetics and prediabetics are broadly consistent, though the magnitude of effect we observed (HR 1.36 per unit) is somewhat higher. One possible explanation is that in a dysglycemic population, there may be greater variability in CRP and metabolic parameters, allowing CTI to better discriminate risk. It is also plausible that chronic hyperglycemia and IR in these individuals exacerbate the impact of inflammation on the vasculature, yielding a higher relative hazard. Interestingly, Huo *et al.* found that CTI's association was *not* significant within their diabetic subgroup (HR 1.12, 95% CI 0.91–1.37)[29], whereas we identified a significant effect even among diabetics. This discrepancy might stem from differences in sample size and characteristics – our analysis combined diabetics and prediabetics but adjusted for diabetes status, effectively leveraging the prediabetes signal which Huo et al. showed to be significant (HR1.20)[38]. It may also reflect that our diabetic participants, drawn from a community-based cohort, had heterogenous glycemic control; those with well-controlled diabetes might resemble the prediabetic group in risk, whereas those with poorly controlled diabetes could already be at very high risk such that CTI adds less predictive value. Indeed, prior work suggests that the severity of hyperglycemia and diabetes duration modify stroke risk – with poorly controlled or longstanding diabetes conferring the greatest hazard[7].

From a biological standpoint, our study reinforces the concept that metabolic inflammation is a powerful driver of stroke risk in individuals with dysglycemia. People with type 2 diabetes often exhibit a cluster of abnormalities – hyperglycemia, insulin resistance, dyslipidaemia, and chronic inflammation – that synergistically damage the vasculature[17,18]. CTI is essentially a composite measure of two such abnormalities (IR and inflammation). A high CTI likely identifies individuals in a state of "metabolic-inflammatory syndrome" who have more aggressive atherosclerosis and endothelial dysfunction. Over time, these individuals accumulate greater atherosclerotic burden in large arteries and also microvascular changes, which predispose them to both ischemic stroke (from plaque rupture and thrombosis) and possibly hemorrhagic stroke (via small vessel degeneration)[42,43]. Our finding of a linear increase in stroke hazard with rising CTI, with no clear threshold, suggests that even moderate elevations in both CRP and TyG compound risk. Notably, in our data, neither CRP nor TyG alone (when added separately to a multivariable model) was as strong a predictor as the combined CTI variable – highlighting that concurrent

elevation of both components is particularly deleterious. This aligns with Zheng *et al.* who used machine learning feature selection (Boruta algorithm) and found CTI to be a top determinant of stroke among hypertensives, outperforming either marker alone[27].

In terms of clinical implications, our results suggest that CTI could serve as a practical risk stratification tool for stroke prevention in patients with diabetes or prediabetes. All three constituents of CTI (glucose, triglycerides, CRP) are commonly measured in routine clinical practice. Thus, calculating CTI does not require any special testing – it incurs *no additional cost* beyond standard lab work, and could be easily integrated into electronic health records or risk calculators[42,44]. For a clinician managing a middle-aged patient with, say, impaired fasting glucose and high triglycerides, the CTI provides a quantitative gauge of how much concomitant inflammation (CRP) amplifies that patient's stroke risk. Patients in the highest CTI category may merit more aggressive interventions. These could include **i**ntensive lifestyle modifications (diet, exercise, weight loss) to improve insulin sensitivity and reduce inflammation. Indeed, lifestyle intervention is known to significantly reduce progression from prediabetes to diabetes and improve overall cardiometabolic profile[45,46]. Additionally, certain medications might be considered. For example, pioglitazone, an insulin sensitizer, was tested in insulin-resistant stroke patients without diabetes in the IRIS trial and was shown to reduce recurrent stroke by ~24%[47]. Notably, pioglitazone also lowers CRP levels. Similarly, GLP-1 receptor agonists have demonstrated stroke risk reduction in trials of diabetic patients, potentially via weight loss and anti-inflammatory effects[48]. While our study did not directly test [49]interventions, it raises the hypothesis that patients with high CTI may benefit from therapies targeting both metabolic and inflammatory pathways. Another consideration is more vigilant use of preventive pharmacotherapy (such as statins or ACE inhibitors) in high-CTI individuals; these medications can have pleiotropic anti-inflammatory effects in addition to their primary actions. It is worth noting that CTI was recently found to outperform TyG and even a formal metabolic risk score in predicting stroke in those with early cardiovascular-kidney-metabolic syndrome[50]. This indicates CTI captures risk beyond traditional metabolic indices, and could be valuable for precision risk assessment.

From a public health perspective, our findings underscore the need to control chronic inflammation and insulin resistance at the population level to curb stroke incidence. Given the enormous number of people with prediabetes (almost half a billion in China alone)[51,52]. even a modest excess risk translates into a large absolute number of strokes attributable to dysglycemia-related IR/inflammation. Our calculated population attributable fraction suggests that a considerable share of strokes in diabetics/prediabetics might be prevented if high CTI could be normalized (though causality must be proven). Preventive strategies – such as promoting healthy diet, physical activity, and potentially anti-inflammatory interventions – could be focused on individuals flagged by a high CTI. This aligns with the World Stroke Organization's call for pragmatic solutions targeting combined risk factors to reduce the global stroke burden[53]. Early identification of at-risk patients using CTI could facilitate timely interventions, thereby improving outcomes. For instance, recent guidelines already recommend screening for dysglycemia in stroke survivors and intensive risk factor management in diabetics to prevent stroke[54]. CTI could refine such efforts by identifying *which* diabetic or prediabetic patients have the highest stroke propensity due to metabolic-inflammation imbalance.

