Research Paper

Association between the sarcopenia index and the risk of stroke in elderly patients with hypertension: a cohort study

Xintian Cai[1,*], Junli Hu[1,*], Mengru Wang[1], Wen Wen[1], Jingyu Wang[2], Wenbo Yang[1], Yujie Dang[1], Qin Luo[1], Jing Hong[1], Nanfang Li[1]

[1]Hypertension Center, Xinjiang Hypertension Institute, NHC Key Laboratory of Hypertension Clinical Research, Key Laboratory of Xinjiang Uygur Autonomous Region, Xinjiang Clinical Medical Research Center for Hypertension Diseases, People's Hospital of Xinjiang Uygur Autonomous Region, Ürümqi, Xinjiang 830000, China
[2]Renal Division, Peking University First Hospital, Beijing 100034, China
[*]Equal contribution

Correspondence to: Nanfang Li; **email:** lnanfang2016@sina.com, https://orcid.org/0000-0003-1505-8566
Keywords: sarcopenia index, hypertension, elderly patients, stroke, cohort study
Received: December 9, 2022 **Accepted:** March 6, 2023 **Published:** March 21, 2023

ABSTRACT

The purpose of this study was to investigate the relationship between the sarcopenia index (SI) and stroke risk in elderly patients with hypertension. This study included 5145 stroke-free elderly hypertensive patients. We used Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of incident stroke. Over a median follow-up of 38 months, we identified 607 (11.80%) individuals with total stroke, of whom 507 (9.85%) had ischemic stroke and 93 (1.81%) had hemorrhagic stroke. The risk of developing stroke decreased with each quartile of SI; after adjustment for multiple confounders, the HRs for the Q4 group versus the Q1 group were 0.46 (95% CI, 0.35–0.59) for total stroke, 0.46 (95% CI, 0.35–0.61) for ischemic stroke, and 0.33 (95% CI, 0.17–0.64) for hemorrhagic stroke. Restricted cubic spline analysis also demonstrated a cumulative increase in the risk of total stroke with decreases in the SI. The addition of SI to the conventional model for total stroke improved (ΔC-statistics = 0.02), an integrated discrimination improvement of 0.03 (95% CI, 0.02–0.04), and a net reclassification improvement of 0.17 (95% CI, 0.10–0.23). Similar results were observed for ischemic stroke and hemorrhagic stroke. This study found that elevated SI was negatively associated with the risk of stroke in elderly patients with hypertension. Uncovering the causality behind the relationship requires further prospective study.

INTRODUCTION

Stroke has become a major public health problem worldwide, and the financial burden associated with stroke treatment and post-stroke care is significant, especially for older adults [1, 2]. Stroke is a common cause of death and disability in the aging population [3]. In China, stroke was the leading cause of death, disability-adjusted life years, and years of life lost in 2017 [2]. Hypertension is the most common risk factor for patients with prevalent stroke in China [4]. In addition, traditional risk factors cannot fully explain all the risks of stroke [5–7]. Therefore, it is clinically important to understand more modifiable risk factors for stroke, especially in older patients with hypertension.

Sarcopenia is a significant geriatric condition that affects aging societies and is characterized by decreased skeletal muscle mass, low muscular strength, and/or poor physical performance [8]. According to several studies, the percentage of elderly Asian individuals who have sarcopenia ranges from 6.8% to 25.7% [9–12]. Many studies have indicated that sarcopenia and heart disease in the elderly have many pathophysiological

aspects in common [13–15]. Sarcopenia is independently associated with prevalent cardiovascular diseases and their associated risk factors [16–18]. Currently, muscle mass is quantified using magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry, and bioelectrical impedance analysis [19–21]. However, these techniques have drawbacks such as radiation exposure and a lack of cost effectiveness, as well as increased needs for skilled experts and specialized equipment [22]. It was recently suggested to use the sarcopenia index (SI), a straightforward alternative screening method based on the ratio of serum creatinine (Cr) to cystatin C (CysC) levels [23]. Recent epidemiological studies have also demonstrated that in various populations, including the elderly, SI can be effectively used to measure muscle mass, strength, and functional status [23–25]. According to Hyun et al., individuals with chronic renal disease had an increased risk of all-cause mortality and cardiovascular events when their blood Cr/CysC ratio was high [26]. A low Cr/CysC ratio has also been linked to cardiovascular disease events and death in older individuals with coronary artery disease and those with obstructive coronary artery disease [27, 28]. However, little research has been done to investigate the association between SI and new-onset strokes. To date, the relationship between SI and the risk of stroke is still unknown, especially in older patients with hypertension.

Therefore, we conducted a cohort study to investigate the association between SI and the risk of stroke in elderly patients with hypertension.

MATERIALS AND METHODS

Patient selection

In this retrospective cohort study, elderly hypertensive patients (age ≥ 60 years) were admitted to the People's Hospital of Xinjiang Uygur Autonomous Region. Detailed descriptions of this study have been reported previously [29]. Those who met the following criteria were excluded: (1) patients had no data on Cr or CysC, (2) patients with kidney disease or an eGFR of less than 60 mL/min/1.73 m^2, (3) loss to follow-up or follow-up duration <6 months, and (4) patients had a history of stroke, malignancy, liver cirrhosis, advanced heart failure, or chronic lung disease. After these exclusions, 5145 participants were included in the final analysis. Participant flow is illustrated in Supplementary Figure 1. Approval was obtained from the Ethical Committee of the People's Hospital of Xinjiang Uygur Autonomous Region (No. KY2021031901). Owing to the retrospective data collection, it was not deemed to require informed consent. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline recommendations.

Data collection and measurements

Data were abstracted electronically from the patient's medical records, including demographics, anthropometric measures, risk factors, diagnoses according to the International Classification of Diseases 10th Revision (ICD-10), prescribed medications, and laboratory data. Smoking status was dichotomized as current smokers vs. non-smokers. A similar classification was used for alcohol use (current drinkers and non-drinkers). All blood samples were collected in the morning, on fasting participants. Laboratory parameters included fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), fasting lipid profile, liver and renal function tests, homocysteine (Hcy), and high-sensitivity C-reactive protein (hs-CRP). Serum Cr level was measured using an enzymatic method, and CysC levels were measured with the immunoturbidimetric assay. The SI was calculated as (serum Cr divided by serum CysC)*100 [23]. eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [30]. Information on disease history was obtained using ICD-10 codes. To ensure the accuracy of diagnoses, coronary heart disease (CHD) (I24 and I25), diabetes (E10-E14), atrial fibrillation (I48), and dyslipidemia (E78) were regarded as present if a participant was treated ≥ 2 times. The burden of comorbidity was measured using the Charlson Comorbidity Index (CCI) [31]. Prescription claims in the last year prior to the concomitant medications identified at baseline. The list of concomitant medications included in this study is shown in Supplementary Table 1.

Follow-up and outcome assessment

Each participant's follow-up period (measured in person-years) was computed from the baseline date to the earliest of the following dates: incidence of stroke, death, loss to follow-up, or 31 December 2021 (the study's end of follow-up), whichever came first. Outcomes of events since participants enrolled in the study were determined through checking medical records, interviews, contact with local disease and death registries, and electronic linkage with the national health insurance claim databases. Trained staff with no knowledge of baseline information used ICD-10 to code all diagnoses and deaths. The primary outcome was the first occurrence of total stroke (ICD-10: I60-I64), including morbidity and mortality. Secondary outcomes included first ischemic stroke (ICD-10: I63) and first hemorrhagic stroke [subarachnoid (ICD-10: I60) or intracerebral (ICD-10: I61)]. An independent clinical

events committee reviewed and centrally adjudicated these outcome events.

Statistical analysis

Details of the missing covariates are shown in Supplementary Table 2. We performed multiple imputation to recover missing covariates. Baseline characteristics were compared between groups categorized by SI levels. The age-adjusted incidence rates were determined by calculating age-specific incidence rates within 1-year age categories. Time to first stroke event was examined using Kaplan-Meier survival curves and compared using log-rank test. Multicollinearity was tested using the variance inflation factor (Supplementary Table 3). Testing for proportional hazards used Schoenfeld residuals (Supplementary Figure 2). Cox regression analysis was used to assess the association between SI and stroke and its subtypes, and hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated. Values for trend tests were assigned using the within-quartile medians. Additionally, we used restricted cubic splines to investigate the non-linear associations between SI and the outcomes. Furthermore, subgroup analyses were done and differences were examined using tests for interaction. Sensitivity analyses assessed robustness of results. First, we specified a 1-year exposure lag to circumvent the potential bias of reverse causation. Second, we did competing-risk analysis that treats non-stroke-related deaths as a competing risk. Third, sensitivity analyses were performed that excluded all individuals with CCI $\geq$ 2. Fourth, participants with atrial fibrillation were excluded. Lastly, potential unmeasured confounding was examined by calculating E-values. The additional value of adding SI to the conventional model was evaluated by C-statistics, the net reclassification index (NRI), and the integrated discrimination index (IDI). More details are found in the Supplementary Materials and Methods.

