Research Square

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Joint Associations of the Triglyceride–Glucose Index, the Atherogenic Index of Plasma, and Systemic Inflammation with Incident Stroke in Middle-Aged and Older Chinese Adults: A 9-Year Prospective Cohort Study

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Abstract

Background

The triglyceride–glucose (TyG) index and the atherogenic index of plasma (AIP) are low-cost serum markers of insulin resistance and atherogenic dyslipidemia. Their joint associations with systemic inflammation and incident stroke in Chinese middle-aged and older adults, and the role of TyG trajectories, are unclear.

Methods

We analyzed 10,068 participants aged 45 years and older from the China Health and Retirement Longitudinal Study who were free of cardiovascular disease and had venous blood biomarkers at baseline (2011) and were followed through 2020. TyG = ln[triglycerides (mg/dL) × fasting glucose (mg/dL)/2]; AIP = log10(triglycerides/HDL-cholesterol). Incident stroke was defined as self-reported physician-diagnosed stroke during follow-up, with the year of first diagnosis recorded. Cox models, restricted cubic splines, joint four-group analyses with high-sensitivity C-reactive protein (hs-CRP), and TyG trajectory analyses were performed.

Results

Over 82,734 person-years (mean follow-up 8.2 years), 657 incident strokes occurred (7.94 per 1,000 person-years). Each standard deviation increase in TyG and AIP was associated with an 18% (HR 1.18, 95% CI 1.09–1.29) and 15% (HR 1.15, 95% CI 1.05–1.25) higher stroke risk after full adjustment. hs-CRP showed a borderline association (HR 1.09, 95% CI 1.00–1.19). In joint analyses, participants with low hs-CRP and high TyG or high AIP had elevated stroke risk (HR 1.37, 95% CI 1.12–1.67 and HR 1.33, 95% CI 1.09–1.62). In the trajectory cohort (n = 6,279), a persistently high TyG showed a trend toward higher stroke risk (HR 1.33, 95% CI 0.99–1.77), whereas a decline from high to low TyG was associated with a 36% lower risk relative to a persistently high TyG (HR 0.64, 95% CI 0.44–0.93).

Conclusions

TyG and AIP independently predicted incident stroke in middle-aged and older Chinese adults, and a reduction in TyG over time was associated with lower stroke risk. These routinely available serum indices may support stroke risk stratification in community settings.

Background

Stroke is the second leading cause of death worldwide and the leading cause of death and disability in China [1, 2]. Between 1990 and 2019, the absolute burden of stroke in China rose by more than 60%,

driven largely by metabolic risk factors including hypertension, dyslipidemia, hyperglycemia, and overweight [3]. Identifying inexpensive markers that capture metabolic risk beyond conventional measures is therefore relevant for primary prevention in aging populations.

Insulin resistance and atherogenic dyslipidemia are central pathways in the development of atherosclerotic cerebrovascular disease [4]. The triglyceride–glucose (TyG) index, derived from fasting triglycerides and glucose, was introduced as a simple surrogate of insulin resistance [5] and has since been linked to cardiovascular outcomes in umbrella-level evidence [6]. The atherogenic index of plasma (AIP), the log-transformed ratio of triglycerides to HDL-cholesterol, reflects the balance between atherogenic and protective lipoproteins and correlates with lipoprotein particle size [7]. Both indices are computable from routine serum biochemistry at negligible cost, which makes them attractive for population screening in resource-constrained settings.

Systemic low-grade inflammation, commonly measured with high-sensitivity C-reactive protein (hs-CRP), contributes to atherosclerotic plaque vulnerability and cerebrovascular injury [8, 9]. Observational and trial evidence supports a causal role of inflammation in cardiovascular disease [10, 11], and meta-analyses have linked higher hs-CRP to incident stroke [12, 13]. Whether the atherogenic indices act independently of, or jointly with, systemic inflammation in the pathogenesis of stroke remains unclear. Recent Chinese cohort studies reported that the cardiometabolic index combined with hs-CRP predicted new-onset stroke [14] and that the TyG index combined with hs-CRP predicted cardiovascular disease [15], but evidence specific to the TyG index and AIP, which require no anthropometric measurement, is still limited.

Longitudinal studies using a single baseline measurement cannot distinguish transient from persistent exposure. Evidence is accumulating that dynamic changes in metabolic markers, rather than a single value, shape cardiovascular risk [16, 17]. Data on TyG trajectories and stroke in Chinese older adults are sparse.

Using nine years of follow-up data from the China Health and Retirement Longitudinal Study (CHARLS), we examined (i) the associations of the TyG index and AIP, two purely serum-derived indices that avoid anthropometric measurement error, with incident stroke; (ii) their joint associations with hs-CRP, with mutual adjustment to delineate the relative contributions of metabolic dysregulation and systemic inflammation; and (iii) the association of TyG trajectories between 2011 and 2015 with subsequent stroke risk, to test whether an improvement in TyG over time is accompanied by a lower risk.

