Lipids in Health and Disease

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Atherogenic index of plasma and triglyceride-glucose index mediate the association between stroke and all-cause mortality: insights from the lipid paradox

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Abstract

Background The "lipid paradox" describes the counterintuitive observation that traditionally unfavorable lipid profiles may be associated with improved outcomes in stroke patients. Non-traditional lipid markers such as the atherogenic index of plasma (AIP) and the triglyceride-glucose (TyG) index have been proposed to better reflect the complex metabolic disturbances following stroke. This study aims to investigate the mediating role of AIP and TyG index in the association between stroke and all-cause mortality and elucidate the potential mechanisms underlying the lipid paradox.

Methods This cohort study used data from the China Health and Retirement Longitudinal Study (CHARLS), including 10,220 participants enrolled from 2011 to 2020, with a maximum follow-up of 10 years. AIP and TyG index were calculated from baseline serum measurements. U-test, chi-square test, restricted cubic spline analysis (RCS), cox proportional hazards regression and mediation model were used to analyze the relationship between baseline AIP, TyG index, stroke and all-cause mortality.

Results A total of 1,421 deaths (13.90%) occurred during an average follow-up of 9.21 years. Compared to survivors, non-survivors were older, had a higher prevalence of stroke, and lower AIP levels ($P < 0.05$), while TyG index showed no significant group difference. RCS analysis revealed a nonlinear association between the TyG index and mortality, but no significant nonlinearity for AIP. Cox regression analysis identified age, gender, marital status, smoking history, hypertension, diabetes, lung disease, stroke, AIP, and the highest TyG quartile (Q4) as independent predictors of all-cause mortality (all $P < 0.05$). Notably, AIP showed a negative association with mortality (HR = 0.87, 95% CI: 0.77–0.98),demonstrating a lipid paradox phenomenon. Furthermore, in the chain mediation model, both AIP (β=-0.03, 95%CI: -0.072 to -0.002) and TyG index (β=-0.016, 95%CI: -0.036 to -0.002) independently mediated the association between stroke and all-cause mortality in a negative manner. However, the positive chain mediating effect of AIP through TyG index (β = 0.028, 95%CI: 0.003–0.066) offset this negative mediation, rendering the overall mediating effect insignificant.

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Conclusions AIP and the TyG index independently or jointly influence the risk of all-cause mortality after stroke. Notably, AIP demonstrates a significant lipid paradox phenomenon. Moreover, the chain mediating effect of AIP and TyG significantly increases post-stroke mortality risk. These findings highlight the complex interplay between lipid and glucose metabolism in stroke prognosis and offer a novel perspective for post-stroke metabolic management.

Research insights

What is currently known about this topic? Stroke is frequently associated with metabolic disorders, including dyslipidemia and impaired glucose metabolism, which are strongly linked to an increased risk of mortality. The AIP, as a novel indicator of lipid metabolism, can reflect the risk of lipid abnormalities and atherosclerosis. TyG index is used to evaluate the level of insulin resistance, which is closely related to glucose metabolism disorders.

What is the key research question? How do fluctuations in AIP and TyG index after stroke affect long-term all-cause mortality?

What is new? This study identifies both AIP and TyG index independently and jointly influence all-cause mortality risk following stroke. AIP exhibits a lipid paradox phenomenon in stroke outcome.

How might this study influence clinical practice? Findings could explain the possible mechanism of the lipid paradox, highlighting the interactive effects of lipid and glucose metabolism on stroke prognosis.

Keywords Atherogenic index of plasma, Atherosclerosis, Triglyceride-glucose index, Insulin resistance, Stroke, All-cause mortality

Introduction

The high morbidity and mortality of stroke present a significant challenge to public health, ranking as the second leading cause of death globally [1]. Despite substantial advancements in modern medicine for primary treatment and secondary prevention, the recurrence rate of stroke and all-cause mortality post-stroke remain elevated. Post-stroke metabolic disorders, such as dyslipidemia and glucose metabolism abnormalities, are closely linked to mortality risk. Various lipid markers, including Triglycerides(TG) and High density lipoprotein cholesterol(HDL), have been utilized to assess stroke outcomes [2]. However, emerging research suggests that favorable lipid profiles may not necessarily be associated with improved stroke prognosis; conversely, suboptimal lipid levels exhibit a protective effect during certain disease stages [3–6]. The "lipid paradox" describes this counterintuitive phenomenon where lipid indicators reflect varying prognostic outcomes in stroke patients due to differing pathological states. This may be attributed to higher lipid levels indicating better nutritional status and energy reserves [7]. Additionally, statin therapy might mitigate the adverse cardiovascular effects typically associated with low lipid levels [8]. Nonetheless, the underlying mechanisms remain incompletely understood, necessitating a reevaluation of lipid indicators' predictive role in stroke prognosis.

Recent studies have shown that non-traditional lipid indicators such as atherogenic index of plasma (AIP) and the triglyceride-glucose (TyG) index play an important role in predicting the clinical outcome of stroke [9–12]. Both AIP and TyG index are important markers of metabolic state after stroke, among which AIP, as a new indicator of lipid metabolism, can reflect the risk of lipid abnormalities and atherosclerosis [13], while TyG index is used to evaluate the level of insulin resistance, which is closely related to glucose metabolism disorders [14]. Elevated levels of AIP and TyG index usually suggest metabolic abnormalities, such as hyperglycemia and hyperlipidemia, which may lead to impaired blood-brain barrier function and aggravate nervous system damage [15, 16]. Compared with traditional lipid indicators, AIP and TyG index can better reflect the interaction between lipid and glucose metabolism, which can provide a new perspective for evaluating the prognosis of stroke.

Compared to traditional lipid indicators, which may exhibit contradictory lipid paradoxes in certain pathological conditions, AIP and TyG index are emerging as significant predictors of cardiovascular disease (CVD). However, the combined role of AIP and TyG index in metabolic pathways and their impact on mortality risk following stroke remains unclear. Therefore, further research with larger sample sizes and prospective cohort studies is warranted to elucidate the roles of AIP and TyG post-stroke and their association with mortality risk. This study aims to investigate the mediating effects of AIP and TyG index on the relationship between stroke and all-cause mortality, validate the chain mediation pathway, and elucidate the potential mechanisms underlying the lipid paradox.

Methods

Participants

The data used in this study were sourced from the CHARLS, a comprehensive national survey conducted by the National Institute of Development at Peking University. CHARLS aims to collect and analyze data on the health, economic status, social support, and

psychological well-being of middle-aged and elderly individuals in China [17]. Using a stratified multistage sampling method, CHARLS gathered health-related and sociological data from middle-aged and elderly Chinese individuals and their families across 450 villages in 180 counties, covering 28 provinces. This study utilized five waves of longitudinal data collected in 2011, 2013, 2015, 2018, and 2020, following the same group of participants over time. The participant selection process is illustrated in Fig. 1. In the baseline year (2011), CHARLS enrolled 17,708 participants. After excluding individuals with missing data from both the baseline and the five follow-up waves, a final sample of 10,220 participants was included in the present analysis. The CHARLS project was approved by the Institutional Review Board of Peking University (IRB00001052-11015) and is updated annually to ensure the continuous collection of high-quality data.