All analyses were performed using R 4.1.1 software, with a two-sided significance p-value < 0.05.

RESULTS

Study population and characteristics

As illustrated in the flowchart (Supplementary Figure 1), a total of 5145 eligible participants were included in the present study. Among the included participants, the average age was 66.54 ± 4.79 years, and 2481 (48.22%) participants were female. The distribution of SI is shown in Supplementary Figure 3. The mean SI index was 90.41 ± 24.04, and we categorized the population into four groups based on the quartiles of the SI (Table 1).

Association of SI with total stroke and its subtypes

Over a median follow-up of 38 months (IQR: 19–64 months), we identified 607 (11.80%) individuals with total stroke, of whom 507 (9.85%) had ischemic stroke and 93 (1.81%) had hemorrhagic stroke. The age-adjusted incidence of total strokes decreased substantially with the magnitude of SI (quartiles), reaching a maximum incidence of 43.34 per 1000 person-years in quartile 4 (Figure 1). Similarly, the risks of ischemic and hemorrhagic stroke decreased as SI quartiles increased. The Kaplan-Meier curve showed that participants in the quartile 1 group had a higher risk of total stroke, ischemic stroke, and hemorrhagic stroke than those in other groups (log-rank test, $P < 0.001$, Figure 2A; $P < 0.001$, Figure 2B; $P = 0.007$, Figure 2C). Overall, lower SI was significantly associated with higher hazards of stroke and its subtypes among elderly patients with hypertension (Figure 3). In the fully-adjusted model that measured the SI as a continuous variable, each 10-unit increment in the SI was associated with a 12% lower risk of total stroke (HR 0.88, 95% CI 0.85–0.92; Table 2). The cumulative hazard of total stroke also decreased with increasing SI, and this trend persisted even after adjusting for potential confounding factors in Model 3 (P for trend < 0.001). The HRs were 0.85 (95% CI, 0.69–1.05), 0.57 (95% CI, 0.45–0.72), and 0.46 (95% CI, 0.35–0.59) for the quartile 2, quartile 3, and quartile 4 groups versus the quartile 1 group of SI (Table 2). The results were similar when the association between SI and ischemic stroke and hemorrhagic stroke was examined (Table 2). In the restricted cubic spline analysis, we observed a significant dose-response relationship between SI and the risk of total stroke (P for non-linear association = 0.003) (Figure 3A). Similar results were observed in ischemic strokes (P for non-linear association = 0.002) (Figure 3B), but not in hemorrhagic strokes (P for non-linear association = 0.525) (Figure 3C).

To investigate the robustness of our findings, we conducted multiple sensitivity analyses. In the sensitivity analyses, the associations of SI with the risk of stroke and its subtypes were not materially changed after excluding participants who developed strokes within the first year of follow-up (Supplementary Table 4), participants with CCI $\geq$ 2 (Supplementary Table 5), participants with atrial fibrillation (Supplementary Table 6), or participants with a competing risk model (Supplementary Table 7). Sensitivity analyses using E-values also revealed that strong unmeasured confounding is required for the observed association to be null (Supplementary Table 8 and Supplementary Figure 4).

Table 1. Population characteristics by quartiles of SI.

Variables	Quartiles of SI			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
	(≤74.03)	(74.04–87.27)	(87.31–103.69)	(≥103.70)
Participants, *N*	1286	1286	1286	1287
Age, years	66.74 (4.87)	66.43 (4.82)	66.39 (4.54)	66.60 (4.92)
Male, *N* (%)	590 (45.88%)	620 (48.21%)	717 (55.75%)	737 (57.26%)
Hypertension duration, years				
≤5	800 (62.21%)	1024 (79.63%)	942 (73.25%)	1009 (78.46%)
>5 to ≤10	146 (11.35%)	77 (5.99%)	180 (14.00%)	179 (13.92%)
>10	340 (26.44%)	185 (14.39%)	164 (12.75%)	98 (7.62%)
Heart rate, bpm	79.68 (9.14)	80.23 (8.99)	79.68 (9.20)	80.12 (9.11)
SBP, mmHg	141.43 (17.77)	140.76 (16.63)	140.23 (17.06)	139.03 (17.38)
DBP, mmHg	84.61 (12.66)	86.24 (12.66)	87.31 (12.62)	89.36 (12.54)
BMI, kg/m^2	24.34 (2.37)	24.44 (2.40)	24.30 (2.33)	24.59 (2.36)
Current smoker, *N* (%)	509 (39.58%)	443 (34.45%)	391 (30.40%)	229 (17.81%)
Current drinker, *N* (%)	482 (37.48%)	381 (29.63%)	322 (25.04%)	180 (14.00%)
Comorbidities, *N* (%)				
Coronary heart disease	225 (17.50%)	197 (15.32%)	209 (16.25%)	220 (17.09%)
Diabetes	326 (25.35%)	384 (29.86%)	363 (28.23%)	361 (28.05%)
Dyslipidemia	799 (62.13%)	807 (62.75%)	771 (59.95%)	783 (60.84%)
Atrial fibrillation	39 (3.03%)	43 (3.34%)	42 (3.27%)	31 (2.41%)
Charlson comorbidity index				
0	415 (32.27%)	577 (44.87%)	629 (48.91%)	673 (52.29%)
1	414 (32.19%)	368 (28.62%)	335 (26.05%)	344 (26.73%)
≥2	457 (35.54%)	341 (26.52%)	322 (25.04%)	270 (20.98%)
Laboratory parameters				
ALT, U/L	21.87 (14.00–31.62)	23.00 (14.36–34.02)	23.98 (15.00–34.30)	25.20 (16.60–34.50)
AST, U/L	21.00 (16.00–28.00)	21.45 (16.89–27.64)	21.26 (16.39–27.28)	21.01 (16.00–27.66)
GGT, U/L	24.22 (15.14–36.60)	25.30 (16.00–38.58)	28.03 (17.94–40.14)	29.00 (19.00–42.22)
Creatinine, mg/dL	0.66 (0.13)	0.77 (0.17)	0.82 (0.19)	0.89 (0.20)
UA, μmol/L	303.68 (79.50)	325.87 (81.20)	334.40 (85.55)	349.45 (85.95)
BUN, mmol/L	5.29 (1.37)	5.17 (1.41)	5.30 (1.42)	5.26 (1.38)
Cystatin C, mg/L	1.07 (0.22)	0.96 (0.21)	0.87 (0.20)	0.75 (0.19)
eGFR, ml/min/1.73 m^2	94.00 (17.75)	93.28 (18.18)	93.56 (17.64)	95.70 (18.54)
TC, mmol/L	4.47 (3.79–5.10)	4.52 (3.77–5.20)	4.52 (3.85–5.15)	4.47 (3.85–5.03)
TG, mmol/L	1.50 (1.06–2.15)	1.49 (1.06–2.25)	1.64 (1.11–2.32)	1.67 (1.15–2.41)
HDL-C, mmol/L	1.08 (0.92–1.26)	1.04 (0.89–1.23)	1.06 (0.89–1.24)	1.02 (0.88–1.21)
LDL-C, mmol/L	2.73 (2.15–3.27)	2.80 (2.20–3.32)	2.79 (2.24–3.33)	2.79 (2.26–3.26)
HbA1c, %	6.08 (0.91)	6.12 (0.90)	6.07 (0.94)	6.10 (0.89)
FPG, mmol/L	5.13 (1.13)	5.09 (1.11)	4.98 (0.98)	5.06 (1.13)
Hcy, μmol/L	14.26 (5.52)	14.62 (5.90)	15.33 (5.74)	15.36 (6.31)
Hs-CRP, mg/L	1.96 (1.10–3.34)	2.00 (1.13–3.46)	2.10 (1.18–3.46)	1.98 (1.11–3.18)
Medications, *N* (%)				
ACEI/ARB	969 (75.35%)	919 (71.46%)	916 (71.23%)	883 (68.61%)
Beta-blocker	495 (38.49%)	490 (38.10%)	459 (35.69%)	458 (35.59%)
Calcium channel blockers	1039 (80.79%)	1046 (81.34%)	1015 (78.93%)	1017 (79.02%)
Diuretic	292 (22.71%)	284 (22.08%)	320 (24.88%)	299 (23.23%)

Insulin	131 (10.19%)	152 (11.82%)	125 (9.72%)	121 (9.40%)
Oral antidiabetic drugs	196 (15.24%)	273 (21.23%)	230 (17.88%)	235 (18.26%)
Statins	597 (46.42%)	553 (43.00%)	633 (49.22%)	598 (46.46%)
Aspirins	901 (70.06%)	907 (70.53%)	883 (68.66%)	906 (70.40%)

Variables were presented as mean (SD), median (IQR), or *N* (%). Abbreviations: SI: sarcopenia index; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HbA1c: hemoglobin A1c; FPG: fasting plasma glucose; Hcy: homocysteine; UA: uric acid; Cr: blood creatinine; BUN: blood urea nitrogen; hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; ACEI: angiotensin-converting enzyme inhibitor; IQR: interquartile range; SD: standard deviation.