Methods

Study design and population

CHARLS is a nationally representative longitudinal survey of Chinese adults aged 45 years and older [18]. The national baseline survey was conducted in 2011 with follow-up waves in 2013, 2015, 2018, and 2020. Venous blood samples were collected and assayed in 2011 and 2015. Details of the sampling

design, blood collection, and laboratory procedures have been described previously [18]. The study was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and all participants provided written informed consent.

Of 11,847 participants with blood biomarker data at baseline, we excluded 1,656 participants with prevalent cardiovascular disease (self-reported physician-diagnosed heart disease or stroke) and 123 participants with missing cardiovascular disease status, leaving 10,068 participants for the primary analysis (Fig. 1).

Exposure assessment

TyG was calculated as ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2] [5]. AIP was calculated as log10(triglycerides/HDL-cholesterol) [7]. hs-CRP was measured in mg/L and dichotomized at 3 mg/L, a widely used clinical threshold for elevated cardiovascular risk [10]. In joint analyses, TyG and AIP were dichotomized at their sample medians (8.59 and 0.322, respectively). For the trajectory analysis, TyG was recalculated from the 2015 venous blood measurements using the same formula, and participants were classified according to whether TyG was below or above the sample median at each wave: low-stable, increasing, decreasing, or high-stable.

Outcome ascertainment

Incident stroke was defined as self-reported physician-diagnosed stroke reported at any follow-up wave (2013, 2015, 2018, or 2020). At each wave, participants were asked whether a doctor had diagnosed them with stroke; affirmative responses were combined across the disease-status and verification questions of each wave. The year of first stroke diagnosis was extracted from the date-of-diagnosis questions whenever available. Participants reporting stroke at baseline were excluded. Self-reported stroke in Asian cohorts has acceptable validity against medical records [19]. The composite outcome of stroke or heart disease was examined in sensitivity analyses; heart disease was analyzed as a secondary outcome.

Covariates

Baseline covariates were collected by structured questionnaire and physical examination: age (years), sex, education (illiterate/primary, middle school, high school or above), marital status, residential area (rural/urban by hukou), current smoking, alcohol drinking, sleep duration, self-reported physician-diagnosed hypertension, diabetes, and dyslipidemia, body mass index (BMI, kg/m²) from measured height and weight, and estimated glomerular filtration rate (eGFR) calculated with the CKD-EPI equation from serum creatinine [20].

Statistical analysis

Baseline characteristics were summarized as median (interquartile range) or number (%) across TyG tertiles. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident stroke, with time since baseline (in years) as the time scale. Model 1 was unadjusted; Model 2 adjusted for age and sex; Model 3 additionally adjusted for education, marital status, residential area, smoking, drinking, sleep duration, hypertension, diabetes, dyslipidemia, BMI, and eGFR. Exposures were modeled per standard deviation (SD) and in tertiles, with tests for linear trend across tertiles. Dose–response shape was examined with restricted cubic splines using three knots at the 10th, 50th, and 90th percentiles; nonlinearity was tested with a Wald test on the spline terms, with a likelihood ratio test as a cross-check, and a four-knot specification (5th, 35th, 65th, 95th percentiles) was examined as a sensitivity analysis. Although the four-knot model had a marginally lower Akaike information criterion, the Bayesian information criterion consistently favored the more parsimonious three-knot model (ΔBIC 0.6 to 5.6 across exposures), and the additional nonlinear term in the four-knot model captured non-monotonic variation in the sparse upper tail that was not statistically distinguishable in the tertile analyses; the three-knot specification was therefore retained as the primary model. hs-CRP was modeled on the natural log scale because of its right-skewed distribution. Curves were referenced to the sample median and plotted over the 1st to 99th percentile range. Joint analyses cross-classified hs-CRP (≥ 3 vs < 3 mg/L) with TyG or AIP (≥ median vs <median) into four groups. Additive interaction was quantified by the relative excess risk due to interaction. Mutual adjustment models examined the independence of TyG and AIP from hs-CRP.

For the trajectory analysis, participants with 2015 blood samples who remained stroke-free through 2015 were followed from 2015 to 2020. Trajectory groups were compared with the low-stable group as reference, and predefined contrasts compared high-stable versus increasing and decreasing versus high-stable.

Sensitivity analyses excluded events occurring within two years of baseline, restricted the cohort to participants who survived the follow-up (to address competing risk of death), and stratified by sex and age (< 60 vs ≥ 60 years). Analyses were performed with Python 3.14 (pandas, lifelines). Two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Among 10,068 participants, the mean age was 58.7 years (SD 9.7) and 52.5% were women. The median TyG was 8.59 (SD 0.67) and the median AIP was 0.322 (SD 0.336). Participants in higher TyG tertiles were more often women, less often smokers, and had higher prevalence of hypertension, diabetes, and dyslipidemia, higher BMI, and higher hs-CRP (Table 1).