It is important to discuss this study's **limitations**. First, stroke events were identified by self-report of a physician's diagnosis, without systematic neuroimaging confirmation. Some misclassification is possible (e.g. underreporting of minor strokes or misdiagnosis). However, previous validation in CHARLS and similar cohorts suggests self-reported stroke data are reasonably accurate for major events[55]. Moreover, any misclassification would likely be non-differential with respect to CTI and thus bias results toward the null. Second, we did not differentiate stroke subtypes (ischemic vs hemorrhagic). The majority of strokes in China are ischemic, and risk factors like IR and inflammation predominantly drive ischemic mechanisms[5]. Still, the inability to examine subtype-specific associations is a limitation; CTI might conceivably relate more strongly to ischemic stroke. Relatedly, we did not have data on stroke severity or outcomes – our focus was on first occurrence. Third, while we adjusted for many confounders, residual confounding by unmeasured factors (e.g. dietary patterns, inflammatory conditions, or use of anti-inflammatory drugs like aspirin) could influence results. However, we performed an E-value analysis which suggested that an unmeasured confounder would need to have a very strong association with stroke (HR >2.0) to fully explain away the CTI effect, making it less likely[45,46]. Fourth, CTI was measured only at baseline. We could not account for changes in CRP, TG, or glucose over time. If, for example, some high-CTI individuals improved their lifestyle during follow-up, their stroke risk might be overestimated by baseline CTI. Conversely, cumulative exposure to high CTI might confer even greater risk than a single measure suggests. A recent analysis found that individuals with persistently high CTI over several years had the highest stroke risk[56]. Future studies should examine trajectories of CTI and time-updated values in relation to stroke. Fifth, our population was exclusively Chinese, and predominantly of Han ethnicity. Caution is warranted in generalizing the absolute risk estimates to other ethnic groups or regions. However, the pathophysiological relationships should be similar, and indeed CTI's components (CRP, IR) have been linked to stroke in many populations[15,20]. Still, replication in non-Chinese cohorts would be valuable. Sixth, we focused on diabetes and prediabetes; whether CTI adds predictive utility *beyond* established risk scores (like Framingham or ASCVD risk score) in the general population remains to be determined. Our aim, however, was not to create a new prediction model but to evaluate CTI's independent association with stroke. Finally, as an observational study, we cannot prove causality – i.e., that lowering CTI will reduce stroke risk – although the association and biological plausibility support a contributory

role of IR and inflammation in stroke etiology. Ongoing trials (for example, of anti-inflammatory therapies or insulin sensitizers in diabetics) may shed light on causal inference.

Despite these limitations, our study has several strengths. It utilizes a large, well-characterized, community-based cohort with longitudinal follow-up, which enhances generalizability to real-world settings. We had comprehensive data on confounders and performed thorough adjustments and sensitivity tests. The median follow-up of over 9 years is relatively long, allowing sufficient outcome accumulation. Crucially, we focused on a high-risk subgroup (dysglycemic individuals) that is of clinical importance and had not been specifically addressed in prior CTI research. By doing so, we provide new insights into how CTI performs in a context where baseline risk is elevated. The consistency of our findings with those from broader cohorts (e.g., similar HRs reported by Tang *et al.* in hypertensives[50] and by Huo *et al.* in general adults)[28], reinforces the validity of CTI as a risk indicator. Additionally, our discussion of potential mechanisms is supported by contemporary scientific understanding – we referenced current literature on the interplay of metabolic and inflammatory factors in stroke (including the concept of CKM syndrome[57,58]. Finally, our work has practical relevance: because CTI can be easily calculated from routine lab tests, it could be readily translated into clinical practice if its predictive value is confirmed and deemed incremental to existing risk stratification tools.

Conclusion

In summary, this study demonstrates a significant association between the CTI and the risk of incident stroke in Chinese adults with diabetes or prediabetes. Higher CTI levels – indicative of combined systemic inflammation and insulin resistance – were associated with substantially elevated stroke risk. These findings suggest that CTI captures a dangerous constellation of metabolic and inflammatory abnormalities that predispose dysglycemic individuals to cerebrovascular events.

Declarations

Data availability

The original data supporting the findings of this study are not publicly available due to sensitivity reasons but can

be obtained from the corresponding author upon reasonable request.

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Author contributions

1. M.C.: conception and design, statistical analysis and result interpretation. M.C.and S.L.: data collection and cleaning. M.C.and L.Z.: validation and supervision. M.C. drafted the manuscript. L.Z. revised the manuscript. All authors reviewed and approved the final manuscript submitted.

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Competing interests

The authors declare no competing interests.

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Tables

Table 1 Baseline Characteristics of participants (N=6350)