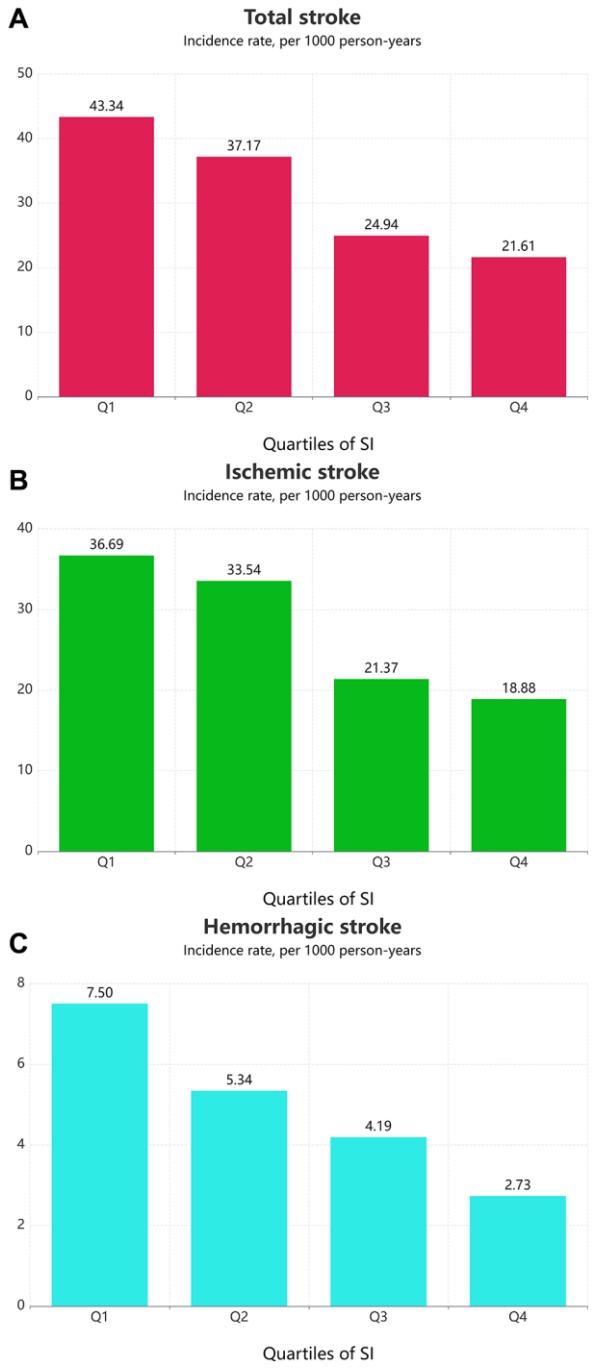


Figure 1. Age-adjusted incidence of outcomes according to the SI quartiles. (**A**) Total stroke; (**B**) Ischemic stroke; (**C**) Hemorrhagic stroke.

Stratified analyses

We further performed exploratory subgroup analyses to assess the association between SI (per 10-unit increment) and the risk of stroke and its subtypes among elderly patients with hypertension (Figure 4). In the stratified analyses, age, sex, BMI, smoking status, drinking status, eGFR, hypertension duration, dyslipidemia, CCI, and coronary heart disease did not significantly modify the association between the SI and the risk of new-onset total strokes (all *P*-interactions > 0.05) (Figure 4A). Although the *P* value for the interaction of diabetes status in elderly hypertensive patients was less than 0.05, due to the similar directionality of the association, the result may not be clinically significant (Figure 4A). None of the variables significantly modified the association between SI and the risk of new-onset ischemic stroke and hemorrhagic stroke (all *P* for interactions > 0.05) (Figure 4B and 4C).

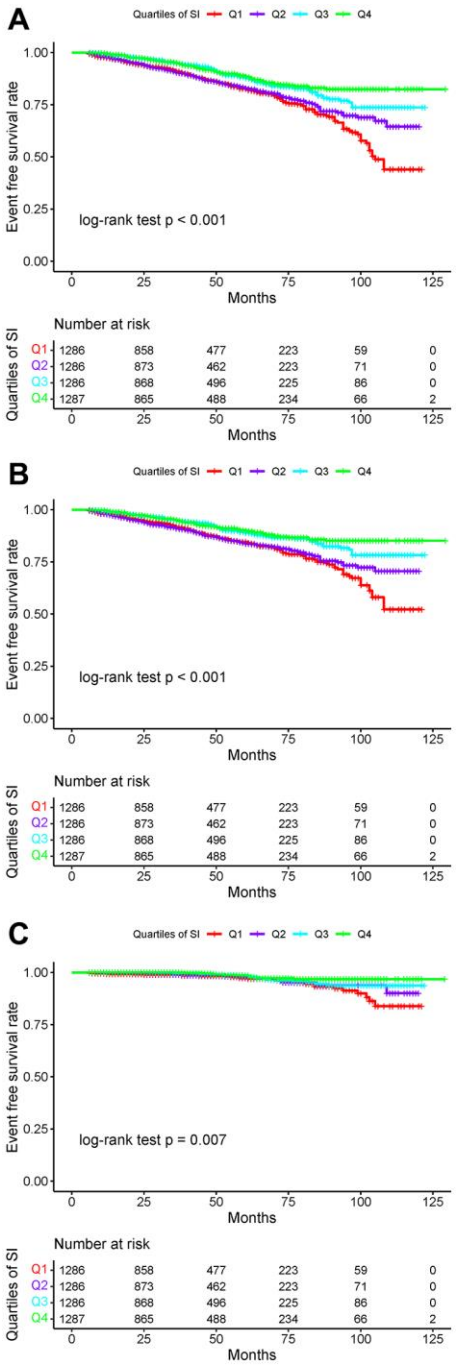


Figure 2. Kaplan-Meier survival curves for total strokes and individual outcomes based on SI quartiles. (**A**) Total stroke; (**B**) Ischemic stroke; (**C**) Hemorrhagic stroke.

Incremental predictive value of SI

We assessed whether SI would boost the traditional model's prediction power even further (Supplementary Table 9). With the addition of SI, the conventional model's C statistics greatly improved (Δ C-statistics = 0.02). With an IDI of 0.03 (95% CI, 0.02–0.04) and an NRI of 0.17 (95% CI, 0.10–0.23), the discriminating power and risk reclassification also seemed to be much superior. Both ischemic and hemorrhagic strokes had similar results.

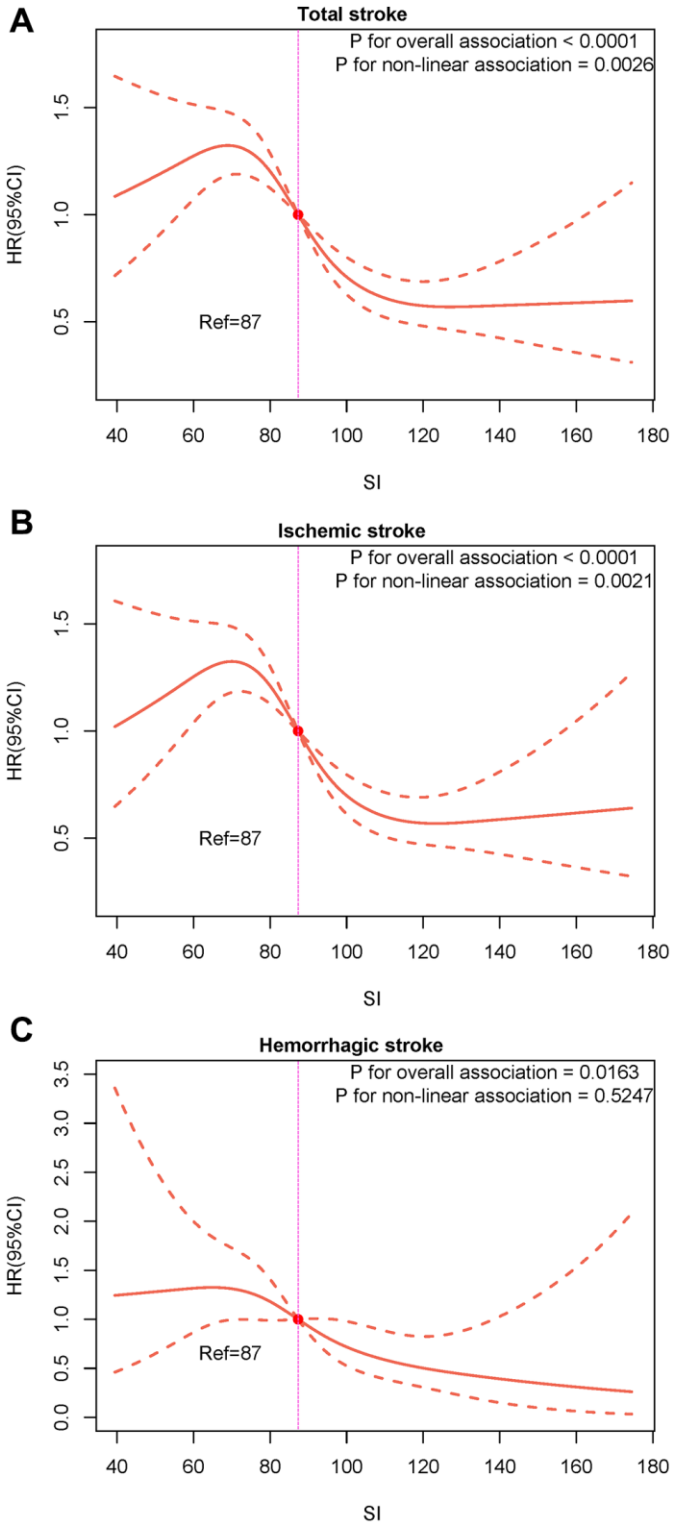


Figure 3. Restricted cubic splines for the associations of SI with the risk of total stroke and its subtypes. (**A**) Total stroke; (**B**) Ischemic stroke; (**C**) Hemorrhagic stroke.