Table 1
Baseline characteristics by tertiles of the triglyceride-glucose index (N = 10,068)

Characteristic	T1 (low)	T2	T3 (high)
n	3,296	3,294	3,295
Age, years	57 (50–65)	58 (52–65)	58 (51–64)
Male, n (%)	1,754 (53.2)	1,509 (45.9)	1,424 (43.3)
Education ≥ middle school, n (%)	1,010 (30.7)	970 (29.5)	1,094 (33.3)
Married, n (%)	2,916 (88.5)	2,927 (88.9)	2,927 (88.8)
Rural residence, n (%)	2,812 (85.3)	2,749 (83.5)	2,618 (79.5)
Current smoker, n (%)	1,417 (43.0)	1,257 (38.2)	1,194 (36.2)
Drinker, n (%)	1,263 (38.4)	1,048 (31.8)	1,057 (32.1)
Sleep duration, h/night	7 (5–8)	6 (5–8)	7 (5–8)
Hypertension, n (%)	492 (15.0)	690 (21.1)	924 (28.2)
Diabetes, n (%)	59 (1.8)	118 (3.6)	280 (8.6)
Dyslipidemia, n (%)	137 (4.2)	201 (6.2)	377 (11.7)
BMI, kg/m²	21.9 (19.9–24.0)	23.0 (20.8–25.5)	24.4 (22.2–27.1)
eGFR, mL/min/1.73 m²	100.5 (91.1–107.0)	99.4 (89.3–105.9)	98.4 (86.1–105.7)
hs-CRP, mg/L	0.8 (0.4–1.8)	0.9 (0.5–2.0)	1.2 (0.7–2.5)
AIP	0.1 (− 0.1–0.2)	0.3 (0.2–0.4)	0.7 (0.5–0.8)
TyG	8.1 (7.9–8.2)	8.6 (8.5–8.7)	9.3 (9.0–9.6)

Values are median (interquartile range) or n (%). The tertile counts sum to 9,885 because TyG values were missing for 183 participants. BMI, body mass index; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; AIP, atherogenic index of plasma; TyG, triglyceride-glucose index.

Associations of TyG, AIP, and hs-CRP with incident stroke

During 82,734 person-years of follow-up (mean 8.2 years), 657 participants (6.5%) developed incident stroke (7.94 per 1,000 person-years). TyG and AIP were associated with incident stroke in all models (Table 2). After full adjustment, each SD increase in TyG corresponded to an 18% higher stroke risk (HR 1.18, 95% CI 1.09–1.29, P < 0.001), and each SD increase in AIP corresponded to a 15% higher risk (HR 1.15, 95% CI 1.05–1.25, P = 0.002). The association of hs-CRP was attenuated after full adjustment (HR 1.09 per SD of log hs-CRP, 95% CI 1.00–1.19, P = 0.056).

Table 2
Associations of TyG, AIP, and hs-CRP (per SD) with incident stroke

Exposure	Model 1 HR (95% CI)	P	Model 2 HR (95% CI)	P	Model 3 HR (95% CI)	P
TyG	1.27 (1.18–1.36)	< 0.001	1.28 (1.20–1.37)	< 0.001	1.18 (1.09–1.29)	< 0.001
AIP	1.22 (1.13–1.31)	< 0.001	1.24 (1.16–1.33)	< 0.001	1.15 (1.05–1.25)	0.002
hs-CRP (log)	1.20 (1.11–1.29)	< 0.001	1.16 (1.08–1.25)	< 0.001	1.09 (1.00–1.19)	0.056

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, education, marital status, residence, smoking, drinking, sleep duration, hypertension, diabetes, dyslipidemia, BMI, and eGFR. SDs: TyG 0.671, AIP 0.336, log hs-CRP 1.089. N = 8,007–8,009 in Model 3; 541 events.

Dose–response associations

In tertile analyses, stroke risk rose across TyG and AIP tertiles (Table 3). Compared with the lowest tertile, the fully adjusted HRs for the middle and highest TyG tertiles were 1.46 (95% CI 1.16–1.82) and 1.35 (95% CI 1.07–1.70) (P for trend = 0.019). The corresponding HRs for AIP tertiles were 1.58 (95% CI 1.26–1.97) and 1.41 (95% CI 1.11–1.78) (P for trend = 0.0095). Restricted cubic splines with three knots indicated nonlinear associations of AIP (P for nonlinearity = 0.003) and of log hs-CRP (P = 0.040) with incident stroke, whereas the association of TyG was consistent with a linear dose-response (P = 0.116) (Fig. 2). For AIP and hs-CRP, the hazard was lowest at the lower end of the distribution and rose to a plateau near the median, with no further elevation at the upper extreme. In a four-knot sensitivity analysis, all three exposures showed significant nonlinearity (TyG P = 0.008, AIP P = 0.001, hs-CRP P = 0.026; Additional file 1: Fig. S1); the additional flexibility captured non-monotonic variation in the sparse upper tail that was not statistically distinguishable in the tertile analyses. Associations of the three indices with all-cause mortality, examined as a secondary outcome, are shown in Additional file 1: Fig. S2; on the log scale, hs-CRP showed a nonlinear association with mortality (P = 0.017), whereas the associations for TyG and AIP were consistent with linearity (P = 0.363 and 0.547, respectively).