Characteristics	CTI tertile			
	T1 (3.17-4.59) n=2117	T2 (4.59-5.12) n=2116	T3 (5.12-7.53) n=2117	*P*-value
Age (years, mean ± SD)	59.07 ± 9.11	59.82 ± 9.24	59.83 ± 9.18	0.009
Systolic blood pressure (mmHg, mean ± SD)	127.98 ± 20.93	131.82 ± 21.32	134.35 ± 21.43	<0.001
Diastolic blood pressure (mmHg, mean ± SD)	74.08 ± 11.59	76.27 ± 12.09	77.98 ± 11.91	<0.001
Body mass index (kg/m2, mean ± SD)	22.45 ± 3.52	24.20 ± 3.72	25.21 ± 4.20	<0.001
Depressive symptoms CESD-10 (mean ± SD)	8.61 ± 6.29	8.33 ± 6.45	8.22 ± 6.12	0.124
Total cholesterol (mg/dL, mean ± SD)	189.61 ± 36.53	198.10 ± 37.53	205.50 ± 44.73	<0.001
Triglyceride (mg/dL, mean ± SD)	87.94 ± 36.44	135.74 ± 65.27	232.41 ± 183.20	<0.001
HDL-C (mg/dL, mean ± SD)	57.75 ± 15.40	49.82 ± 14.08	41.78 ± 13.52	<0.001
LDL-C (mg/dL, mean ± SD)	116.46 ± 32.28	122.35 ± 35.45	114.80 ± 41.83	<0.001
C-reactive protein (mg/dL, mean ± SD)	0.58 ± 0.34	1.42 ± 0.95	6.59 ± 11.33	<0.001
CTI (mean ± SD)	4.27 ± 0.24	4.85 ± 0.15	5.58 ± 0.39	<0.001
Sex, n (%)				0.009
Female	1071 (50.59)	1144 (54.06)	1166 (55.08)	
Male	1046 (49.41)	972 (45.94)	951 (44.92)	
Marital statusn , n (%)				0.763
No spouse	258 (12.19)	273 (12.90)	261 (12.34)	
Married with spouse	1858 (87.81)	1843 (87.10)	1854 (87.66)	
Area of residence, n (%)				<0.001
Urban	642 (30.33)	829 (39.18)	891 (42.09)	
Rural	1475 (69.67)	1287 (60.82)	1226 (57.91)	
Education, n (%)				0.287
Illiterate	1016 (48.11)	1001 (47.37)	998 (47.25)	
Primary	465 (22.02)	436 (20.63)	447 (21.16)	
Middle	431 (20.41)	453 (21.44)	420 (19.89)	
College or higher	200 (9.47)	223 (10.55)	247 (11.70)	
Hypertension, n (%)				<0.001
No	1665 (78.65)	1487 (70.27)	1279 (60.42)	
Yes	436 (20.60)	610 (28.83)	814 (38.45)	
Missing	16 (0.76)	19 (0.90)	24 (1.13)	
Diabetes, n (%)				<0.001
Prediabetes	1766 (83.42)	1619 (76.51)	1194 (56.40)	
Diabetes	351 (16.58)	497 (23.49)	923 (43.60)	
lung, n (%)				0.536
No	1907 (90.08)	1917 (90.60)	1888 (89.18)	
Yes	197 (9.31)	184 (8.70)	210 (9.92)	

Missing	13 (0.61)	15 (0.71)	19 (0.90)	
Heart disease, n (%)				<0.001
No	1889 (89.23)	1825 (86.25)	1744 (82.38)	
Yes	209 (9.87)	272 (12.85)	354 (16.72)	
Missing	19 (0.90)	19 (0.90)	19 (0.90)	
Arthritis, n (%)				0.165
No	1416 (66.89)	1349 (63.75)	1347 (63.63)	
Yes	691 (32.64)	754 (35.63)	758 (35.81)	
Missing	10 (0.47)	13 (0.61)	12 (0.57)	
dyslipidaemia, n (%)				<0.001
No	1934 (91.36)	1812 (85.63)	1689 (79.78)	
Yes	145 (6.85)	239 (11.29)	374 (17.67)	
Missing	38 (1.79)	65 (3.07)	54 (2.55)	
liver, n (%)				0.842
No	2012 (95.04)	2024 (95.65)	2022 (95.51)	
Yes	81 (3.83)	68 (3.21)	70 (3.31)	
Missing	24 (1.13)	24 (1.13)	25 (1.18)	
Kidney, n (%)				0.178
No	1982 (93.62)	1986 (93.86)	1963 (92.73)	
Yes	115 (5.43)	106 (5.01)	138 (6.52)	
Missing	20 (0.94)	24 (1.13)	16 (0.76)	
Digestive disease, n (%)				0.028
No	1588 (75.01)	1643 (77.65)	1676 (79.17)	
Yes	516 (24.37)	461 (21.79)	428 (20.22)	
Missing	13 (0.61)	12 (0.57)	13 (0.61)	
cancer, n (%)				0.870
No	2081 (98.30)	2075 (98.06)	2077 (98.11)	
Yes	15 (0.71)	20 (0.95)	21 (0.99)	
Missing	21 (0.99)	21 (0.99)	19 (0.90)	
Drinking, n (%)				0.031
Never	1179 (55.69)	1253 (59.22)	1278 (60.37)	
Current	753 (35.57)	680 (32.14)	646 (30.51)	
Ever	175 (8.27)	175 (8.27)	181 (8.55)	
Missing	10 (0.47)	8 (0.38)	12 (0.57)	
Smoking, n (%)				0.015
Never	1281 (60.51)	1318 (62.29)	1280 (60.46)	
Current	636 (30.04)	556 (26.28)	574 (27.11)	
Ever	157 (7.42)	195 (9.22)	211 (9.97)	
Missing	43 (2.03)	47 (2.22)	52 (2.46)	

Annual income groups, n (%)				<0.001
< 15000	773 (36.51)	739 (34.92)	700 (33.07)	
15000-25000	125 (5.90)	152 (7.18)	142 (6.71)	
> =25000	378 (17.86)	456 (21.55)	514 (24.28)	
Missing	841 (39.73)	769 (36.34)	761 (35.95)	
Depressive symptoms, n (%)				0.333
No	1239 (61.55)	1277 (63.41)	1277 (63.60)	
Yes	774 (38.45)	737 (36.59)	731 (36.40)	
BMI groups, n (%)				<0.001
Underweight <18.5	156 (7.37)	75 (3.54)	65 (3.07)	
Normal weight 18.5-24	1147 (54.18)	803 (37.95)	649 (30.66)	
Overweight or obesity >=24	500 (23.62)	901 (42.58)	1064 (50.26)	
Missing	314 (14.83)	337 (15.93)	339 (16.01)	

Notes: Results in table: Mean (SD) Median (T1–T3)/n (%). Among the 6350 patients,

Abbreviations: CESD-10, Depressive symptoms CESD-10; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CTI, c-reactive protein-triglyceride-glycemic index; BMI, Body mass index.