Table 2. Association of SI with incident stroke.

Outcome	HR (95% CI)		
	Model 1	Model 2	Model 3
Total stroke			
Per 10-unit increment	0.89 (0.86, 0.92)	0.89 (0.86, 0.92)	0.88 (0.85, 0.92)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.86 (0.70, 1.05)	0.85 (0.69, 1.04)	0.85 (0.69, 1.05)
Q3	0.57 (0.45, 0.71)	0.58 (0.46, 0.73)	0.57 (0.45, 0.72)
Q4	0.49 (0.39, 0.63)	0.48 (0.37, 0.61)	0.46 (0.35, 0.59)
P for trend	<0.001	<0.001	<0.001
Ischemic stroke			
Per 10-unit increment	0.89 (0.86, 0.93)	0.89 (0.85, 0.93)	0.88 (0.85, 0.92)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.91 (0.73, 1.13)	0.90 (0.72, 1.12)	0.90 (0.73, 1.13)
Q3	0.58 (0.45, 0.74)	0.58 (0.46, 0.75)	0.58 (0.45, 0.74)
Q4	0.51 (0.40, 0.66)	0.49 (0.37, 0.63)	0.46 (0.35, 0.61)
P for trend	<0.001	<0.001	<0.001
Hemorrhagic stroke			
Per 10-unit increment	0.86 (0.79, 0.95)	0.86 (0.78, 0.95)	0.85 (0.77, 0.94)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.71 (0.42, 1.18)	0.71 (0.42, 1.20)	0.71 (0.42, 1.20)
Q3	0.55 (0.32, 0.95)	0.54 (0.31, 0.94)	0.52 (0.29, 0.93)
Q4	0.36 (0.19, 0.67)	0.35 (0.18, 0.68)	0.33 (0.17, 0.64)
P for trend	0.001	0.001	0.001

Model 1, adjusted for age and sex. Model 2, adjusted for variables in model 1 plus SBP, DBP, BMI, hypertension duration, heart rate, smoking status, drinking status, and comorbidities. Model 3, adjusted for variables in model 2 plus ALT, AST, GGT, UA, BUN, eGFR, TC, TG, HDL-C, LDL-C, HbA1c, FPG, Hcy, use of statins, use of aspirins, use of insulins, use of oral antidiabetic drugs, and antihypertensive drugs. Abbreviations: CI: confidence interval; HR: hazard ratio. Other abbreviations as presented in Table 1.

DISCUSSION

This study examined the relationship between SI and incident stroke in elderly hypertensive patients. After controlling for multiple confounders, the results showed that the risk of stroke was substantially associated with SI. Furthermore, in the restricted cubic spline analysis, we observed a significant dose-response relationship between SI and the risk of total strokes and ischemic strokes. These findings were consistent in both the sensitivity and subgroup analyses. Overall, the current investigation showed that low SI was associated with a higher risk of incident stroke, independent of other traditional risk variables. To our knowledge, this is the first large cohort study to demonstrate a link between SI and the risk of incident stroke among elderly hypertensive patients.

Currently, China has the world's largest elderly population [32]. According to the results of the seventh national census in 2020, the population aged 60 and above accounted for 18.7% of China's total population, amounting to 264 million people [33]. Population aging has become a significant trend in China's social development, and the aging of China's population has further intensified. In our aging society, sarcopenia, or reduced muscle mass, is a growing health concern [34]. Sarcopenia, which is a widespread and gradual reduction in skeletal muscle mass and function that impairs mobility and work capability

in elderly people, is regarded as a geriatric syndrome [8]. Skeletal muscle degeneration, according to epidemiological research, starts after the age of 40 and gets worse with time. Skeletal muscle deteriorates in both number and quality at a rate of 8% each year [35]. The results of a recent meta-analysis showed that the prevalence of sarcopenia among the Chinese elderly aged 60 years and older was about 11.2% to 33.7% [36]. Stroke is the leading cause of disability and death among the elderly in China [37]. Some studies have linked skeletal muscle weakness to eating disorders, lack of exercise, insulin resistance, inflammation, and atherosclerosis and found that these are independent risk factors for cardiovascular disease in older adults [17, 38–41]. Sarcopenia imposes a significant burden on society by significantly increasing hospitalization and mortality rates in elderly patients [42, 43]. Screening for sarcopenia in elderly hypertensive patients at an early stage is therefore critical in clinical practice.

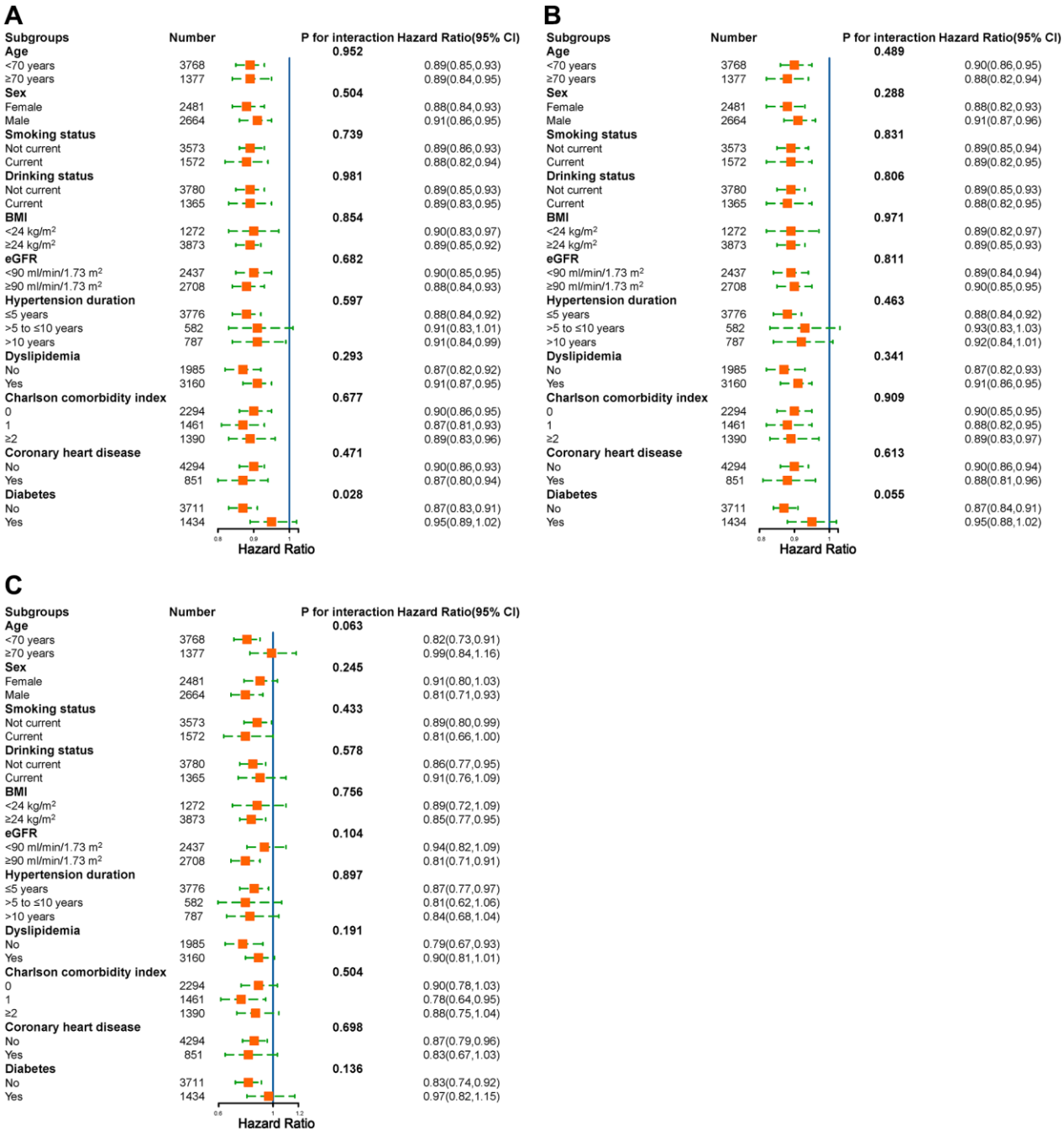


Figure 4. Adjusted hazard ratios of stroke associated with per 10 unit increase in SI. (**A**) Total stroke; (**B**) Ischemic stroke; (**C**) Hemorrhagic stroke.