Table 3
Tertiles of TyG, AIP, and hs-CRP in relation to incident stroke (Model 3)

Exposure	T2 HR (95% CI)	P	T3 HR (95% CI)	P	P for trend
TyG	1.46 (1.16–1.82)	0.001	1.35 (1.07–1.70)	0.011	0.019
AIP	1.58 (1.26–1.97)	< 0.001	1.41 (1.11–1.78)	0.004	0.0095
hs-CRP	1.11 (0.89–1.39)	0.355	1.31 (1.05–1.63)	0.016	0.013

Reference group is the lowest tertile (T1). Model 3 adjusted as in Table 2.

Joint associations with hs-CRP

In the four-group analysis, stroke risk was elevated in the low-CRP/high-TyG group (HR 1.37, 95% CI 1.12–1.67) and in the low-CRP/high-AIP group (HR 1.33, 95% CI 1.09–1.62) relative to the low-CRP/low-index reference (Table 4). The high-CRP/high-AIP group had an HR of 1.36 (95% CI 1.02–1.82). Estimates of additive interaction did not indicate synergy beyond independent effects (relative excess risk due to interaction − 0.07 to − 0.26, all P > 0.05). In mutual adjustment models, TyG remained associated with stroke after adjustment for hs-CRP (HR 1.18, 95% CI 1.08–1.28), as did AIP (HR 1.14, 95% CI 1.04–1.24), whereas hs-CRP was no longer associated after adjustment for either index (HR 1.07–1.08). When TyG and AIP were modeled together, TyG predominated (HR 1.26, 95% CI 1.05–1.51) and AIP was attenuated (HR 0.93, 95% CI 0.77–1.12), consistent with their shared dependence on triglycerides.

Table 4
Joint associations of hs-CRP with TyG and AIP in relation to incident stroke

Group	hs-CRP × TyG HR (95% CI)	P	hs-CRP × AIP HR (95% CI)	P
Low CRP, low index	1.00 (ref)	—	1.00 (ref)	—
Low CRP, high index	1.37 (1.12–1.67)	0.002	1.33 (1.09–1.62)	0.005
High CRP, low index	1.22 (0.86–1.72)	0.261	1.09 (0.76–1.57)	0.626
High CRP, high index	1.32 (0.98–1.79)	0.066	1.36 (1.02–1.82)	0.039

Model 3 adjusted as in Table 2. High CRP defined as hs-CRP ≥ 3 mg/L; high index defined as ≥ sample median (TyG ≥ 8.59, AIP ≥ 0.322).

TyG trajectory between 2011 and 2015

Among 6,491 participants with blood samples at both waves, 6,279 remained stroke-free through 2015 and were followed for 350 incident strokes through 2020. Compared with the low-stable group, the high-stable group showed a trend toward the highest stroke risk (HR 1.33, 95% CI 0.99–1.77, P = 0.054), whereas increasing (HR 0.94, 95% CI 0.63–1.38) and decreasing (HR 0.90, 95% CI 0.61–1.33) trajectories were not associated with elevated risk (Table 5, Fig. 3). In predefined contrasts, a persistently high TyG carried higher risk than a transiently high TyG (HR 1.53, 95% CI 1.05–2.22), and a decline from high to low TyG was associated with a 36% lower risk than a persistently high TyG (HR 0.64, 95% CI 0.44–0.93). The continuous change in TyG per SD was not associated with stroke (HR 0.95, 95% CI 0.85–1.06), indicating that the persistent state, rather than the magnitude of change, carried the risk.

Table 5
TyG trajectory (2011 to 2015) and incident stroke (2015 to 2020)

Trajectory	n	Events	HR (95% CI)	P
Low-stable	2,245	105	1.00 (ref)	—
Increasing	955	47	0.94 (0.63–1.38)	0.740
Decreasing	894	41	0.90 (0.61–1.33)	0.598
High-stable	2,185	157	1.33 (0.99–1.77)	0.054
High-stable vs increasing	—	—	1.53 (1.05–2.22)	0.027
Decreasing vs high-stable	—	—	0.64 (0.44–0.93)	0.020

Model 3 adjusted as in Table 2, with age at 2015 as the time scale origin. Groups defined by TyG below or above the sample median at each wave (2011 median 8.58; 2015 median 8.62). N = 5,202 in the adjusted model; 299 events.

Sensitivity analyses

Associations for TyG and AIP were consistent in sensitivity analyses (Table 6). Excluding strokes within the first two years of follow-up did not materially change the estimates (TyG HR 1.19, 95% CI 1.09–1.30; AIP HR 1.15, 95% CI 1.05–1.26). Restricting to participants who survived the follow-up yielded similar results (TyG HR 1.16; AIP HR 1.14); in this subgroup hs-CRP became significant (HR 1.14, 95% CI 1.04–1.25). Associations were consistent across sex and age strata, with somewhat stronger TyG associations in women (HR 1.21) and participants aged 60 years or older (HR 1.20). When the composite outcome of stroke or heart disease was used, associations were attenuated (TyG HR 1.05, 95% CI 0.99–1.10), and no association was observed for heart disease alone (TyG HR 0.99, 95% CI 0.93–1.05), indicating that the associations were specific to stroke.