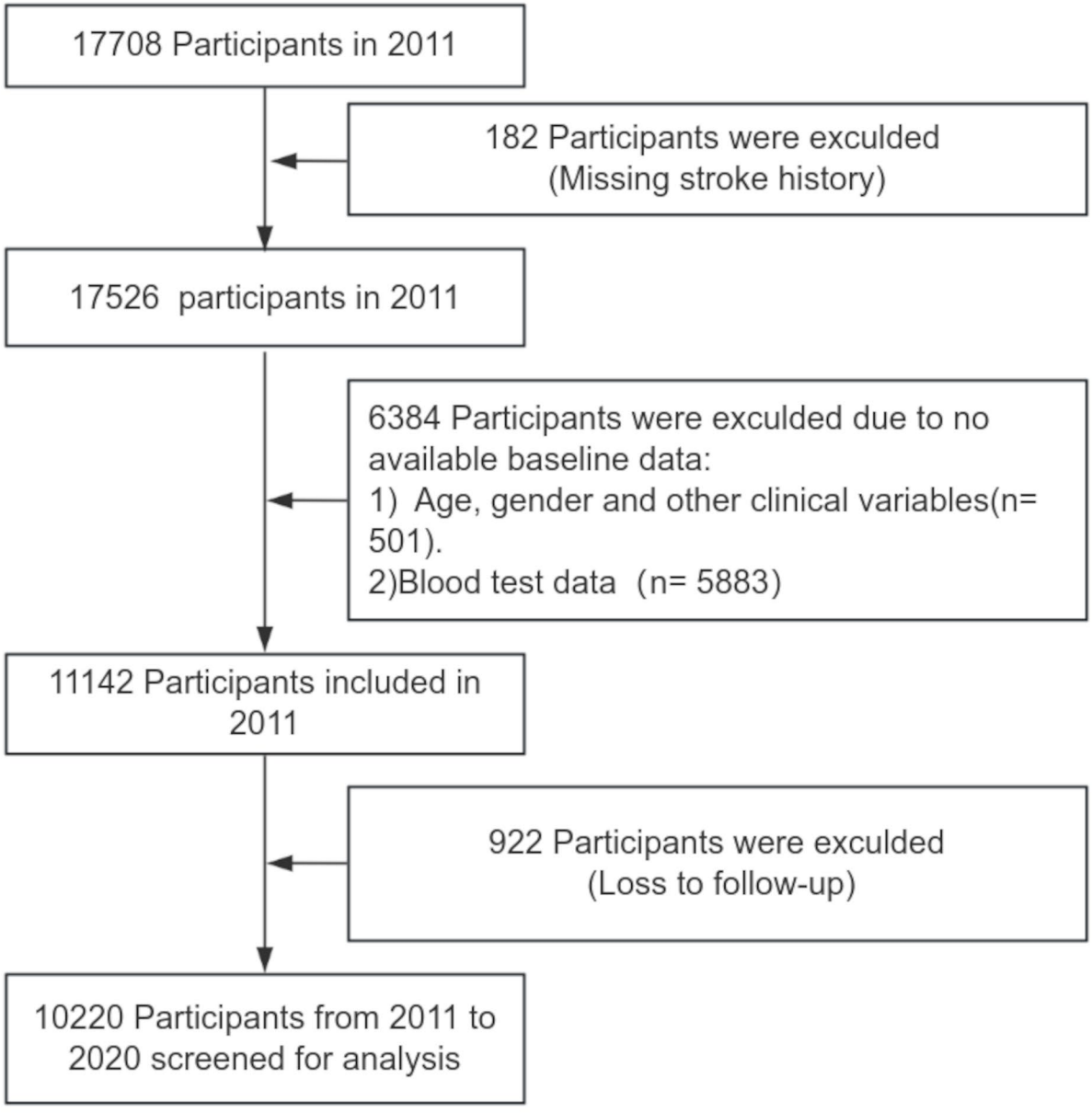

Fig. 1 Participant selection flow chart. Clinical variables: age, gender, marital status, smoking history, alcohol history, hypertension, diabetes, lung disease, kidney disease, and heart disease. Blood test data: fasting blood glucose, triglycerides, cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and glycosylated hemoglobin

Table 1 Baseline characteristics between survivors and non-survivors

Variables	Total (*n* = 10220)	Survivors (*n* = 8799)	non-survivors (*n* = 1421)	Statistic	*P*
Age, M (Q_1, Q_3)	58.00 (51.00, 65.00)	57.00 (50.00, 63.00)	69.00 (61.00, 76.00)	Z=-34.36	**< 0.001**
Male, n(%)	4742 (46.40)	3891 (44.22)	851 (59.89)	χ^2=120.74	**< 0.001**
Married, n(%)	8999 (88.05)	7954 (90.40)	1045 (73.54)	χ^2=330.46	**< 0.001**
Smoking history, n(%)	3990 (39.04)	3243 (36.86)	747 (52.57)	χ^2=126.91	**< 0.001**
Alcohol history, n(%)	3960 (38.75)	3301 (37.52)	659 (46.38)	χ^2=40.47	**< 0.001**
Hypertension, n(%)	2735 (26.76)	2217 (25.20)	518 (36.45)	χ^2=79.10	**< 0.001**
Diabetes, n(%)	617 (6.04)	483 (5.49)	134 (9.43)	χ^2=33.49	**< 0.001**
Lung disease, n(%)	987 (9.66)	725 (8.24)	262 (18.44)	χ^2=145.83	**< 0.001**
Kidney disease, n(%)	577 (5.65)	476 (5.41)	101 (7.11)	χ^2=6.62	**< 0.001**
Heart disease, n(%)	1225 (11.99)	986 (11.21)	239 (16.82)	χ^2=36.54	**< 0.001**
FBG, M (Q_1, Q_3)	102.42 (94.32, 113.40)	102.06 (94.14, 112.50)	104.40 (94.68, 118.98)	Z=-5.14	**< 0.001**
HbA1c, M (Q_1, Q_3)	5.10 (4.90, 5.40)	5.10 (4.90, 5.40)	5.10 (4.90, 5.50)	Z=-1.53	0.125
Cholesterol, M (Q_1, Q_3)	189.82 (166.62, 214.95)	190.21 (167.40, 215.14)	186.73 (160.83, 214.95)	Z=-3.18	**0.001**
TG, M (Q_1, Q_3)	105.32 (75.22, 155.76)	106.20 (75.22, 156.65)	102.66 (72.57, 149.57)	Z=-3.03	**0.002**
HDL, M (Q_1, Q_3)	49.29 (40.21, 59.92)	49.10 (40.21, 59.54)	50.26 (40.21, 61.47)	Z=-2.13	**0.033**
LDL, M (Q_1, Q_3)	114.05 (92.78, 136.86)	114.43 (93.56, 137.24)	110.18 (87.76, 134.54)	Z=-4.28	**< 0.001**
Stroke, n(%)	271 (2.65)	185 (2.10)	86 (6.05)	χ^2=73.93	**< 0.001**
AIP, M (Q_1, Q_3)	0.75(0.28, 1.29)	0.76(0.29, 1.29)	0.68 (0.22, 1.22)	Z=-3.06	**0.002**
Tyg, M (Q_1, Q_3)	8.60(8.23, 9.06)	8.60(8.23, 9.06)	8.61 (8.20, 9.06)	Z=-0.23	0.822