In this context, the quantification of skeletal muscle mass is particularly important. To assess skeletal muscle mass, several options have been proposed: magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry, and bioelectrical impedance analysis [44]. However, these measurements are not universally applicable in clinical practice due to their high cost, possible radiation exposure, and the requirements for specialized technicians and sophisticated equipment [45]. Therefore, there is a need for more applicable and reliable alternative serum biomarkers for the assessment of sarcopenia in elderly patients with hypertension. Recently, the SI has been proposed as a simple alternative screening tool [23]. The results of numerous studies have suggested that the Cr/CysC ratio may serve as a marker for predicting muscle atrophy and dysfunction [44–48]. The Cr/CysC ratio has been positively correlated with muscle mass and strength in various populations [46, 49, 50]. In particular, the accuracy of the Cr/CysC ratio as a measure of muscle mass has been validated by computed tomography in the assessment of muscle mass in different populations, including the elderly and cancer patients [45, 51, 52]. Furthermore, evidence that the Cr/CysC ratio is superior to bioelectrical impedance analysis in the detection of muscle weakness further supports its accuracy [52].

In this study, we confirmed that SI was independently associated with an increased risk of stroke in elderly patients with hypertension. And we also observed a significant dose-response relationship between SI and the risk of total and ischemic strokes. Our findings are consistent with those of several previous studies. The difference is that previous studies have focused on patients with chronic renal insufficiency, older patients undergoing transcatheter aortic valve replacement, and patients with obstructive coronary artery disease [22, 53–55]. Further, they usually focus on looking at the risk of SI with cardiovascular death, all-cause death, and major adverse cardiovascular events. The underlying mechanism leading to this association may be multifactorial and has not yet been identified. Several potential explanations may account for this result. Skeletal muscle is a major site of glucose uptake, deposition, and actin secretion [56]. Therefore, the reduced glucose uptake caused by low skeletal muscle mass loss may contribute to enhanced insulin resistance [57, 58]. Insulin resistance can produce chronic hyperglycemia, which in turn triggers oxidative stress, causing an inflammatory response and cell damage [59]. Insulin resistance can also alter systemic lipid metabolism, leading to the development of dyslipidemia. This, combined with endothelial dysfunction, insulin resistance, and dyslipidemia, can all lead to atherosclerosis and eventually progress to ischemic stroke [60]. Increased muscle strength is associated with lower blood pressure and improved hemodynamics, suggesting a protective role for muscle in the development of atherosclerosis [61]. Another possible mechanism of poor prognosis is a decrease in skeletal muscle and endocrine function as secretory organs [62]. Myogenic factors are cytokines or other peptides produced, expressed, and released by skeletal muscle fibers that may help regulate beneficial cardiovascular effects [63]. Myocytes perform endocrine functions by secreting cardiovascular-beneficial myokines [64]. In patients with low muscle mass, decreased muscle cell numbers and decreased endocrine function may lead to adverse clinical outcomes [65]. These factors, together with pre-existing chronic comorbidities, explain the high risk of stroke. There are also studies showing that in older patients with skeletal myasthenia, long-term systemic chronic inflammation appears to be associated with the overall course of cardiovascular disease [66, 67]. Aging-related secretory phenotyping, one of the key factors in the chronic inflammation-induced instability of atherosclerotic plaques, is part of the pathogenesis of atherosclerosis, and is an independent risk factor for cardiovascular disease and cardiovascular mortality [66, 68, 69]. Research has also shown that inflammation activates the body's catabolic pathway and promotes the hydrolysis of muscle proteins, leading to an imbalance between protein synthesis and catabolism, which further exacerbates the development of sarcopenia [70].

The present study has multiple strengths. Initially, this study is the first to use data from a cohort study to identify SI as a predictor of stroke in elderly patients with hypertension. Our findings should be considered in clinical practice and prospective clinical trials to prevent or treat pre-existing sarcopenia in older patients with hypertension. Second, we adjusted for as many confounders as possible in our study to improve the reliability of the results. Finally, this study used subgroup analysis and restricted cubic spline curve analysis, which helped enrich the interpretation of the relationship between SI and the risk of stroke. This study still has the following limitations: First, the observational, retrospective design limits the determination of causality. Second, we did not use methods such as dual energy X-ray absorptiometry or magnetic resonance imaging to assess actual residual muscle mass in these patients or analyze the association between SI and skeletal muscle mass, or sarcopenia. However, our goal was to focus more on the prognostic value of SI and obtain results that might be helpful in actual clinical practice. Third, we used measurements from only one point in time, so trends and changes in SI could not be determined. Fourth, this study was conducted only in hypertensive patients

aged 60 years and older, and therefore our results may not be fully generalizable to younger people or other populations. Finally, although we examined measured covariates for potential confounding, residual confounding resulting from unmeasured factors such as frailty, physical activity, and dietary factors cannot be excluded.

In summary, this study found that elevated SI was negatively associated with the risk of stroke in elderly patients with hypertension. Uncovering the causality behind the relationship requires further prospective study.

Abbreviations

SI: sarcopenia index; HRs: hazard ratios; CIs: confidence intervals; Cr: creatinine; ICD-10: International Classification of Diseases 10th Revision; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; Hcy: homocysteine; hs-CRP: high-sensitivity C-reactive protein; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CHD: coronary heart disease; CCI: Charlson Comorbidity Index; NRI: net reclassification index; IDI: integrated discrimination index.

AUTHOR CONTRIBUTIONS

Conception and design of the work: CXT, HJL, and LNF. Provision of study materials or patients: LNF. Acquisition of data: YWB, DYJ, and WW. Analysis of data: CXT, WMR, WJY, and HJ. CXT drafted the manuscript. LNF, LQ, and HJL substantially revised the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

Contributions from all participants are appreciated.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this study.

ETHICAL STATEMENT AND CONSENT

The study procedures were carried out by the Declaration of Helsinki. Approval was obtained from the Ethical Committee of People's Hospital of Xinjiang Uygur Autonomous Region (No. KY2021031901). The need for written informed consent was waived by the (People's Hospital of Xinjiang Uygur Autonomous Region) ethics committee due to retrospective nature of the study.

FUNDING

This work was supported by the Key Research and Development Project of Xinjiang Uygur Autonomous Region (Nos. 2022B03009 and 2022B03009-1).

REFERENCES

1. Ma Q, Li R, Wang L, Yin P, Wang Y, Yan C, Ren Y, Qian Z, Vaughn MG, McMillin SE, Hay SI, Naghavi M, Cai M, et al. Temporal trend and attributable risk factors of stroke burden in China, 1990-2019: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health. 2021; 6:e897–906. https://doi.org/10.1016/S2468-2667(21)00228-0 PMID:34838196

2. Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, Li X, Wang L, Wang L, Liu Y, Liu J, Zhang M, Qi J, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2019; 394:1145–58. https://doi.org/10.1016/S0140-6736(19)30427-1 PMID:31248666

3. Lindley RI. Stroke Prevention in the Very Elderly. Stroke. 2018; 49:796–802. https://doi.org/10.1161/STROKEAHA.117.017952 PMID:29371430

4. Tu WJ, Hua Y, Yan F, Bian H, Yang Y, Lou M, Kang D, He L, Chu L, Zeng J, Wu J, Chen H, Han J, et al. Prevalence of stroke in China, 2013-2019: A population-based study. Lancet Reg Health West Pac. 2022; 28:100550. https://doi.org/10.1016/j.lanwpc.2022.100550 PMID:36507089

5. Nie J, Xie L, Zhao BX, Li Y, Qiu B, Zhu F, Li GF, He M, Wang Y, Wang B, Liu S, Zhang H, Guo H, et al. Serum Trimethylamine N-Oxide Concentration Is Positively Associated With First Stroke in Hypertensive Patients. Stroke. 2018; 49:2021–8. https://doi.org/10.1161/STROKEAHA.118.021997 PMID:30354996

6. Xie L, Zhao BX, Luo J, Li Y, Zhu F, Li GF, He M, Wang B, Zhang H, Cai Y, Huo Y, Wang X, Hou FF, et al. A U-shaped association between serum betaine and incident risk of first ischemic stroke in hypertensive patients. Clin Nutr. 2020; 39:2517–24. https://doi.org/10.1016/j.clnu.2019.11.011 PMID:31806397