Table 6
Sensitivity analyses for TyG and AIP in relation to incident stroke (Model 3)

Analysis	TyG HR (95% CI)	P	AIP HR (95% CI)	P
Main analysis	1.18 (1.09–1.29)	< 0.001	1.15 (1.05–1.25)	0.002
Excluding events ≤ 2 years	1.19 (1.09–1.30)	< 0.001	1.15 (1.05–1.26)	0.002
Survivors only	1.16 (1.07–1.27)	< 0.001	1.14 (1.05–1.25)	0.003
Men	1.13 (1.00–1.28)	0.042	1.12 (0.99–1.27)	0.070
Women	1.21 (1.08–1.36)	0.001	1.14 (1.01–1.29)	0.032
Age < 60 years	1.14 (1.01–1.28)	0.027	1.16 (1.03–1.31)	0.013
Age ≥ 60 years	1.20 (1.06–1.36)	0.003	1.11 (0.98–1.25)	0.108
Model 3 adjusted as in Table 2 (sex omitted in sex-stratified analyses). Exposures per SD.				

Discussion

In this 9-year prospective cohort of 10,068 middle-aged and older Chinese adults free of cardiovascular disease at baseline, the TyG index and AIP, two serum-derived markers obtainable from routine biochemistry, were independently associated with incident stroke. Each SD increase corresponded to an 18% and 15% higher stroke risk for TyG and AIP, respectively, with dose–response gradients across tertiles. The associations were independent of hs-CRP and of conventional metabolic risk factors, and they were robust across sensitivity analyses that excluded early events, restricted to survivors, and stratified by sex and age. The trajectory analysis added two observations: a persistently high TyG showed only a trend toward higher risk, and, more importantly, a decline from high to low TyG was associated with a 36% lower stroke risk than a persistently high state. This study contributes three elements to this literature: serum-only indices free of anthropometric measurement error, a demonstration that metabolic dysregulation dominates systemic inflammation in driving stroke risk, and evidence that improving TyG over four years is accompanied by a lower stroke risk.

Our estimates align with prior work linking the TyG index to stroke and cardiovascular disease in Chinese populations [6, 15, 21, 22]. An umbrella review of 29 meta-analyses concluded that a high TyG index was associated with stroke, including a 26% higher stroke risk among individuals with diabetes (RR 1.26, 95% CI 1.18–1.33) [6]. In a parallel CHARLS analysis, participants with a concurrently high TyG index and elevated hs-CRP had a 33% higher stroke risk than those with low levels of both (HR 1.333, 95% CI 1.093–1.628) [15], a pattern consistent with the joint associations we observed here. The HR of 1.18 per SD that we observed in a community-based, stroke-free sample is consistent with these estimates and extends them to a general population of middle-aged and older adults, in whom the exposure range is broader than in disease-specific cohorts. The stroke-specific pattern we observed, with no association for heart disease alone, is notable and requires interpretation. The CHARLS heart disease item combines

myocardial infarction, angina, heart failure, and other cardiac conditions, a heterogeneous grouping that may dilute exposure–outcome associations; stroke, by contrast, is a more homogeneous and severe endpoint, and the cerebrovascular circulation may be particularly sensitive to the small vessel and large artery atherosclerosis that these indices track. Prior CHARLS analyses reported a nonlinear association of the triglyceride-to-HDL-cholesterol ratio, the arithmetic basis of AIP, with stroke, with risk increasing below a ratio of 1.85 (HR 1.28, 95% CI 1.06–1.54) and plateauing above it [21]. Our AIP results extend this work in two ways: by using the log-transformed index, which better approximates lipoprotein particle size, and by showing that the association is independent of hs-CRP and of self-reported dyslipidemia, indicating that the lipid ratio carries information beyond a diagnosis of dyslipidemia alone.

Compared with the recently reported cardiometabolic index, which incorporates waist-to-height ratio and therefore requires anthropometry [14, 23], TyG and AIP are computable from serum alone. This distinction has practical consequences. Triglycerides, glucose, and HDL-cholesterol are measured in standard lipid and metabolic panels, so TyG and AIP can be computed at no additional cost in most clinical and community screening settings, without the equipment, staff training, and standardization required for reliable waist measurement. This property makes the two indices especially suitable for large-scale and resource-limited screening programs, and it removes a source of measurement error that can arise from anthropometry in field surveys.

Our mutual adjustment models showed that TyG and AIP predicted stroke independently of hs-CRP, while hs-CRP was largely explained by the metabolic indices. This suggests that in this population the metabolic component of stroke risk dominates the inflammatory component. The joint analyses indicated that elevated TyG or AIP was sufficient to increase stroke risk even when hs-CRP was low, which supports metabolic screening regardless of inflammatory status. Two interpretations are possible. Metabolic dysregulation may initiate cerebrovascular atherosclerosis before a measurable systemic inflammatory response develops, and inflammation may act partly as a downstream consequence of insulin resistance and dyslipidemia, although the causal direction cannot be resolved from observational data [10, 11]. Either interpretation supports measuring the metabolic indices, rather than hs-CRP alone, for stroke risk stratification in this population.