Table 2 Relationship between CTI and New-onset stroke

Outcome	Non-adjusted		Adjust I		Adjust II	
	HR(95CI)	*P*-value	HR(95CI)	*P*-value	HR(95CI)	*P*-value
CTI	1.54 (1.37, 1.74)	<0.0001	1.53 (1.36, 1.74)	<0.0001	1.36 (1.18, 1.56)	<0.0001
CTI tertile						
T1(3.17-4.59)	1.0		1.0		1.0	
T2(4.59-5.12)	1.46 (1.19, 1.80)	0.0004	1.44 (1.16, 1.77)	0.0007	1.28 (1.03, 1.58)	0.0239
T3(5.12-7.53)	1.95 (1.60, 2.38)	<0.0001	1.92 (1.57, 2.35)	<0.0001	1.57 (1.27, 1.95)	<0.0001
CTI tertile continuous	1.39 (1.26, 1.53)	<0.0001	1.38 (1.25, 1.52)	<0.0001	1.25 (1.13, 1.39)	<0.0001
P for trend	<0.05		<0.01		<0.001	

Notes: Adjust Ⅰ adjusted for age (years), sex, Area of residence, Drinking, Smoking, Annual income groups, Education. Adjust II adjusted for age (years), sex, area of residence, drinking, smoking, annual income groups, hypertension, diabetes, BMI (kg/m^2)groups, education, diabetes.

Table 3 Stratified analysis of CTI and incidence of New-onset stroke

Sub-group	N	HR (95% CI)	P-value
Age (years) group			
45-54	2019	1.50 (1.15, 1.95)	0.0025
55-62	2161	1.79 (1.46, 2.19)	<0.0001
63-96	2170	1.36 (1.13, 1.65)	0.0013
Sex			
Female	3381	1.50 (1.26, 1.78)	<0.0001
Male	2969	1.60 (1.34, 1.90)	<0.0001
Marital status			
No spouse	792	1.36 (0.97, 1.92)	0.0726
Married with spouse	5555	1.57 (1.38, 1.79)	<0.0001
Area of residence			
Urban	2362	1.69 (1.37, 2.08)	<0.0001
Rural	3988	1.48 (1.27, 1.72)	<0.0001
Education			
Illiterate	3015	1.38 (1.15, 1.64)	0.0004
Primary	1348	1.68 (1.29, 2.18)	<0.0001
Middle	1304	1.61 (1.22, 2.13)	0.0008
College or higher	670	2.00 (1.38, 2.91)	0.0003
Hypertension			
No	4431	1.61 (1.35, 1.91)	<0.0001
Yes	1860	1.20 (1.00, 1.43)	0.0487
Missing	59	0.75 (0.22, 2.54)	0.6475
Diabetes			
No	5630	1.52 (1.32, 1.74)	<0.0001
Yes	629	1.40 (1.03, 1.89)	0.0306
Missing	91	1.68 (0.64, 4.42)	0.2901
lung			
No	5712	1.64 (1.45, 1.87)	<0.0001
Yes	591	0.79 (0.51, 1.23)	0.2936
Missing	47	1.63 (0.53, 5.07)	0.3965
Heart disease			
No	5458	1.56 (1.36, 1.79)	<0.0001
Yes	835	1.33 (1.00, 1.75)	0.047
Missing	57	1.20 (0.43, 3.34)	0.7296
Arthritis			
No	4112	1.48 (1.26, 1.73)	<0.0001
Yes	2203	1.64 (1.35, 1.99)	<0.0001
Missing	35	2.08 (0.58, 7.52)	0.2636

dyslipidaemia			
No	5435	1.48 (1.28, 1.70)	<0.0001
Yes	758	1.48 (1.14, 1.93)	0.0038
Missing	157	0.69 (0.27, 1.78)	0.4434
liver			
No	6058	1.57 (1.38, 1.77)	<0.0001
Yes	219	1.05 (0.57, 1.93)	0.8797
Missing	73	1.91 (0.70, 5.20)	0.2053
Kidney			
No	5931	1.54 (1.36, 1.75)	<0.0001
Yes	359	1.44 (0.95, 2.19)	0.0864
Missing	60	2.02 (0.77, 5.32)	0.1529
Digestive disease			
No	4907	1.50 (1.31, 1.73)	<0.0001
Yes	1405	1.72 (1.32, 2.24)	<0.0001
Missing	38	1.40 (0.42, 4.69)	0.5822
cancer			
No	6233	1.55 (1.37, 1.75)	<0.0001
Yes	56	2.61 (0.65, 10.53)	0.1767
Missing	61	0.97 (0.33, 2.91)	0.9628
Drinking			
Never	3710	1.62 (1.37, 1.91)	<0.0001
Current	2079	1.57 (1.28, 1.94)	<0.0001
Ever	531	1.12 (0.76, 1.65)	0.5626
Missing	30	1.63 (0.47, 5.60)	0.4381
Smoking			
Never	3879	1.56 (1.33, 1.84)	<0.0001
Current	1766	1.44 (1.15, 1.81)	0.0016
Ever	563	1.34 (0.93, 1.93)	0.1146
Missing	142	3.37 (1.64, 6.91)	0.001
Annual income groups			
< 15000	2212	1.45 (1.20, 1.76)	0.0002
15000-25000	419	1.30 (0.79, 2.14)	0.3081
> =25000	1348	1.94 (1.49, 2.54)	<0.0001
Missing	2371	1.49 (1.21, 1.85)	0.0002
Depressive symptoms			
No	3793	1.60 (1.35, 1.91)	<0.0001
Yes	2242	1.43 (1.20, 1.71)	<0.0001
Systolic blood pressure (mmHg) group			