Values in **bold** indicate $p < 0.05$. FBG: Fasting blood glucose, HbA1c: Glycated Hemoglobin, TG: Triglycerides, HDL: High density lipoprotein cholesterol, LDL: Low density lipoprotein cholesterol, AIP: Atherogenic index of plasma, TyG: Triglyceride-glucose index, Z: Mann-Whitney test, χ^2: Chi-square test, M: Median, Q_1: 1st Quartile, Q_3: 3st Quartile

Definitions

Stroke status at baseline, which included both embolic and hemorrhagic subtypes, was determined using the following questions: "Have you been diagnosed with stroke by a doctor? " and "Do you know if you have had a stroke?". All blood tests were conducted **after** the questionnaire interview. The AIP is an important indicator of lipid metabolism, calculated as the base-10 logarithm of the ratio of TG to HDL [9]. The formula is as follows: $AIP = log\left(\frac{\mathrm{TG}}{\mathrm{HDL-C}}\right)$. The TyG index is an important indicator of insulin resistance, calculated as the natural logarithm of half the product of TG and Fasting Blood Glucose(FBG) [11]. The formula is as follows: $TyG = \ln\left(\frac{\mathrm{TG}\times \mathrm{FPG}}{2}\right)$. All measurements of TG, HDL, and FBG are expressed in mmol/L.

Follow up of endpoint events

The outcome event in this study was all-cause mortality recorded during four follow-up waves over a 10-year period, including deaths due to disease, injury, or any other cause. Mortality data were determined based on the survival status of participants in Waves 2, 3, 4, and 5, including deaths caused by diseases, injuries, or any other reasons. Mortality information was obtained from the CHARLS annual survey questionnaires. In Wave 2, only the death dates of deceased participants were collected, and the mortality data were obtained through the question: "What was the date on which [Respondent] died?". In Waves 3, 4, and 5, the survival status of all participants from the previous wave was recorded, and the mortality data were obtained through the question: "Is [Respondent] still alive?".

Statistical analysis

In this study, IBM SPSS Statistics 27.0 was used for data analysis. The selection of covariates was based on prior literature, biological plausibility, and clinical relevance. Four categories of covariates were considered: (1) demographic factors (age, sex, marital history), (2) behavioral factors (smoking history, alcohol history), (3) chronic diseases (hypertension, diabetes, lung disease, kidney disease, heart disease), and (4) metabolic biomarkers (FBG, glycated hemoglobin, cholesterol, TG, HDL, LDL). All continuous variables in this study were non-normally distributed and are presented as median (interquartile

range), with comparisons performed using the Mann-Whitney U test. Categorical variables were summarized as frequencies (n) and percentages (%) and analyzed using the chi-square test.

To evaluate the potential nonlinear relationships of AIP and TyG index with all-cause mortality, restricted cubic spline (RCS) analyses were conducted within a Cox proportional hazards regression framework, including age, sex, marital status, smoking history, alcohol history, hypertension, diabetes, lung disease, kidney disease, and heart disease. Given that our primary objective was to explore the chain mediating effect of AIP and TyG index between stroke and all-cause mortality, we included TyG index as an additional covariate in the RCS model for AIP. The both RCS models incorporated four knots, positioned at the 5th, 35th, 65th, and 95th percentiles of the respective exposure variable distributions, ensuring sufficient flexibility to capture potential nonlinear trends. Given the time-to-event nature of the data, Cox proportional hazards regression analysis instead of Logistic regression was performed to identify independent predictors of all-cause mortality while adjusting for the same set of confounders (age, sex, marital status, smoking history, alcohol history, hypertension, diabetes, lung disease, kidney disease, and heart disease). Finally, based on the independent risk factors identified in the Cox regression model, a chain mediation model was constructed to investigate the pathways linking AIP and TyG index with stroke and all-cause mortality. The chain mediation model was executed using the PROCESS macro (Model 6) in IBM SPSS Statistics 27.0. A P-value < 0.05 was considered statistically significant.

Results

General characteristics of participants

Presents the baseline characteristics of the eligible participants ($N = 10{,}220$). Among them, 1,421 participants experienced outcome events during an average follow-up of 9.21 years, accounting for 13.90% of the total evaluable respondents. Significant differences were observed between survivors and non-survivors in gender, age, marital status, smoking history, alcohol history, hypertension, diabetes, lung disease, kidney disease, heart disease, AIP, and stroke (all $P \leq 0.01$). However, no significant difference was found for the TyG index

Restricted cubic splines

We conducted a RCS analysis to assess the nonlinear relationships between AIP, TyG index, and all-cause mortality (Figs. 2 and 3). The results revealed a significant nonlinear association between the TyG index and the risk of all-cause mortality. In contrast, AIP showed a significant linear association with all-cause mortality.

Cox proportional hazards model

In the prior RCS analysis, the TyG index exhibited a nonlinear association with all-cause mortality. To account for this nonlinearity and reduce potential bias, the TyG index was categorized into quartiles in the Cox regression model. After adjusting for confounding factors, including age, sex, and marital status, both AIP and the highest quartile of the TyG index remained significantly associated with all-cause mortality (Table 2). Specifically, participants in the highest quartile of the TyG index (Q4) had a significantly increased risk of all-cause mortality (HR = 1.33, 95% CI: 1.04–1.70, $P = 0.024$), while no significant differences were observed in Q2 and Q3. To assess the robustness of our findings, we conducted sensitivity analyses by categorizing AIP into quartiles in the Cox model and employing logistic regression instead of Cox regression. Both approaches yielded consistent trends, reinforcing the reliability of our results (Supplementary Tables 1 and 2).

Furthermore, to further underscore the rationale for selecting the TyG index over its individual components, we constructed additional Cox regression models replacing TyG with either FBG or TG (Supplementary Tables 3 and 4). When FBG was included in place of TyG, it remained a significant predictor; however, AIP lost its statistical significance. Similarly, when TG replaced TyG, neither TG nor AIP showed a significant association with all-cause mortality. These findings highlight that the TyG index, as an integrated marker of glucose and lipid metabolism, not only retains the predictive information of its components but also enhances model robustness and interpretability.