7. Wang Z, Ma H, Song Y, Lin T, Liu L, Zhou Z, Wei Y, Huang X, Chen P, Liu C, Li Y, Wang B, Li J, et al. Plasma selenium and the risk of first stroke in adults with hypertension: a secondary analysis of the China

Stroke Primary Prevention Trial. Am J Clin Nutr. 2022; 115:222–31.
https://doi.org/10.1093/ajcn/nqab320
PMID:34549258

8. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. Nat Rev Endocrinol. 2018; 14:513–37.
https://doi.org/10.1038/s41574-018-0062-9
PMID:30065268

9. Tanimoto Y, Watanabe M, Sun W, Sugiura Y, Tsuda Y, Kimura M, Hayashida I, Kusabiraki T, Kono K. Association between sarcopenia and higher-level functional capacity in daily living in community-dwelling elderly subjects in Japan. Arch Gerontol Geriatr. 2012; 55:e9–13.
https://doi.org/10.1016/j.archger.2012.06.015
PMID:22795189

10. Kim YS, Lee Y, Chung YS, Lee DJ, Joo NS, Hong D, Song Ge, Kim HJ, Choi YJ, Kim KM. Prevalence of sarcopenia and sarcopenic obesity in the Korean population based on the Fourth Korean National Health and Nutritional Examination Surveys. J Gerontol A Biol Sci Med Sci. 2012; 67:1107–13.
https://doi.org/10.1093/gerona/gls071
PMID:22431554

11. Kitamura A, Seino S, Abe T, Nofuji Y, Yokoyama Y, Amano H, Nishi M, Taniguchi Y, Narita M, Fujiwara Y, Shinkai S. Sarcopenia: prevalence, associated factors, and the risk of mortality and disability in Japanese older adults. J Cachexia Sarcopenia Muscle. 2021; 12:30–8.
https://doi.org/10.1002/jcsm.12651
PMID:33241660

12. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, Jang HC, Kang L, Kim M, Kim S, Kojima T, Kuzuya M, Lee JSW, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J Am Med Dir Assoc. 2020; 21:300–7.e2.
https://doi.org/10.1016/j.jamda.2019.12.012
PMID:32033882

13. Curcio F, Testa G, Liguori I, Papillo M, Flocco V, Panicara V, Galizia G, Della-Morte D, Gargiulo G, Cacciatore F, Bonaduce D, Landi F, Abete P. Sarcopenia and Heart Failure. Nutrients. 2020; 12:211.
https://doi.org/10.3390/nu12010211
PMID:31947528

14. Gao K, Cao LF, Ma WZ, Gao YJ, Luo MS, Zhu J, Li T, Zhou D. Association between sarcopenia and cardiovascular disease among middle-aged and older adults: Findings from the China health and retirement longitudinal study. EClinicalMedicine. 2022; 44:101264.
https://doi.org/10.1016/j.eclinm.2021.101264
PMID:35059617

15. Xue Q, Wu J, Ren Y, Hu J, Yang K, Cao J. Sarcopenia predicts adverse outcomes in an elderly population with coronary artery disease: a systematic review and meta-analysis. BMC Geriatr. 2021; 21:493.
https://doi.org/10.1186/s12877-021-02438-w
PMID:34521369

16. Xia MF, Chen LY, Wu L, Ma H, Li XM, Li Q, Aleteng Q, Hu Y, He WY, Gao J, Lin HD, Gao X. Sarcopenia, sarcopenic overweight/obesity and risk of cardiovascular disease and cardiac arrhythmia: A cross-sectional study. Clin Nutr. 2021; 40:571–80.
https://doi.org/10.1016/j.clnu.2020.06.003
PMID:32593523

17. Barbalho SM, Flato UAP, Tofano RJ, Goulart RA, Guiguer EL, Detregiachi CRP, Buchaim DV, Araújo AC, Buchaim RL, Reina FTR, Biteli P, Reina DOB, Bechara MD. Physical Exercise and Myokines: Relationships with Sarcopenia and Cardiovascular Complications. Int J Mol Sci. 2020; 21:3607.
https://doi.org/10.3390/ijms21103607
PMID:32443765

18. Pizzimenti M, Meyer A, Charles AL, Giannini M, Chakfé N, Lejay A, Geny B. Sarcopenia and peripheral arterial disease: a systematic review. J Cachexia Sarcopenia Muscle. 2020; 11:866–86.
https://doi.org/10.1002/jcsm.12587
PMID:32648665

19. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet. 2006; 368:666–78.
https://doi.org/10.1016/S0140-6736(06)69251-9
PMID:16920472

20. Han A, Bokshan SL, Marcaccio SE, DePasse JM, Daniels AH. Diagnostic Criteria and Clinical Outcomes in Sarcopenia Research: A Literature Review. J Clin Med. 2018; 7:70.
https://doi.org/10.3390/jcm7040070
PMID:29642478

21. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M, and European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010; 39:412–23.
https://doi.org/10.1093/ageing/afq034
PMID:20392703

22. Lu YW, Tsai YL, Chou RH, Kuo CS, Chang CC, Huang PH, Lin SJ. Serum creatinine to cystatin C ratio is associated with major adverse cardiovascular events in patients with obstructive coronary artery disease. Nutr Metab Cardiovasc Dis. 2021; 31:1509–15. https://doi.org/10.1016/j.numecd.2021.01.024 PMID:33810966

23. Kashani KB, Frazee EN, Kukrálová L, Sarvottam K, Herasevich V, Young PM, Kashyap R, Lieske JC. Evaluating Muscle Mass by Using Markers of Kidney Function: Development of the Sarcopenia Index. Crit Care Med. 2017; 45:e23–9. https://doi.org/10.1097/CCM.0000000000002013 PMID:27611976

24. Fujita K, Ohkubo H, Nakano A, Takeda N, Fukumitsu K, Fukuda S, Kanemitsu Y, Uemura T, Tajiri T, Maeno K, Ito Y, Oguri T, Ozawa Y, et al. Serum creatinine/cystatin C ratio is a surrogate marker for sarcopenia in patients with idiopathic pulmonary fibrosis. BMC Pulm Med. 2022; 22:203. https://doi.org/10.1186/s12890-022-02000-3 PMID:35606777

25. Tang T, Xie L, Hu S, Tan L, Lei X, Luo X, Yang L, Yang M. Serum creatinine and cystatin C-based diagnostic indices for sarcopenia in advanced non-small cell lung cancer. J Cachexia Sarcopenia Muscle. 2022; 13:1800–10. https://doi.org/10.1002/jcsm.12977 PMID:35297568

26. Hyun YY, Lee KB, Kim H, Kim Y, Chung W, Park HC, Han SH, Oh YK, Park SK, Oh KH. Serum creatinine to cystatin C ratio and clinical outcomes in adults with non-dialysis chronic kidney disease. Front Nutr. 2022; 9:996674. https://doi.org/10.3389/fnut.2022.996674 PMID:36225865

27. Shin JY. Low serum creatinine to cystatin C ratio is independently associated with sarcopenia and high carotid plaque score in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis. 2022; 32:1454–62. https://doi.org/10.1016/j.numecd.2022.02.005 PMID:35256230

28. Hashimoto Y, Takahashi F, Okamura T, Osaka T, Okada H, Senmaru T, Majima S, Ushigome E, Nakanishi N, Asano M, Hamaguchi M, Yamazaki M, Fukui M. Relationship between serum creatinine to cystatin C ratio and subclinical atherosclerosis in patients with type 2 diabetes. BMJ Open Diabetes Res Care. 2022; 10:e002910. https://doi.org/10.1136/bmjdrc-2022-002910 PMID:35738823

29. Cai X, Hu J, Wen W, Wang M, Zhu Q, Liu S, Yang W, Dang Y, Hong J, Li N. Association between the geriatric nutritional risk index and the risk of stroke in elderly patients with hypertension: A longitudinal and cohort study. Front Nutr. 2022; 9:1048206. https://doi.org/10.3389/fnut.2022.1048206 PMID:36562034

30. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006 PMID:19414839

31. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol. 2004; 57:1288–94. https://doi.org/10.1016/j.jclinepi.2004.03.012 PMID:15617955

32. Bao J, Zhou L, Liu G, Tang J, Lu X, Cheng C, Jin Y, Bai J. Current state of care for the elderly in China in the context of an aging population. Biosci Trends. 2022; 16:107–18. https://doi.org/10.5582/bst.2022.01068 PMID:35431289

33. Tu WJ, Zeng X, Liu Q. Aging tsunami coming: the main finding from China's seventh national population census. Aging Clin Exp Res. 2022; 34:1159–63. https://doi.org/10.1007/s40520-021-02017-4 PMID:34727357

34. Ko BJ, Chang Y, Jung HS, Yun KE, Kim CW, Park HS, Chung EC, Shin H, Ryu S. Relationship Between Low Relative Muscle Mass and Coronary Artery Calcification in Healthy Adults. Arterioscler Thromb Vasc Biol. 2016; 36:1016–21. https://doi.org/10.1161/ATVBAHA.116.307156 PMID:27034471