70.5 - 119.5	1746	1.46 (1.10, 1.95)	0.0095
120 - 137	1799	1.48 (1.16, 1.88)	0.0015
137.5 - 215	1829	1.40 (1.16, 1.70)	0.0005
Diastolic blood pressure (mmHg) group			
33.5 - 70	1736	1.65 (1.27, 2.15)	0.0002
70.5 - 80	1771	1.34 (1.04, 1.71)	0.0233
80.5 - 141.5	1868	1.46 (1.20, 1.78)	0.0002
Body mass index (kg/m2) group			
11.7 - 22	1787	1.31 (1.00, 1.72)	0.0529
22 - 25.2	1786	1.68 (1.33, 2.12)	<0.0001
25.3 - 71.2	1787	1.40 (1.13, 1.75)	0.0026
BMI groups			
Underweight <18.5	296	1.21 (0.54, 2.70)	0.6461
Normal weight 18.5-24	2599	1.63 (1.33, 2.00)	<0.0001
Overweight or obesity >=24	2465	1.37 (1.13, 1.65)	0.0013
Missing	990	1.52 (1.10, 2.10)	0.0117
Depressive symptoms CESD-10 group			
0-4	1972	1.43 (1.11, 1.84)	0.0054
5-9	1821	1.81 (1.42, 2.31)	<0.0001
10-30	2242	1.43 (1.20, 1.71)	<0.0001
Total cholesterol (mg/dL) group			
77.7- 178.6	2113	1.75 (1.40, 2.18)	<0.0001
178.9 - 210.3	2118	1.52 (1.21, 1.92)	0.0003
210.6 - 627	2119	1.38 (1.13, 1.67)	0.0014
Triglyceride (mg/dL) group			
2.6 - 91.1	2087	1.66 (1.26, 2.18)	0.0004
92 - 150.4	2143	1.34 (1.03, 1.73)	0.0272
151 - 1837.2	2119	1.51 (1.20, 1.90)	0.0004
HDL-C (mg/dL) group			
5- 41.3	2065	1.49 (1.20, 1.85)	0.0003
41.7 - 54.1	2162	1.56 (1.24, 1.97)	0.0002
54.5 - 158.8	2123	1.64 (1.27, 2.12)	0.0002
LDL-C (mg/dL) group			
0.3 - 101.2	2093	1.79 (1.47, 2.18)	<0.0001
101.6- 129	2106	1.45 (1.14, 1.84)	0.0022
130.2 - 385.8	2132	1.47 (1.17, 1.83)	0.0007
C-reactive protein (mg/dL) group			
0.02 - 0.7	2105	1.77 (1.23, 2.57)	0.0023
0.7 - 1.7	2123	1.58 (1.13, 2.21)	0.0076

1.7 - 170.5	2121	1.47 (1.14, 1.89)	0.0026
Diabetes			
Prediabetes	4579	1.61 (1.36, 1.90)	<0.0001
Diabetes	1771	1.39 (1.13, 1.70)	0.0018

Note: Adjusting variables: None.

Among the 6350 patients, the amount of missing values for the covariates were 59 (0.75) for Hypertension; 91(1.68) for Diabetes; 47(1.63) for lung; 57(1.20) for Heart disease; 35(2.08) for Arthritis; 157(0.69) for dyslipidaemia; 73(1.91) for liver; 60(2.02) for Kidney; 38(1.40) for Digestive disease; 61(0.97) for cancer; 30(1.63) for Drinking; 142(3.37) for Smoking; 2371(1.49) for Annual income groups; 990(1.52) for BMI groups.

Abbreviations: CTI, c-reactive protein-triglyceride-glycemic index; BMI, Body mass index.

Table 4 K-M plots of incidence rates for new-onset stroke(in middle-aged and elderly populations with diabetes and prediabetes) based on cuCTI3(0), cuCTI3 (1), and cuCTI3 clustering (2)