Chained mediation of AIP and TYG

We investigated the mediating effect of stroke on mortality risk through AIP and TyG index (Fig. 4). The analysis revealed a statistically significant direct effect of stroke on all-cause mortality (Effect = 0.729, $p < 0.001$). AIP and TyG index, as mediators, influenced mortality risk through distinct and opposing pathways. Specifically, the individual mediating effects of AIP and TyG index reduced the risk of all-cause mortality after stroke, while the chain mediation effect of AIP through TyG index increased this risk. As the mediating effects along paths 1 and 2 were offset by the opposing effect along path 3, the overall mediating effect between stroke and all-cause mortality was not statistically significant (Table 3).

Discussion

To explore the influencing factors and potential mechanisms of all-cause mortality in stroke survivors, this study examined the association between the AIP and the TyG index with all-cause mortality, using a large sample of middle-aged and older adults combined with

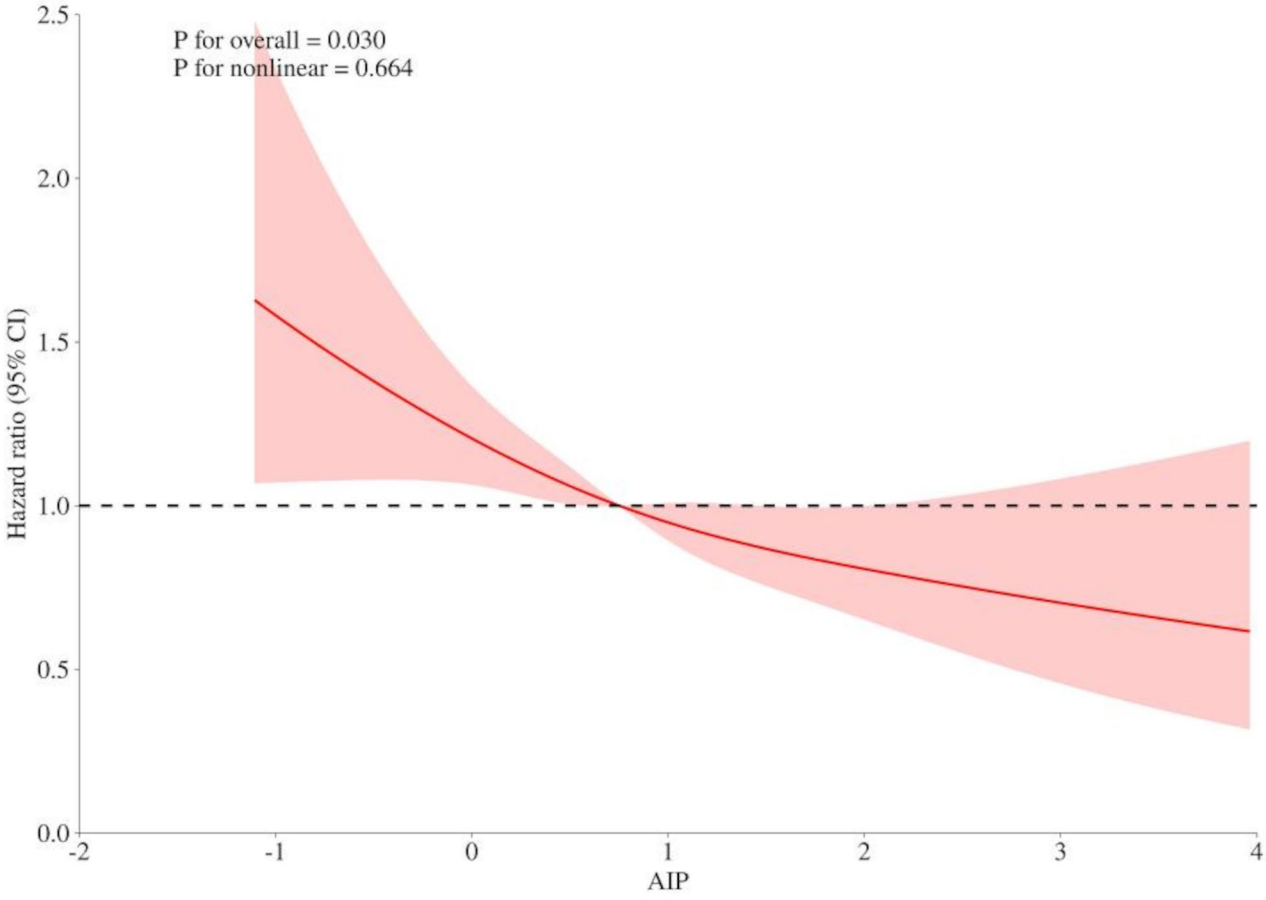

Fig. 2 Association of AIP and the risk of all-cause mortality using a multivariable-adjusted restricted cubic spines model. AIP: Atherogenic index of plasma

chain mediation analysis. Both AIP and TyG index independently mediated the relationship between stroke and all-cause mortality in a negative direction, whereas the chain mediation effect of AIP through TyG index showed a positive impact. In post-stroke health management, abnormal lipid and glucose metabolism should be considered critical factors when assessing the risk of all-cause mortality.

All-cause mortality

In this study, the all-cause mortality rate was 13.90% over an average follow-up of 9.21 years, compared with 14.83% over 8.13 years in the Beijing Elderly Comprehensive Health Cohort Study (95% CI: 13.79–15.86%) [18]. Compared to survivors, non-survivors had a higher prevalence of stroke, lower AIP levels, and no significant difference in the TyG index. However, Cox proportional hazards regression analysis identified both AIP and TyG index as independent predictors of all-cause mortality. This suggests that the association between the TyG index and all-cause mortality may be influenced by potential moderating or mediating factors.

Chain mediation effect

Stroke disrupts oxygen and energy supply to brain tissue, triggering a cascade of pathophysiological changes, including increased blood-brain barrier permeability, neuroinflammation, neuronal apoptosis, autophagy, excitotoxicity, ion imbalance, and oxidative stress [19, 20]. Animal studies have shown that stroke induces an acute systemic metabolic response, characterized by imbalances in lipid synthesis and degradation, leading to lipid metabolic disorders [21]. Although the overall mediating effect was not statistically significant, the roles of AIP and TyG index—key indicators of lipid metabolism and insulin resistance—in post-stroke mortality warrant further investigation.