35. Foley RN, Wang C, Ishani A, Collins AJ, Murray AM. Kidney function and sarcopenia in the United States general population: NHANES III. Am J Nephrol. 2007; 27:279–86. https://doi.org/10.1159/000101827 PMID:17440263

36. Chen Z, Li WY, Ho M, Chau PH. The Prevalence of Sarcopenia in Chinese Older Adults: Meta-Analysis and Meta-Regression. Nutrients. 2021; 13:1441. https://doi.org/10.3390/nu13051441 PMID:33923252

37. Xia X, Yue W, Chao B, Li M, Cao L, Wang L, Shen Y, Li X. Prevalence and risk factors of stroke in the elderly in Northern China: data from the National Stroke Screening Survey. J Neurol. 2019; 266:1449–58.
https://doi.org/10.1007/s00415-019-09281-5
PMID:30989368

38. Le Couteur DG, Solon-Biet SM, Cogger VC, Ribeiro R, de Cabo R, Raubenheimer D, Cooney GJ, Simpson SJ. Branched chain amino acids, aging and age-related health. Ageing Res Rev. 2020; 64:101198.
https://doi.org/10.1016/j.arr.2020.101198
PMID:33132154

39. Nascimento CM, Ingles M, Salvador-Pascual A, Cominetti MR, Gomez-Cabrera MC, Viña J. Sarcopenia, frailty and their prevention by exercise. Free Radic Biol Med. 2019; 132:42–9.
https://doi.org/10.1016/j.freeradbiomed.2018.08.035
PMID:30176345

40. Hong SH, Choi KM. Sarcopenic Obesity, Insulin Resistance, and Their Implications in Cardiovascular and Metabolic Consequences. Int J Mol Sci. 2020; 21:494.
https://doi.org/10.3390/ijms21020494
PMID:31941015

41. Kitada M, Koya D. Autophagy in metabolic disease and ageing. Nat Rev Endocrinol. 2021; 17:647–61.
https://doi.org/10.1038/s41574-021-00551-9
PMID:34508250

42. Gümüşsoy M, Atmış V, Yalçın A, Bahşi R, Yiğit S, Arı S, Dokuyan HC, Gözükara MG, Silay K. Malnutrition-sarcopenia syndrome and all-cause mortality in hospitalized older people. Clin Nutr. 2021; 40:5475–81.
https://doi.org/10.1016/j.clnu.2021.09.036
PMID:34656028

43. Shu X, Lin T, Wang H, Zhao Y, Jiang T, Peng X, Yue J. Diagnosis, prevalence, and mortality of sarcopenia in dialysis patients: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2022; 13:145–58.
https://doi.org/10.1002/jcsm.12890
PMID:34989172

44. Kashani K, Sarvottam K, Pereira NL, Barreto EF, Kennedy CC. The sarcopenia index: A novel measure of muscle mass in lung transplant candidates. Clin Transplant. 2018; 32:e13182.
https://doi.org/10.1111/ctr.13182
PMID:29274246

45. Barreto EF, Poyant JO, Coville HH, Dierkhising RA, Kennedy CC, Gajic O, Nystrom EM, Takahashi N, Moynagh MR, Kashani KB. Validation of the sarcopenia index to assess muscle mass in the critically ill: A novel application of kidney function markers. Clin Nutr. 2019; 38:1362–7.
https://doi.org/10.1016/j.clnu.2018.05.031
PMID:29921462

46. Fu X, Tian Z, Wen S, Sun H, Thapa S, Xiong H, Liu H, Li L, Yu S. A new index based on serum creatinine and cystatin C is useful for assessing sarcopenia in patients with advanced cancer. Nutrition. 2021; 82:111032.
https://doi.org/10.1016/j.nut.2020.111032
PMID:33172686

47. Barreto EF, Kanderi T, DiCecco SR, Lopez-Ruiz A, Poyant JO, Mara KC, Heimgartner J, Gajic O, Rule AD, Nystrom EM, Kashani KB. Sarcopenia Index Is a Simple Objective Screening Tool for Malnutrition in the Critically Ill. JPEN J Parenter Enteral Nutr. 2019; 43:780–8.
https://doi.org/10.1002/jpen.1492
PMID:30561031

48. Ding P, Guo H, Sun C, Chen S, Yang P, Tian Y, Lowe S, Zhao Q. Serum creatinine/cystatin C ratio is a systemic marker of sarcopenia in patients with gastrointestinal stromal tumours. Front Nutr. 2022; 9:963265.
https://doi.org/10.3389/fnut.2022.963265
PMID:36118766

49. Osaka T, Hamaguchi M, Hashimoto Y, Ushigome E, Tanaka M, Yamazaki M, Fukui M. Decreased the creatinine to cystatin C ratio is a surrogate marker of sarcopenia in patients with type 2 diabetes. Diabetes Res Clin Pract. 2018; 139:52–8.
https://doi.org/10.1016/j.diabres.2018.02.025
PMID:29496508

50. Lin YL, Chen SY, Lai YH, Wang CH, Kuo CH, Liou HH, Hsu BG. Serum creatinine to cystatin C ratio predicts skeletal muscle mass and strength in patients with non-dialysis chronic kidney disease. Clin Nutr. 2020; 39:2435–41.
https://doi.org/10.1016/j.clnu.2019.10.027
PMID:31732290

51. Tabara Y, Kohara K, Okada Y, Ohyagi Y, Igase M. Creatinine-to-cystatin C ratio as a marker of skeletal muscle mass in older adults: J-SHIPP study. Clin Nutr. 2020; 39:1857–62.
https://doi.org/10.1016/j.clnu.2019.07.027
PMID:31431305

52. Ulmann G, Kaï J, Durand JP, Neveux N, Jouinot A, De Bandt JP, Goldwasser F, Cynober L. Creatinine-to-cystatin C ratio and bioelectrical impedance analysis for the assessement of low lean body mass in cancer

patients: Comparison to L3-computed tomography scan. Nutrition. 2021; 81:110895. https://doi.org/10.1016/j.nut.2020.110895 PMID:32739656

53. Lin YL, Chang IC, Liou HH, Wang CH, Lai YH, Kuo CH, Hsu BG. Serum indices based on creatinine and cystatin C predict mortality in patients with non-dialysis chronic kidney disease. Sci Rep. 2021; 11:16863. https://doi.org/10.1038/s41598-021-96447-9 PMID:34413438

54. Romeo FJ, Chiabrando JG, Seropian IM, Raleigh JV, de Chazal HM, Garmendia CM, Smietniansky M, Cal M, Agatiello CR, Berrocal DH. Sarcopenia index as a predictor of clinical outcomes in older patients undergoing transcatheter aortic valve replacement. Catheter Cardiovasc Interv. 2021; 98:E889–96. https://doi.org/10.1002/ccd.29799 PMID:34043281

55. Tang T, Zhuo Y, Xie L, Wang H, Yang M. Sarcopenia index based on serum creatinine and cystatin C is associated with 3-year mortality in hospitalized older patients. Sci Rep. 2020; 10:1260. https://doi.org/10.1038/s41598-020-58304-z PMID:31988356

56. Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases. Lancet Diabetes Endocrinol. 2014; 2:819–29. https://doi.org/10.1016/S2213-8587(14)70034-8 PMID:24731660

57. Wang C, Bai L. Sarcopenia in the elderly: basic and clinical issues. Geriatr Gerontol Int. 2012; 12: 388–96. https://doi.org/10.1111/j.1447-0594.2012.00851.x PMID:22530761

58. Abbatecola AM, Paolisso G, Fattoretti P, Evans WJ, Fiore V, Dicioccio L, Lattanzio F. Discovering pathways of sarcopenia in older adults: a role for insulin resistance on mitochondria dysfunction. J Nutr Health Aging. 2011; 15:890–5. https://doi.org/10.1007/s12603-011-0366-0 PMID:22159778

59. Petersen MC, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. Physiol Rev. 2018; 98:2133–223. https://doi.org/10.1152/physrev.00063.2017 PMID:30067154

60. Laakso M, Kuusisto J. Insulin resistance and hyperglycaemia in cardiovascular disease development. Nat Rev Endocrinol. 2014; 10:293–302. https://doi.org/10.1038/nrendo.2014.29 PMID:24663222

61. Wilmore JH, Stanforth PR, Gagnon J, Rice T, Mandel S, Leon AS, Rao DC, Skinner JS, Bouchard C. Heart rate and blood pressure changes with endurance training: the HERITAGE Family Study. Med Sci Sports Exerc. 2001; 33:107–16. https://doi.org/10.1097/00005768-200101000-00017 PMID:11194095

62. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol. 2012; 8:457–65. https://doi.org/10.1038/nrendo.2012.49 PMID:22473333

63. Parmacek MS. Myocardin-related transcription factors: critical coactivators regulating cardiovascular development and adaptation. Circ Res. 2007; 100:633–44. https://doi.org/10.1161/01.RES.0000259563.61091.e8 PMID:17363709