Follow-up time (year)	N.Risk	N.Event	N.Censor	Low: Surv	Low: 95%CI low	Low: 95CI upp	Middle: Surv	Middle: 95CI low	Middle: 95CI upp	High: Surv	High: 95CI low	High: 95CI upp
1.49	6348	1	5	0.9999	0.9997	1.0000	0.9998	0.9995	1.0000	0.9998	0.9994	1.0000
1.67	6340	2	16	0.9997	0.9993	1.0000	0.9995	0.9990	1.0000	0.9994	0.9987	1.0000
1.92	6313	7	42	0.9989	0.9982	0.9996	0.9984	0.9974	0.9994	0.9979	0.9966	0.9992
2.00	6277	18	125	0.9970	0.9958	0.9982	0.9956	0.9939	0.9973	0.9941	0.9919	0.9963
2.08	6134	11	57	0.9958	0.9943	0.9972	0.9938	0.9918	0.9959	0.9917	0.9890	0.9944
2.16	6066	3	16	0.9954	0.9939	0.9970	0.9933	0.9912	0.9955	0.9911	0.9883	0.9939
2.33	6039	1	13	0.9953	0.9938	0.9969	0.9932	0.9910	0.9953	0.9908	0.9880	0.9937
3.49	6030	2	8	0.9951	0.9935	0.9967	0.9928	0.9906	0.9951	0.9904	0.9875	0.9933
3.59	6022	1	2	0.9950	0.9934	0.9966	0.9927	0.9904	0.9949	0.9902	0.9872	0.9931
3.67	6020	1	11	0.9949	0.9932	0.9965	0.9925	0.9902	0.9948	0.9900	0.9870	0.9930
3.75	6008	1	14	0.9948	0.9931	0.9964	0.9923	0.9900	0.9947	0.9897	0.9867	0.9928
3.84	5993	2	12	0.9945	0.9928	0.9962	0.9920	0.9896	0.9944	0.9893	0.9862	0.9924
3.92	5979	18	86	0.9925	0.9904	0.9946	0.9890	0.9862	0.9919	0.9853	0.9816	0.9890
4.00	5875	23	171	0.9898	0.9873	0.9924	0.9852	0.9817	0.9886	0.9802	0.9758	0.9846
4.08	5681	25	96	0.9869	0.9839	0.9899	0.9808	0.9768	0.9849	0.9744	0.9693	0.9795
4.16	5560	3	5	0.9865	0.9835	0.9896	0.9803	0.9762	0.9844	0.9737	0.9685	0.9789
6.49	5551	1	4	0.9864	0.9833	0.9895	0.9801	0.9760	0.9843	0.9735	0.9683	0.9787
6.59	5545	2	4	0.9861	0.9830	0.9893	0.9798	0.9756	0.9840	0.9730	0.9678	0.9783
6.67	5541	8	15	0.9852	0.9819	0.9884	0.9784	0.9740	0.9827	0.9711	0.9657	0.9767
6.75	5518	4	0	0.9847	0.9814	0.9880	0.9777	0.9732	0.9821	0.9702	0.9646	0.9758
6.84	5514	5	7	0.9841	0.9807	0.9875	0.9768	0.9722	0.9814	0.9690	0.9633	0.9748
6.92	5502	75	93	0.9749	0.9701	0.9797	0.9634	0.9572	0.9697	0.9514	0.9438	0.9590
7.00	5334	200	232	0.9497	0.9415	0.9580	0.9272	0.9170	0.9375	0.9038	0.8919	0.9159
7.08	4902	86	73	0.9383	0.9285	0.9481	0.9109	0.8990	0.9229	0.8825	0.8688	0.8965
7.16	4743	1	2	0.9381	0.9283	0.9480	0.9107	0.8988	0.9228	0.8823	0.8685	0.8962
8.49	4727	1	33	0.9380	0.9282	0.9479	0.9105	0.8986	0.9226	0.8820	0.8683	0.8960
8.59	4690	1	52	0.9379	0.9280	0.9478	0.9103	0.8983	0.9224	0.8818	0.8680	0.8958
8.67	4653	2	63	0.9376	0.9277	0.9475	0.9099	0.8979	0.9221	0.8813	0.8674	0.8953
8.75	4588	3	39	0.9372	0.9272	0.9472	0.9093	0.8972	0.9215	0.8805	0.8666	0.8946
8.84	4546	2	84	0.9369	0.9269	0.9469	0.9089	0.8968	0.9212	0.8800	0.8660	0.8941
8.92	4460	37	889	0.9315	0.9209	0.9423	0.9013	0.8884	0.9143	0.8701	0.8554	0.8851
9.00	3534	58	2265	0.9209	0.9089	0.9331	0.8863	0.8718	0.9010	0.8508	0.8344	0.8676
9.08	1211	32	1119	0.9041	0.8891	0.9193	0.8627	0.8447	0.8811	0.8206	0.8000	0.8417
9.16	60	1	58	0.8940	0.8689	0.9198	0.8486	0.8159	0.8827	0.8027	0.7629	0.8446

Note: This study was designed as a retrospective cohort based on the CHARLS database. The outcome event was defined as self-reported new-onset stroke during follow-up. Survival analysis was performed using the Kaplan-Meier method, with intergroup comparisons conducted via the log-rank test. The CTI was calculated using the formula Ln(CRP×TG×FPG) and categorized into low, intermediate, and high

groups by quintiles. The figure includes follow-up time (years), the number of risk-set individuals, the number of events, as well as the survival rates and their 95 confidence intervals for each group at each time point.

Abbreviations: CTI, c-reactive protein-triglyceride-glucose index.