Mediation effect of AIP

In addition to adipose tissue, the nervous system constitutes the largest lipid reservoir in the human body, and dyslipidemia plays a pivotal role in both the pathogenesis and prognosis of stroke [4]. Dyslipidemia, characterized by elevated TG and reduced HDL, can alter the secretion pattern of adipocytokines, thereby influencing metabolic and inflammatory processes. These alterations impair

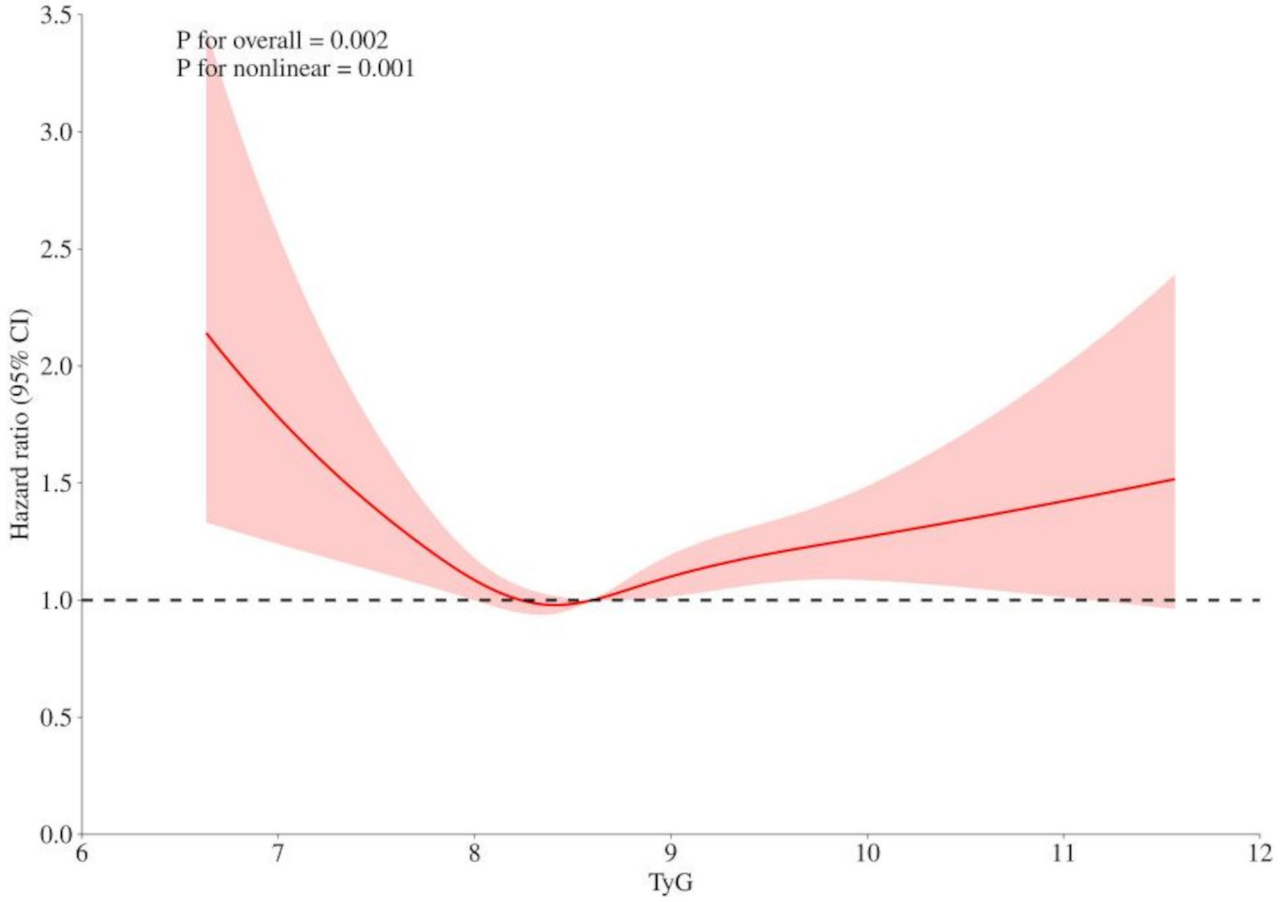

Fig. 3 Association of TyG index and the risk of all-cause mortality using a multivariable-adjusted restricted cubic spines model. TyG: Triglyceride-glucose index

Table 2 Cox regression analysis of factors associated with all-cause mortality

Variables	β	S.E	Z	*P*	HR [95%CI]
Age	0.08	0.00	29.39	**< 0.001**	1.09 [1.08 ~ 1.09]
Gender	0.35	0.08	4.64	**< 0.001**	1.42 [1.23 ~ 1.65]
Married	-0.32	0.07	-4.84	**< 0.001**	0.73 [0.64 ~ 0.83]
Smoking history	0.23	0.07	3.23	**0.001**	1.26 [1.09 ~ 1.44]
Alcohol history	0.08	0.06	1.31	0.189	1.08 [0.96 ~ 1.23]
Hypertension	0.18	0.06	3.01	**0.003**	1.19 [1.06 ~ 1.34]
Diabetes	0.38	0.10	3.97	**< 0.001**	1.46 [1.21 ~ 1.76]
Lung disease	0.43	0.07	6.16	**< 0.001**	1.54 [1.34 ~ 1.76]
Kidney disease	0.18	0.11	1.70	0.089	1.20 [0.97 ~ 1.47]
Heart disease	0.10	0.07	1.35	0.178	1.11 [0.96 ~ 1.28]
Stroke	0.48	0.11	4.23	**< 0.001**	1.62 [1.30 ~ 2.03]
AIP	-0.14	0.06	-2.27	**0.023**	0.87 [0.77 ~ 0.98]
TyG					
Q2	-0.03	0.08	-0.40	0.691	0.97 [0.83 ~ 1.14]
Q3	0.15	0.09	1.64	0.100	1.17 [0.97 ~ 1.40]
Q4	0.29	0.13	2.25	**0.024**	1.33 [1.04 ~ 1.70]

Values in **bold** indicate $p < 0.05$. AIP: Atherogenic index of plasma, TyG: Triglyceride-glucose index, HR: Hazard Ratio, CI: Confidence Interval

metabolic health and increase the risk of CVD and insulin resistance [22].The AIP, which reflects the ratio of TG to HDL, is closely associated with atherosclerosis risk. Higher AIP values typically correspond to smaller, denser LDL particles that are more prone to oxidation, contributing to CVD [23, 24]. However, this study revealed a negative mediating effect of AIP in stroke patients, where higher AIP levels were associated with lower all-cause mortality—a phenomenon known as the "lipid paradox". Previous studies have highlighted a lipid paradox in the relationship between TG and HDL with all-cause mortality.For instance, the Chinese Longitudinal Healthy Longevity Survey(CLHLS) reported that higher TG levels were significantly linked to lower all-cause mortality (HR = 0.79, 95% CI: 0.69–0.89) [25]. Similarly, a study on HDL and all-cause mortality in the Chinese population showed that HDL levels exceeding 70 mg/dL were linked to 4.64 deaths per 100,000 individuals (95% UI: 0.24–9.76) [26].