The trajectory findings extend cross-sectional evidence in two directions. First, the contrast between high-stable and increasing groups (HR 1.53) indicates that persistent exposure is more informative than a single elevated reading. Second, the 36% lower risk associated with moving from high to low TyG between 2011 and 2015 implies that TyG reflects a modifiable metabolic state. These observations parallel reports that dynamic changes in metabolic syndrome scores and in hs-CRP track stroke and mortality risk in Chinese cohorts [16, 17]. The clinical implication is meaningful: weight loss, dietary modification, and pharmacotherapy for glucose and lipid control are established means of lowering TyG, and our data suggest that such improvements may translate into reduced stroke risk over a four-year horizon. Because the continuous TyG change was not associated with stroke, the association appears to depend on the achieved metabolic state rather than the magnitude of the change itself, which emphasizes the value of sustained rather than transient improvement.

Biologically, TyG captures the joint effect of hypertriglyceridemia and hyperglycemia, a proxy for insulin resistance. Insulin resistance drives compensatory hyperinsulinemia, which promotes sodium retention, sympathetic activation, endothelial dysfunction, and a prothrombotic state through reduced nitric oxide bioavailability and increased plasminogen activator inhibitor-1 [5, 24]. AIP reflects the balance of atherogenic triglyceride-rich lipoproteins against HDL and correlates with small dense LDL particles that are more readily retained in the arterial wall and oxidized [7]. hs-CRP marks a pro-inflammatory plaque phenotype and has been linked to atherosclerotic vulnerability and to stroke recurrence [8, 9]. These three markers therefore index distinct but interacting components of the atherosclerotic process, namely insulin resistance, atherogenic lipoprotein burden, and inflammation, which converge on atherosclerotic disease of the cerebral vasculature. This mechanistic convergence is consistent with the stroke-specific association we observed, although the absence of neuroimaging data precludes attribution to any particular stroke subtype.

Strengths of this study include the large, nationally representative sample, nine years of follow-up, use of the recorded year of first stroke diagnosis for event timing, examination of two complementary serum indices with mutual adjustment, joint inflammation analyses, and a trajectory design with repeated blood measurements. Several limitations warrant consideration. Stroke was self-reported, which may introduce misclassification, although its validity in Asian cohorts is acceptable [19], and stroke subtypes could not be distinguished. New stroke diagnoses among the original cohort were incompletely captured at the 2013 wave, and event times were approximated with wave years when diagnosis years were unavailable. Covariates in the trajectory analysis were measured at baseline rather than in 2015. hs-CRP was measured at a single baseline time point and may not capture temporal variation in inflammation. Death was treated as a censoring event in the primary Cox models, which estimate cause-specific hazards and are appropriate for etiologic inference; a survivors-only analysis was presented as a sensitivity analysis but may be subject to selection bias from conditioning on future vital status, and a formal Fine-Gray subdistribution hazard model was not fitted. The sample was restricted to Chinese adults aged 45 years and older, which limits generalizability to other populations and age groups. Residual confounding by unmeasured factors, such as diet, physical activity, and medication use, cannot be excluded, and although we excluded events within the first two years to reduce reverse causation, some residual reverse causation remains possible. Finally, the observational design precludes causal inference.

Conclusions

Among middle-aged and older Chinese adults, the TyG index and AIP were independently and dose-dependently associated with incident stroke over nine years, independent of systemic inflammation and conventional risk factors. A decline from a high to a low TyG over four years was associated with a 36% lower stroke risk, whereas a persistently high TyG showed only a trend toward increased risk. These low-cost serum indices may support stroke risk stratification in community populations.

Abbreviations

AIP: atherogenic index of plasma; BMI: body mass index; CHARLS: China Health and Retirement Longitudinal Study; CI: confidence interval; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; HR: hazard ratio; hs-CRP: high-sensitivity C-reactive protein; SD: standard deviation; TyG: triglyceride-glucose.

Declarations

Ethics approval and consent to participate

The CHARLS study was conducted in accordance with the principles of the **Declaration of Helsinki**. The study was approved by the Biomedical Ethics Review Committee of Peking University (approval number IRB00001052-11015), and all participants provided written informed consent. This secondary analysis used de-identified public-use data and **was exempt from additional ethical approval**.

Clinical trial number: not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The de-identified CHARLS data used in this study are available to registered researchers through the official CHARLS website (https://charls.pku.edu.cn/) after completion of the data-use application and approval process. The authors are not authorized to redistribute participant-level CHARLS data.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Shu-Juan Fan: investigation, methodology, formal analysis, writing (original draft). Liang-Ru Liu: investigation, writing (original draft). Yu-Yao Zhai: investigation, formal analysis.Yun-Long Ma: investigation, writing (review and editing). Dao-Liang Chen: investigation, software, formal analysis. Jun-Xi Xiang: conceptualization, supervision, writing (review and editing). All authors read and approved the final manuscript.