Figures

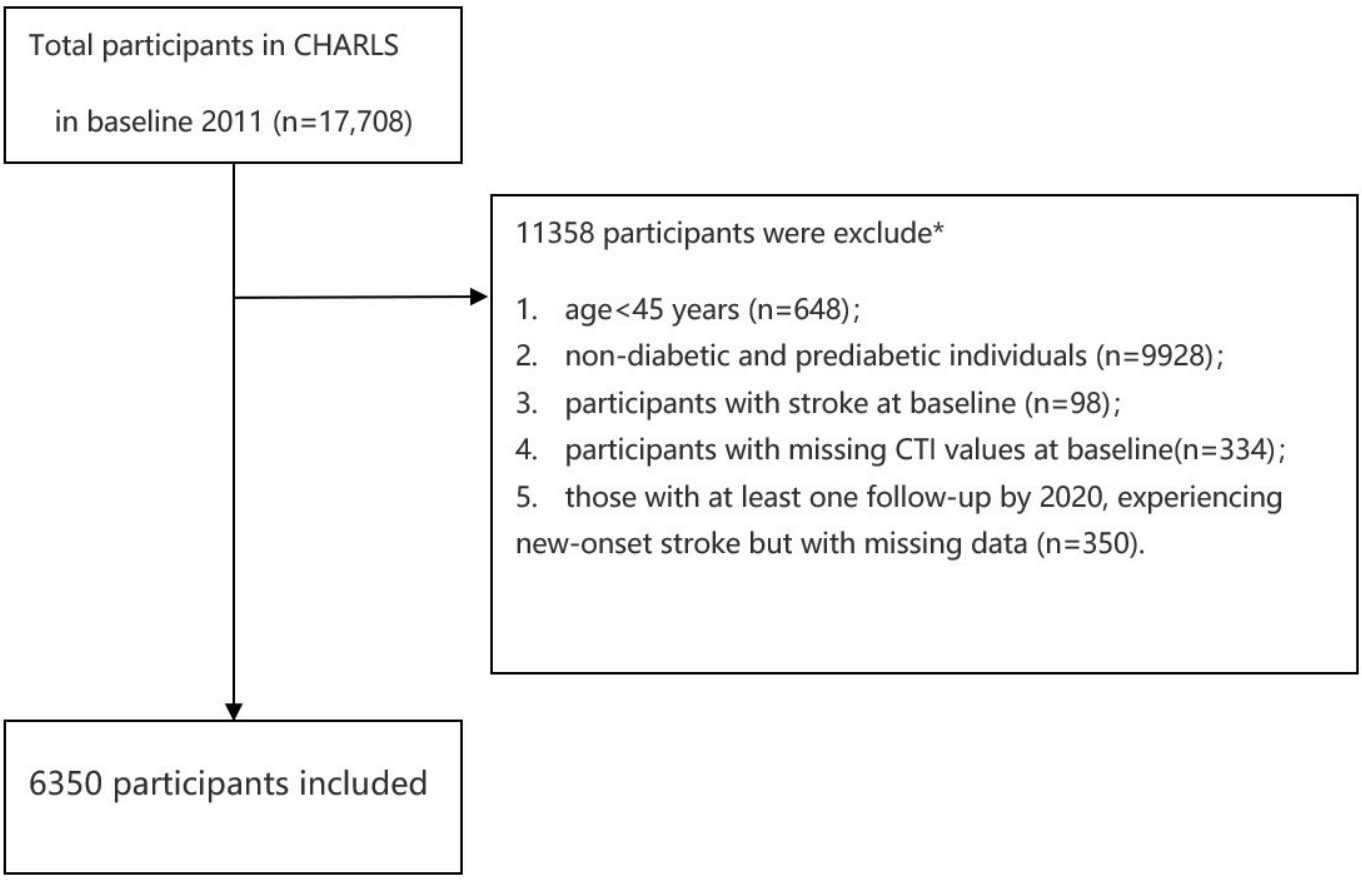


Figure 1

Flow chart of the study population.

This flowchart illustrates the selection process of participants for the retrospective cohort study, showing the initial number of participants, exclusion criteria, and the final cohort of patients included in the analysis.

*Subjects selected after each step. First, individuals younger than 45 years at wave 1 were excluded, accounting for 648 participants, to focus on an age group more susceptible to the issues under investigation. Second, we excluded 9928 participants who is non-diabetic and non-prediabetic individual. Third, 98 participants with stroke at baseline and 334 participants with missing CTI values at baseline were excluded to maintain data accuracy. Lastly, we excluded those with at least one follow-up by 2020, experiencing new-onset stroke but with missing data, ccounting for 350 participants. After applying these criteria, a total of 6350 individuals were included in the final cohort, as depicted in figure.

CTI: c-reactive protein-triglyceride-glucose index.