Thus, AIP, which consists of TG and HDL, exhibits the lipid paradox due to the complex physiological mechanisms of its components. This phenomenon may reflect a

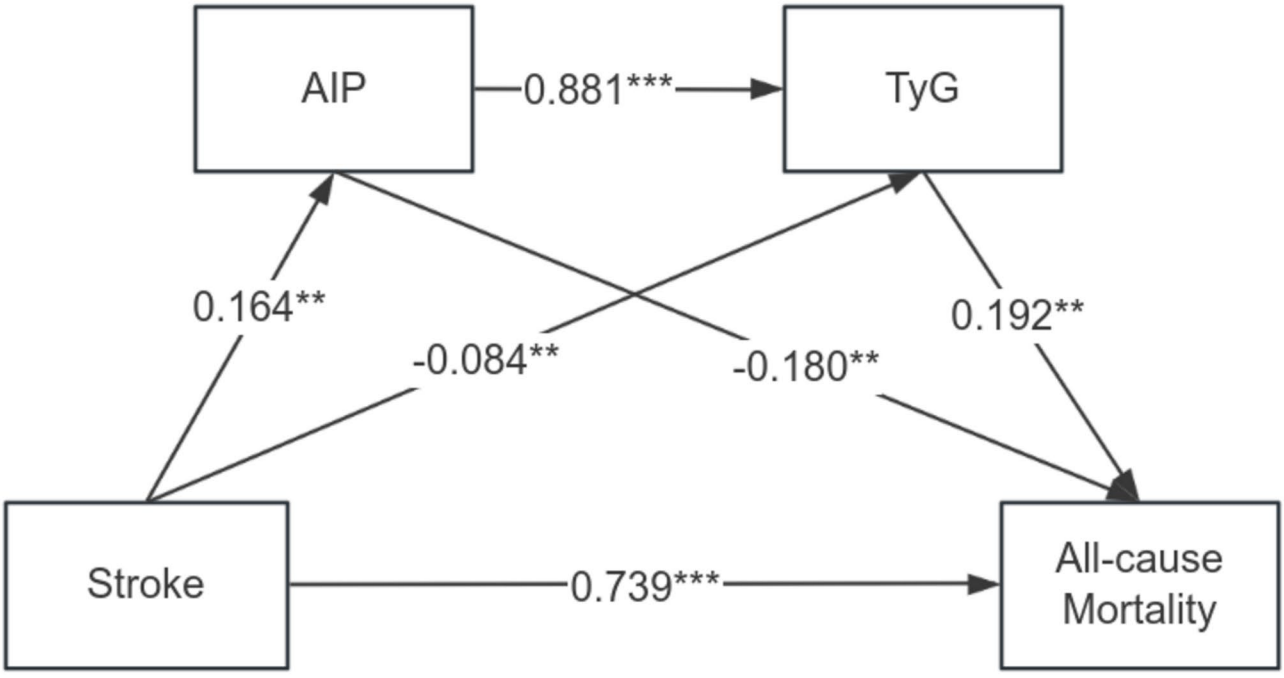

Fig. 4 Diagram of the chained mediation model.(*$p < 0.05$,** $p < 0.01$, ***< 0.001)

Table 3 Effects of the individual paths of the chained mediation model

DIRECT AND INDIRECT EFFECTS	effect	SE	LLCI	ULCI
Direct effect	0.739	0.154	0.437	1.041
Total indirect effect	-0.018	0.011	-0.041	0.001
Ind1: Stroke → AIP→ Dead	-0.030	0.018	-0.072	-0.003
Ind2: Stroke → TyG→ Dead	-0.016	0.009	-0.036	-0.002
Ind3: Stroke→ AIP→ TyG→ Dead	0.028	0.017	0.003	0.066

AIP: Atherogenic index of plasma, TyG: Triglyceride-glucose index

short-term compensatory mechanism or metabolic adaptation following stroke. Elevated lipid levels might exert protective effects on prognosis by promoting cellular repair, stabilizing membrane structures, and providing essential energy. Recent studies have demonstrated that triolein, a symmetric TG, can attenuate neuronal autophagy and reduce post-stroke inflammatory responses by inhibiting the activation of the AKT/mTOR signaling pathway [27]. Moreover, an alternative explanation for the lipid paradox suggests that lower lipid levels may indicate frailty, malnutrition, or advanced disease stages [28]. Although such individuals may have "ideal" lipid profiles in the conventional sense, their actual mortality risk is higher due to compromised baseline health conditions [29, 30].The lipid paradox highlights that abnormal lipid levels post-stroke may reflect a compensatory response aimed at tissue repair, rather than serving as an indicator of long-term disease risk. This underscores the importance of evaluating AIP comprehensively, considering the stroke recovery phase, individual nutritional status, and overall metabolic profile, rather than simply categorizing AIP levels as "harmful" or "beneficial".

Mediation effect of TyG index

Dysglycemia following stroke is a common complication strongly associated with adverse outcomes [31]. A longitudinal study on glucose metabolism in stroke patients revealed that, despite intensive post-stroke management, a significant proportion of patients progressed to prediabetes (33.9% vs. 44.1%) or developed type 2 diabetes (21.5% vs. 23.4%) within the first year [32]. In this context, the TyG index has emerged as a widely used marker for assessing insulin resistance [33].Research indicates that individuals with elevated TyG index have a 1.5-fold increased risk of stroke recurrence and a 1.4-fold higher likelihood of mortality [34]. In addition, higher TyG index levels are associated with an increased risk of all-cause mortality. A meta-analysis of 18 studies (592,635 ischemic stroke cases) further confirmed the association between elevated TyG index and both stroke recurrence and mortality [35]. In the Cox survival regression analysis, the fourth quartile of the TyG index was identified as an independent predictor of mortality risk. This finding aligns with the study by Pu et al. [11], which demonstrated that patients in the highest TyG index quartile had the greatest mortality risk. Further mediation analysis revealed a negative mediating effect of the TyG index between stroke and mortality, suggesting that stroke may lead to a reduction in TyG levels, which, in turn, is significantly associated with lower mortality risk. This finding

implies that post-stroke metabolic improvements and enhanced insulin sensitivity may partially mitigate the risk of death in stroke patients. Therefore, changes in the TyG index following stroke may serve as novel predictors and potential intervention targets for improving stroke prognosis.

Notably, in this study, the TyG index did not show a significant difference in baseline characteristics analysis. While mediation analysis suggested a protective effect of the TyG index on mortality risk, this effect will not consistently observed across all stroke patients. The RCS analysis further revealed a nonlinear association between the TyG index and all-cause mortality, indicating that a simple comparison of medians between groups may not fully capture the complexity of this relationship. Univariate analysis may have underestimated the influence of the TyG index, as its effect on mortality could be mediated or modified by interactions with other metabolic indicators and risk factors [36, 37]. Additionally, individual metabolic profiles, stroke subtypes, and variations in metabolic responses during treatment may influence the predictive value of the TyG index in stroke prognosis. Given these findings, future research should further explore the role of the TyG index as a mediator, particularly by investigating its impact across different TyG strata and its interactions with other metabolic risk factors.

Chaind mediation effect of AIP and TyG index

There exists a complex interplay between abnormal lipid metabolism and disordered glucose metabolism, both of which contribute significantly to the pathophysiology of stroke. Research has shown that individuals with elevated AIP levels exhibit higher rates of obesity, hypertension, diabetes, and metabolic syndrome [38]. Furthermore, elevated AIP levels are closely linked to insulin resistance, which, in turn, is strongly associated with an increased risk of cardiovascular events [39]. Given the close relationship between both AIP and the TyG index with stroke occurrence and prognosis, as well as their significant roles in the development of CVD, this study incorporated AIP and TyG index into a chain mediation model to explore their mechanisms in influencing all-cause mortality post-stroke.The findings revealed that the chain mediation effect of AIP and TyG index substantially contributed to the increased risk of all-cause mortality following stroke. This suggests that stroke-induced metabolic disturbances, such as the deterioration of lipid and glucose metabolism, often lead to heightened insulin resistance, thereby increasing the risk of mortality. These results are consistent with the study by Li et al., which showed that FBG plays a mediating role in the association between TG, AIP, and acute ischemic stroke, influencing stroke risk in patients with intracranial atherosclerotic stenosis [40].