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Use of artificial intelligence

Artificial intelligence tools (DeepSeek V4.0 flash) were solely used to assist with data cleaning, reference organization and language editing of this manuscript. All analyses were verified by the authors, who take full responsibility for the accuracy and integrity of the work.

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Figures

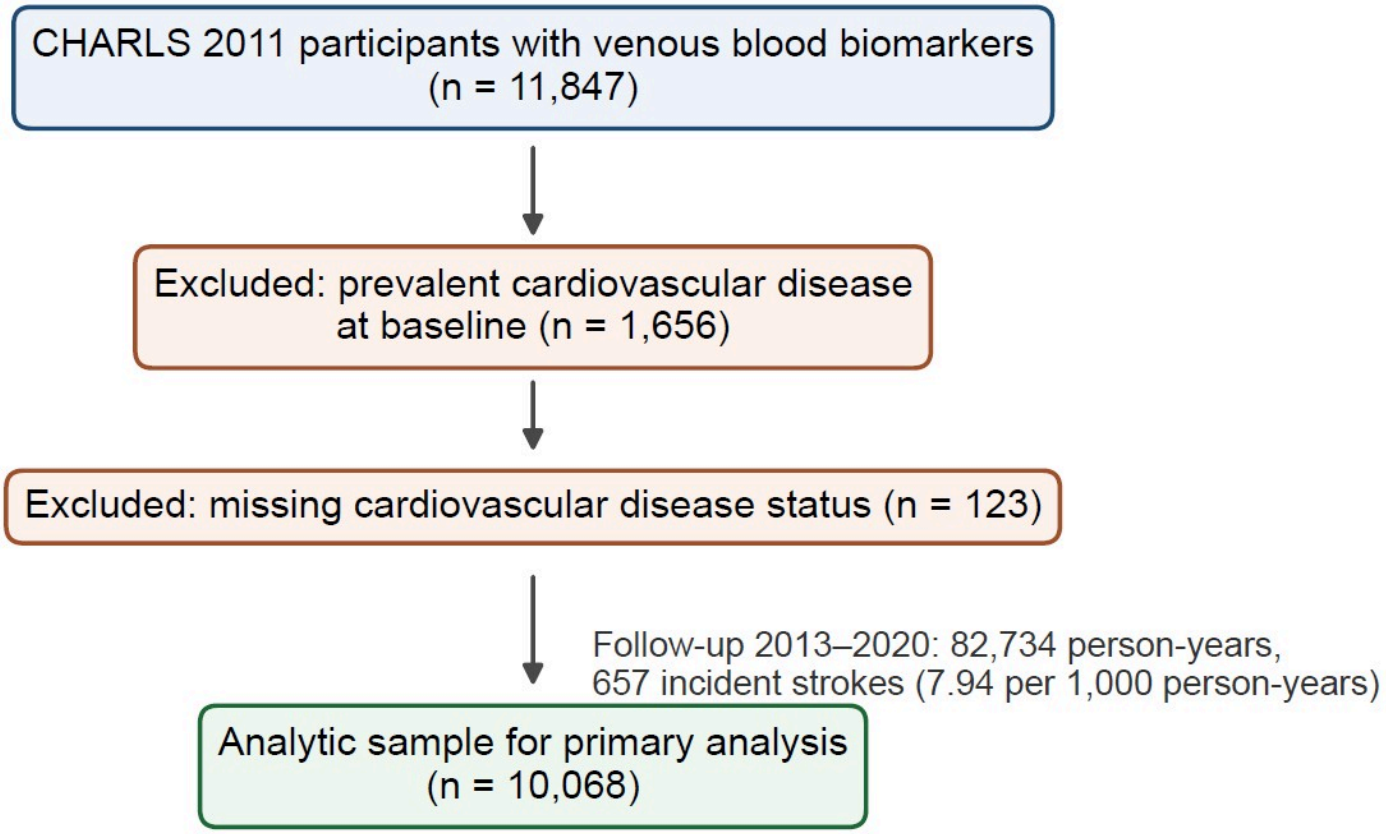


Figure 1

Flowchart of participant selection. CHARLS participants with blood biomarkers in 2011 were eligible; participants with prevalent cardiovascular disease at baseline or missing cardiovascular disease status were excluded, yielding 10,068 participants for the primary analysis.