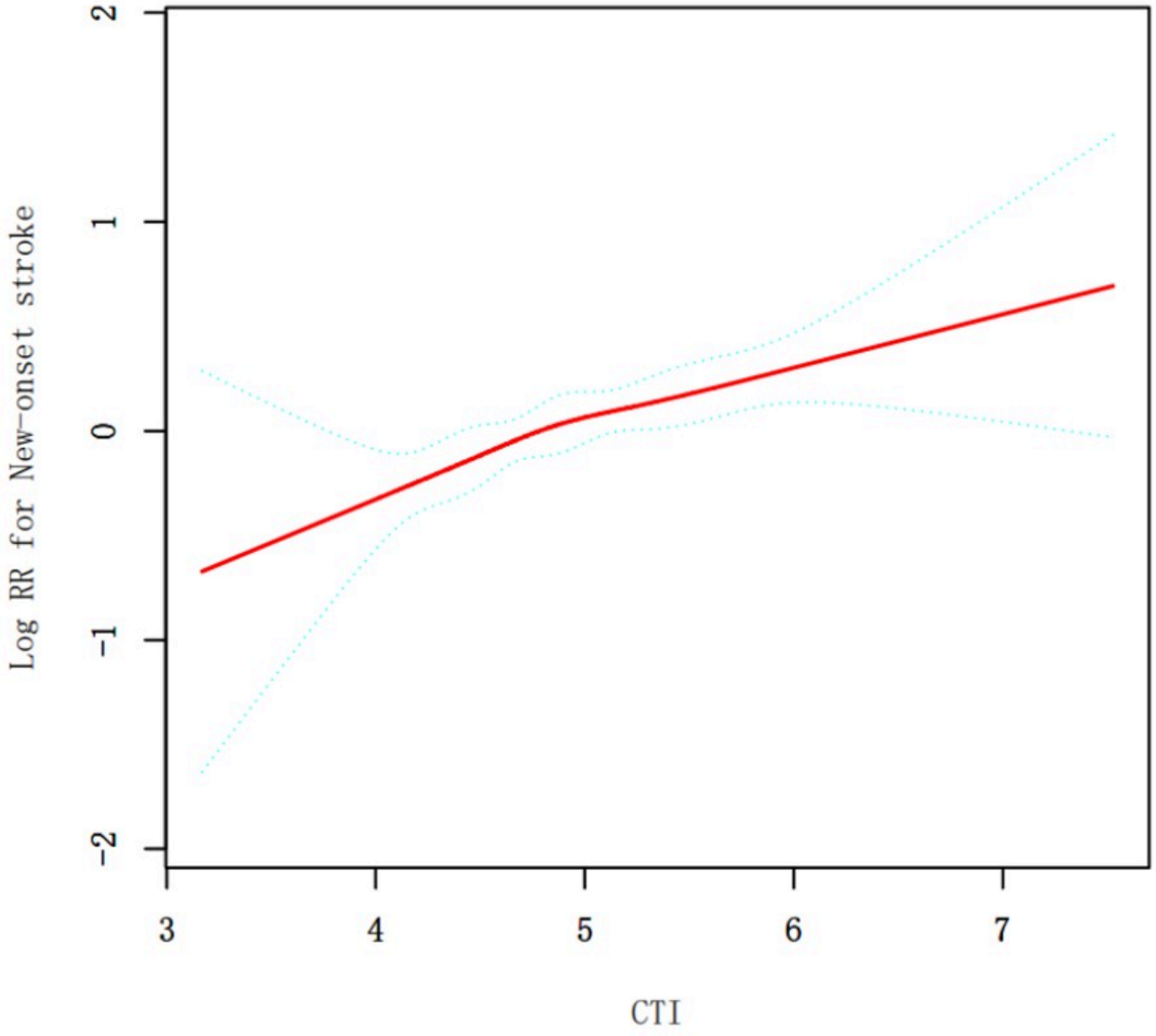


Figure 2

Association between CTI and New-onset stroke in Middle-aged and elderly individuals with diabetes mellitus and prediabetes.

The red line represents the smoothed fit curve between variables, while the blue bands represent the 95 of confidence interval from the fit. Adjusted for age(years), gender, rural, drinking, smoking status, income, hibpe, diabetes, BMI(kg/m^2), edu. And after restricted cubic spline smoothing were applied, a positive linearly increasing trend between CTI and risk of new-onset stroke was found in a generalized additive model (GAM).

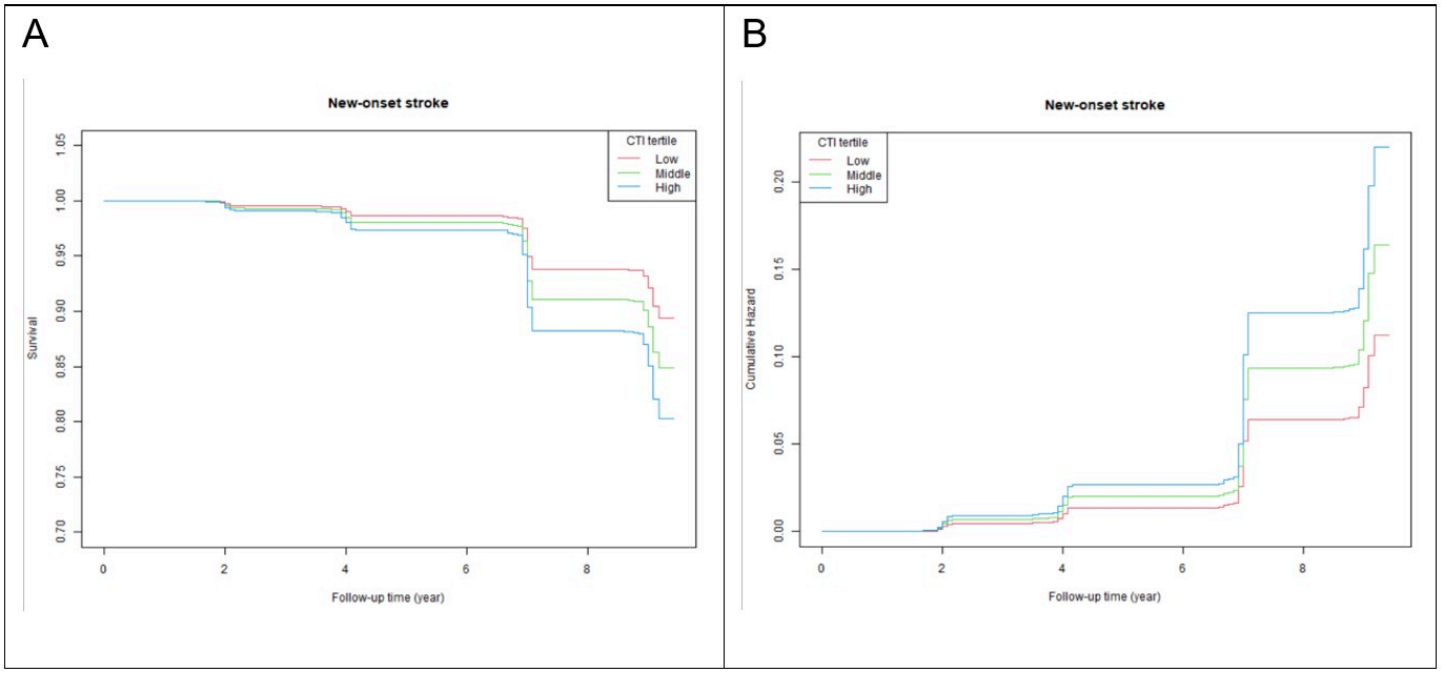


Figure 3

Multivariable-adjusted Kaplan-Meier plot for the association of the CTI groups with the incidence of New-onset stroke.

The outcome event was defined as self-reported new-onset stroke during follow-up. Survival and New-onset stroke Risk Analysis were performed using the Kaplan-Meier methodt. The CTI was categorized into low, intermediate, and high groups by tertiles. The figure includes follow-up time (years), the number of risk-set individuals, the number of events , as well as the survival rates, and acumulative hazard and their 95 confidence intervals for each group at each time point.

CTI: c-reactive protein-triglyceride-glucose index