While the individual mediating effects of AIP and TyG index may mitigate post-stroke mortality risk, their combined chain mediation effect may exacerbate this risk. The interaction mechanism between these indices is complex. Specifically, due to opposing directional effects among different mediation pathways (individual pathways exhibited negative effects, whereas the chained pathway exhibited a positive effect), an additive effect occurred among these pathways, partially offsetting each other. This explains why the overall mediating effect did not reach statistical significance. When AIP is combined with TyG index, the AIP no longer exhibits a lipid paradox but functions as a conventional risk factor. The synergistic effects of dyslipidemia and insulin resistance help explain the lipid paradox phenomenon. For example, Zhou et al. identified a threshold effect between AIP and insulin resistance, noting that the risk of type 2 diabetes increases significantly when AIP levels exceed − 0.268 [41]. The lipid paradox associated with AIP may arise from an underrepresentation of the negative effects of insulin resistance, creating a false protective effect of AIP. This suggests that relying solely on AIP may not fully capture the influence of metabolic syndrome on all-cause mortality post-stroke. However, when the chain mediation pathway is further analyzed, the persistent adverse effects of insulin resistance on mortality may obscure or counteract the lipid paradox seen with AIP in certain contexts, reverting to a conventional high-risk pattern. Similarly, compared to groups with low TyG index and low AIP, the hazard ratio for CVD in groups with high TyG index and high AIP levels was 1.27 (95% CI: 1.10–1.43), indicating a significant co-exposure effect of TyG index and AIP on CVD [36].

The chain mediation effect of AIP and TyG index between stroke and mortality provides a more comprehensive understanding of the impact of metabolic disorders after stroke, elucidating how lipid metabolism and insulin resistance jointly influence stroke patient mortality. Future studies should focus on investigating the dynamic changes in metabolic indicators following stroke and their long-term effects on mortality risk, with the goal of optimizing metabolic management strategies for stroke patients.

Limitations

To the best of our knowledge, this study is the first to explore the relationship between AIP and TyG index with all-cause mortality following stroke. However, several limitations should be acknowledged. First, this study utilized only baseline measurements of AIP and the TyG index, which limits the ability to capture their dynamic changes over time. These indicators may not only

fluctuate after stroke but also act as upstream risk factors that contribute to stroke onset, thereby indirectly influencing all-cause mortality. Second, the dataset lacked detailed information on medications such as statins, niacin, fibrates, or novel hypoglycemic agents, which could have influenced lipid and glucose metabolism and, consequently, the study outcomes. Additionally, the study population primarily consisted of middle-aged and older Chinese adults, which may limit the generalizability of our findings to other age groups or ethnicities. Cultural, genetic, and environmental differences may influence both metabolic profiles and stroke outcomes. Therefore, future studies involving more diverse and international populations are needed to verify the broader applicability of these results. Finally, our study was unable to differentiate between embolic and hemorrhagic stroke subtypes, in which the effects of AIP and the TyG index on all-cause mortality may vary accordingly. Investigations incorporating detailed stroke subtype classification are warranted to clarify these relationships.

Summary

This study demonstrated that the AIP and the TyG index independently mediated the relationship between stroke and all-cause mortality in a negative direction, in which AIP supporting the lipid paradox. However, their chain mediation effects of AIP and TyG index were associated with an increased risk of mortality, emphasizing the interactive impact of lipid and glucose metabolism on stroke prognosis.

Abbreviations

AIP	Atherogenic index of plasma
TyG	Triglyceride-glucose
CHARLS	China Health and Retirement Longitudinal Survey
CLHLS	Chinese Longitudinal Healthy Longevity Survey
CVD	Cardiovascular disease
FBG	Fasting blood glucose
TG	Triglycerides
HDL	High density lipoprotein cholesterol
LDL	Low density lipoprotein cholesterol
LLCI	Lower limit of confidence interval
ULCI	Upper limit of confidence interval
HR	Hazard Ratio
SD	Standard deviation

Supplementary Information

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Supplementary Material 1

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Author contributions

JQ and LZ contributed to the study design. JQ drafted the manuscript. JQ, QC, and CQ were responsible for data collection. QC and FX performed the statistical analysis. WD, TW and LZ participated in data review and manuscript revision.

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Data availability

The datasets generated and/or analysed during the current study are available in the China Health and Retirement Longitudinal Study repository, http://charls.pku.edu.cn.

Declarations

Ethics approval and consent to participate

The CHARLS project was approved by the Institutional Review Board of Peking University (IRB00001052-11015) and is updated annually to ensure the continuous collection of high-quality data.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Feigin VL, Owolabi MO, World Stroke Organization–Lancet Neurology Commission Stroke Collaboration Group. Pragmatic solutions to reduce the global burden of stroke: a world stroke Organization-Lancet neurology commission. Lancet Neurol. 2023;22(12):1160–206.
2. Liu H, Liu K, Pei L, et al. Atherogenic index of plasma predicts outcomes in acute ischemic stroke. Front Neurol. 2021;12:741754.
3. Vainshelboim B, Myers J. Dyslipidemia paradox: analysis from the veterans exercise testing study. PLoS ONE. 2023;18(7):e0287923.
4. Hellström S, Sajanti A, Srinath A, et al. Common lipidomic signatures across distinct acute brain injuries in patient outcome prediction. Neurobiol Dis. 2025;204:106762.
5. Zhao Z, Wang H, Hou Q, Zhou Y, Zhang Y. Non-traditional lipid parameters as potential predictors of carotid plaque vulnerability and stenosis in patients with acute ischemic stroke. Neurol Sci. 2023;44(3):835–43.
6. Shen FC, Lin HY, Tsai WC, et al. Non-insulin-based insulin resistance indices for predicting all-cause mortality and renal outcomes in patients with stage 1–4 chronic kidney disease: another paradox. Front Nutr. 2023;10:1136284.
7. Neeland IJ, Poirier P, Després JP. Cardiovascular and metabolic heterogeneity of obesity: clinical challenges and implications for management. Circulation. 2018;137(13):1391–406.
8. Kim JT, Lee JS, Kim BJ, et al. Admission LDL-cholesterol, Statin pretreatment and early outcomes in acute ischemic stroke. J Clin Lipidol. 2023;17(5):612–21.
9. Onat A, Can G, Kaya H, Hergenç G. Atherogenic index of plasma (log10 triglyceride/high-density lipoprotein-cholesterol) predicts high blood pressure, diabetes, and vascular events. J Clin Lipidol. 2010;4(2):89–98.
10. Yu S, Yan L, Yan J, et al. The predictive value of nontraditional lipid parameters for intracranial and extracranial atherosclerotic stenosis: a hospital-based observational study in China. Lipids Health Dis. 2023;22(1):16.
11. Pu Y, Xing N, Wang Y, Wang H, Xu J, Li X. Differential impact of TyG and TyG-BMI indices on short- and long-term mortality in critically ill ischemic stroke patients. BMC Cardiovasc Disord. 2024;24(1):754.