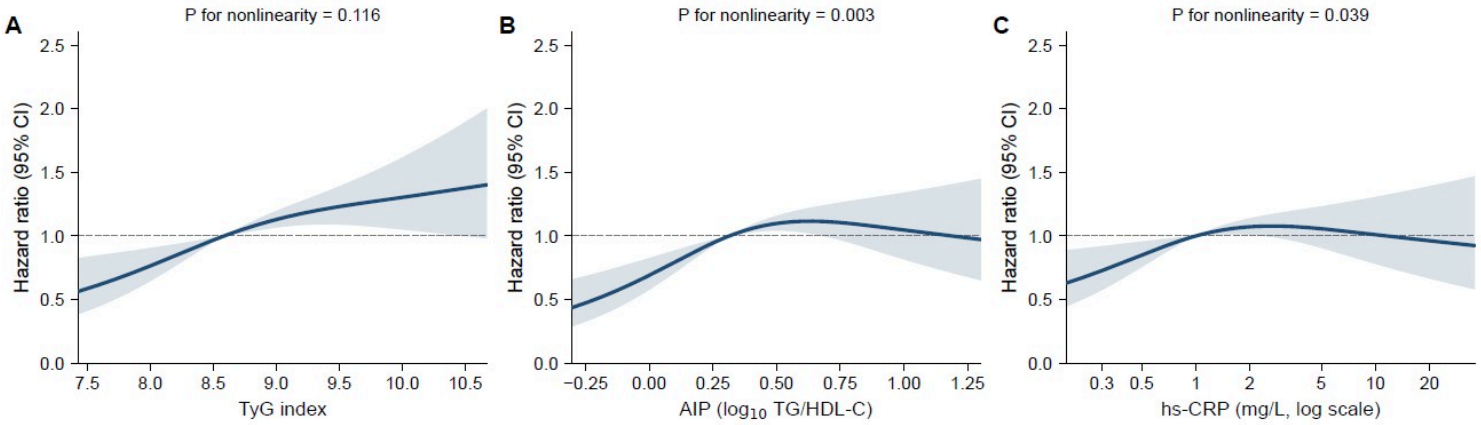


Figure 2

Dose–response associations of (A) the TyG index, (B) AIP, and (C) hs-CRP with incident stroke. Hazard ratios (solid lines) with 95% confidence intervals (shaded bands) are from Cox models with restricted cubic splines (three knots at the 10th, 50th, and 90th percentiles), adjusted as in Model 3, referenced to the sample median and plotted over the 1st to 99th percentile range; the hs-CRP panel uses a logarithmic x-axis. P for nonlinearity (Wald test): TyG 0.116, AIP 0.003, hs-CRP 0.040.

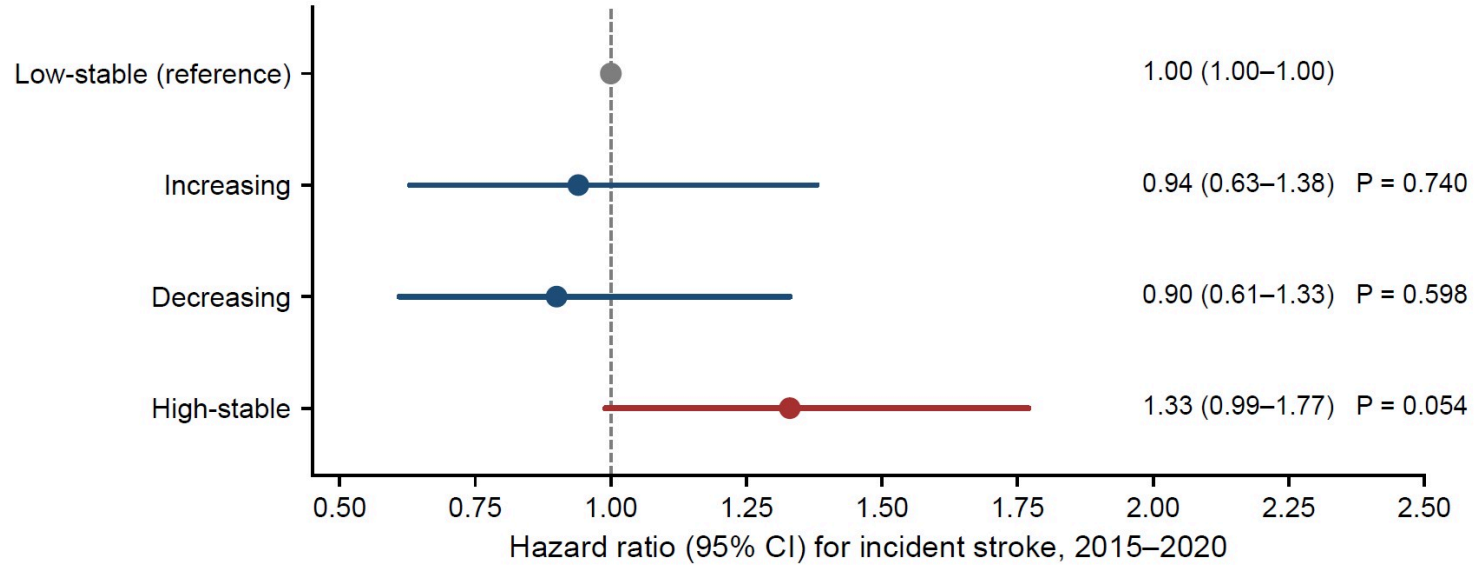


Figure 3

TyG trajectory groups between 2011 and 2015 and incident stroke during 2015 to 2020. Hazard ratios are relative to the low-stable group, adjusted as in Model 3.

Supplementary Files

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