12. Liu Y, Wang Z, Zhang Z, et al. Correlation between triglyceride-glucose index and early neurological deterioration in patients with acute mild ischemic stroke. Front Neurol. 2024;15:1441116.
13. Liu Z, Zhang L, Wang L, et al. The predictive value of cumulative atherogenic index of plasma (AIP) for cardiovascular outcomes: a prospective community-based cohort study. Cardiovasc Diabetol. 2024;23(1):264.
14. Liu D, Ren B, Tian Y, Chang Z, Zou T. Association of the TyG index with prognosis in surgical intensive care patients: data from the MIMIC-IV. Cardiovasc Diabetol. 2024;23(1):193.
15. Wu S, Mao Y, Chen S, et al. Safety and efficacy of tight versus loose glycemic control in acute stroke patients: A meta-analysis of randomized controlled trials. Int J Stroke. 2024;19(7):727–34.
16. Imeh-Nathaniel E, Imeh-Nathaniel S, Imeh-Nathaniel A, Coker-Ayo O, Kulkarni N, Nathaniel TI. Sex differences in severity and risk factors for ischemic stroke in patients with hyperlipidemia. Neurosci Insights. 2024;19:26331055241246745.
17. Zhao Y, Hu Y, Smith JP, et al. Cohort profile: the China health and retirement longitudinal study (CHARLS)[J]. Int J Epidemiol. 2014;43(1):61–8.
18. Wang ZRH,Li, Liying et al. Association of changes in frailty status with the risk of all-cause mortality and cardiovascular death in older people: results from the Chinese Longitudinal Healthy Longevity Survey (CLHLS)[J].BMC Geriatr,2024,24(1):96.
19. Bernoud-Hubac N, Lo Van A, Lazar AN, Lagarde M. Ischemic brain injury: involvement of lipids in the pathophysiology of stroke and therapeutic strategies. Antioxid (Basel). 2024;13(6):634.
20. Wei W, Lattau S, Xin W, et al. Dynamic brain lipid profiles modulate microglial lipid droplet accumulation and inflammation under ischemic conditions in mice. Adv Sci (Weinh). 2024;11(41):e2306863.
21. Haley MJ, White CS, Roberts D, et al. Stroke induces prolonged changes in lipid metabolism, the liver and body composition in mice. Transl Stroke Res. 2020;11(4):837–50.
22. Islam MS, Wei P, Suzauddula M, et al. The interplay of factors in metabolic syndrome: Understanding its roots and complexity. Mol Med. 2024;30(1):279.
23. Wang Y, Wang S, Sun S, et al. The predictive value of atherogenic index of plasma for cardiovascular outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention with LDL-C below 1.8mmol/L. Cardiovasc Diabetol. 2023;22(1):150.
24. Kim SH, Cho YK, Kim YJ, et al. Association of the atherogenic index of plasma with cardiovascular risk beyond the traditional risk factors: a nationwide population-based cohort study. Cardiovasc Diabetol. 2022;21(1):81.
25. Lv YB, Mao C, Gao X, et al. Triglycerides paradox among the oldest old: the lower the better?? J Am Geriatr Soc. 2019;67(4):741–8.
26. Lu J, Han G, Liu X, et al. Association of high-density lipoprotein cholesterol with all-cause and cause-specific mortality in a Chinese population of 3.3 million adults: a prospective cohort study. Lancet Reg Health West Pac. 2024;42:100874.
27. Wang C, Li Y, Zhang Y, et al. Triolein alleviates ischemic stroke brain injury by regulating autophagy and inflammation through the AKT/mTOR signaling pathway. Mol Med. 2024;30(1):242.
28. Lu YW, Lu SF, Chou RH, et al. Lipid paradox in patients with acute myocardial infarction: potential impact of malnutrition. Clin Nutr. 2019;38(5):2311–8.
29. Chen L, Chen S, Bai X, et al. Low-Density lipoprotein cholesterol, cardiovascular disease risk, and mortality in China. JAMA Netw Open. 2024;7(7):e2422558.
30. Nair L, Asuzu P, Dagogo-Jack S. Ethnic disparities in the risk factors, morbidity, and mortality of cardiovascular disease in people with diabetes. J Endocr Soc. 2024;8(7):bvae116.
31. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke. 2001;32(10):2426–32.
32. Moelgg K, Karisik A, Scherer L et al. Prediabetes and diabetes mellitus type II after ischemic stroke. Eur Stroke J. 2025: 23969873241304301.
33. Cao J, Zhou D, Yao Z, et al. Insulin resistance, vulnerable plaque and stroke risk in patients with carotid artery stenosis. Sci Rep. 2024;14(1):30453.
34. Paul S, Candelario-Jalil E. Emerging neuroprotective strategies for the treatment of ischemic stroke: an overview of clinical and preclinical studies. Exp Neurol. 2021;335:113518.
35. Yang Y, Huang X, Wang Y, et al. The impact of triglyceride-glucose index on ischemic stroke: a systematic review and meta-analysis. Cardiovasc Diabetol. 2023;22(1):2.
36. Zeng Q, Zhong Q, Zhao L, An Z, Li S. Combined effect of triglyceride-glucose index and atherogenic index of plasma on cardiovascular disease: a National cohort study. Sci Rep. 2024;14(1):31092.
37. Luo YD, Gan YY, Liao Q, Li X, Huo RR. Interacting and joint effects of triglyceride-glucose index and hypertension on stroke risk in middle-aged and older Chinese adults: a population-based prospective cohort study. Front Cardiovasc Med. 2024;11:1363049.
38. Zhu X, Yu L, Zhou H, et al. Atherogenic index of plasma is a novel and better biomarker associated with obesity: a population-based cross-sectional study in China. Lipids Health Dis. 2018;17(1):37.
39. Salazar MR, Carbajal HA, Espeche WG, et al. Comparison of the abilities of the plasma triglyceride/high-density lipoprotein cholesterol ratio and the metabolic syndrome to identify insulin resistance. Diab Vasc Dis Res. 2013;10(4):346–52.
40. Li S, Wang Y, Zhu X, et al. Lipid on stroke in intracranial artery atherosclerotic stenosis: a mediation role of glucose. Front Endocrinol (Lausanne). 2024;15:1322114.
41. Zhou Q, Wu Y, Li M. Association between the atherogenic index of plasma and long-term risk of type 2 diabetes: a 12-year cohort study based on the Japanese population. Cardiovasc Diabetol. 2025;24(1):50.

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