64. Severinsen MCK, Pedersen BK. Muscle-Organ Crosstalk: The Emerging Roles of Myokines. Endocr Rev. 2020; 41:594–609. https://doi.org/10.1210/endrev/bnaa016 PMID:32393961

65. Lee HS, Park KW, Kang J, Ki YJ, Chang M, Han JK, Yang HM, Kang HJ, Koo BK, Kim HS. Sarcopenia Index as a Predictor of Clinical Outcomes in Older Patients with Coronary Artery Disease. J Clin Med. 2020; 9:3121. https://doi.org/10.3390/jcm9103121 PMID:32992530

66. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018; 15:505–22. https://doi.org/10.1038/s41569-018-0064-2 PMID:30065258

67. Stojanović SD, Fiedler J, Bauersachs J, Thum T, Sedding DG. Senescence-induced inflammation: an important player and key therapeutic target in atherosclerosis. Eur Heart J. 2020; 41: 2983–96. https://doi.org/10.1093/eurheartj/ehz919 PMID:31898722

68. Childs BG, Li H, van Deursen JM. Senescent cells: a therapeutic target for cardiovascular disease. J Clin Invest. 2018; 128:1217–28. https://doi.org/10.1172/JCI95146 PMID:29608141

69. Ferrucci L, Penninx BW, Volpato S, Harris TB, Bandeen-Roche K, Balfour J, Leveille SG, Fried LP, Md JM. Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. J Am Geriatr Soc. 2002; 50:1947–54.
https://doi.org/10.1046/j.1532-5415.2002.50605.x
PMID:12473005

70. Batsis JA, Mackenzie TA, Jones JD, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity and inflammation: Results from the 1999-2004 National Health and Nutrition Examination Survey. Clin Nutr. 2016; 35:1472–83.
https://doi.org/10.1016/j.clnu.2016.03.028
PMID:27091774

SUPPLEMENTARY MATERIALS

Supplementary Materials and Methods

Details of the statistical analyses

To address the missing data in the covariates (Supplementary Table 2), we applied multivariate imputation using chained equations. We conducted 10 rounds of multiple imputations, then combined them into final estimates according to Rubin's rule (function "with/pool" in R package "mice"). The results of the analyses with imputation of missing variables were similar to those obtained from complete case analyses. Therefore, all analyses reported here were performed with multiple imputation of missing values. Continuous variables were expressed as mean ± standard deviation (SD) or medians with interquartile ranges depending on their distributions, and categorical variables were expressed as frequencies and percentages. Normality of datasets was tested using the KS or D'Agostino-Pearson omnibus normality test methods. To compare the characteristics among different SI groups, the chi-square test was performed for categorical variables, and one-way analysis of variance or the Kruskal-Wallis test was performed for continuous variables with normal and skewed distributions.

The age-adjusted incidence rates were determined by calculating age-specific incidence rates within 1-year age categories. The time to the first stroke event was examined using Kaplan-Meier survival curves and compared using the log-rank test. To assess for collinearity, we measured the variance inflation factor (VIF) in all models using a predetermined threshold of 5 as suggestive of multicollinearity (Supplementary Table 3). Variables with VIFs above 5 were removed. The proportional hazard assumptions were evaluated by visualization of Schoenfeld residuals, and no potential violation was observed (Supplementary Figure 2). Three multivariate Cox proportional hazard regressions were constructed to estimate the association of the SI with the risk of stroke by calculating the hazard ratio (HR) and 95% confidence interval (CI). In the first model, we adjusted for age and sex. The second model was adjusted for model 1 plus SBP, DBP, BMI, hypertension duration, heart rate, smoking status, drinking status, and comorbidities. The third model was adjusted for model 2 plus ALT, AST, GGT, UA, BUN, eGFR, TC, TG, HDL-C, LDL-C, HbA1c, FPG, Hcy, use of statins, use of aspirins, use of insulins, use of oral antidiabetic drugs, and antihypertensive drugs. In addition, we also assessed the associations of SI with stroke subtypes, including IS and HS. Trend tests were performed in the regression models after the median SI values of each quartile were entered into the model and treated as a continuous variable.

Additionally, restricted cubic splines were performed to examine the shape of the associations between SI and outcomes with five knots (at the 5th, 25th, 50th, 75th, and 95th percentiles). The reference point for SI was the median of the reference group, and the HR was adjusted for all confounding variables. The potential nonlinear relationships of SI with outcomes were explored.

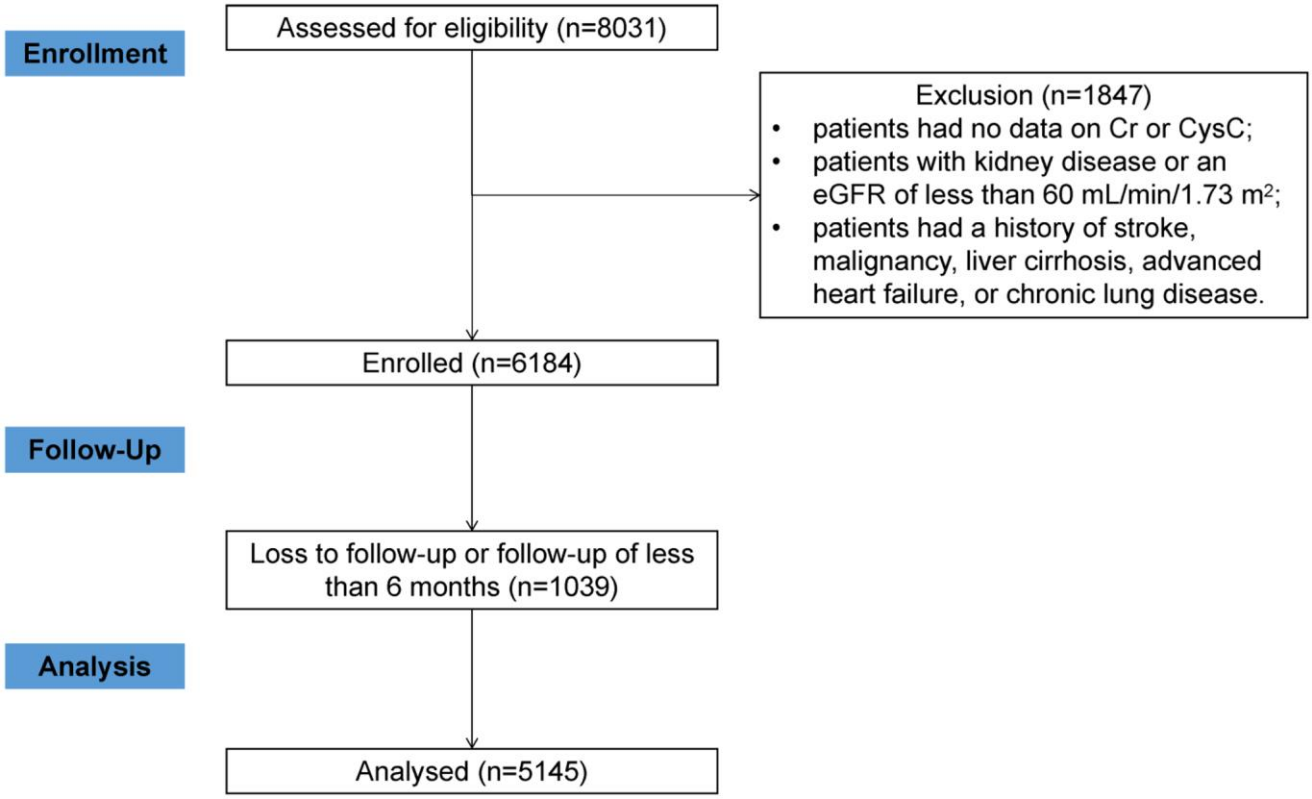
In addition, possible modifications of the association between SI (per 10-unit increment) and outcomes were also assessed for the following variables: age (<70 or ≥70 years), sex (male or female), BMI (<24 or ≥24 kg/m^2), eGFR (<90 or ≥90 ml/min/1.73 m^2), current smokers (yes or no), current drinkers (yes or no), diabetes (yes or no), coronary heart disease (yes or no), CCI (0 or 1 or ≥2), hypertension duration (≤5 or 5–10 or >10 years), and hyperlipidemia (yes or no). Heterogeneity across subgroups was assessed by Cox proportional hazards models, and interactions between subgroups and SI were examined by likelihood ratio testing.

Sensitivity analyses were undertaken to evaluate the robustness of the results. First, to explore the potential impact of reverse causality, we repeated the primary analysis using a 1-year lag period, excluding participants who developed strokes within the first year of follow-up. Second, sensitivity analyses were also conducted to examine whether competing risks of non-stroke events were present. Third, sensitivity analyses were performed in subgroups from which all individuals with CCI ≥2 were excluded. Fourth, participants with atrial fibrillation were excluded. Lastly, potential unmeasured confounding was examined by calculating E-values.

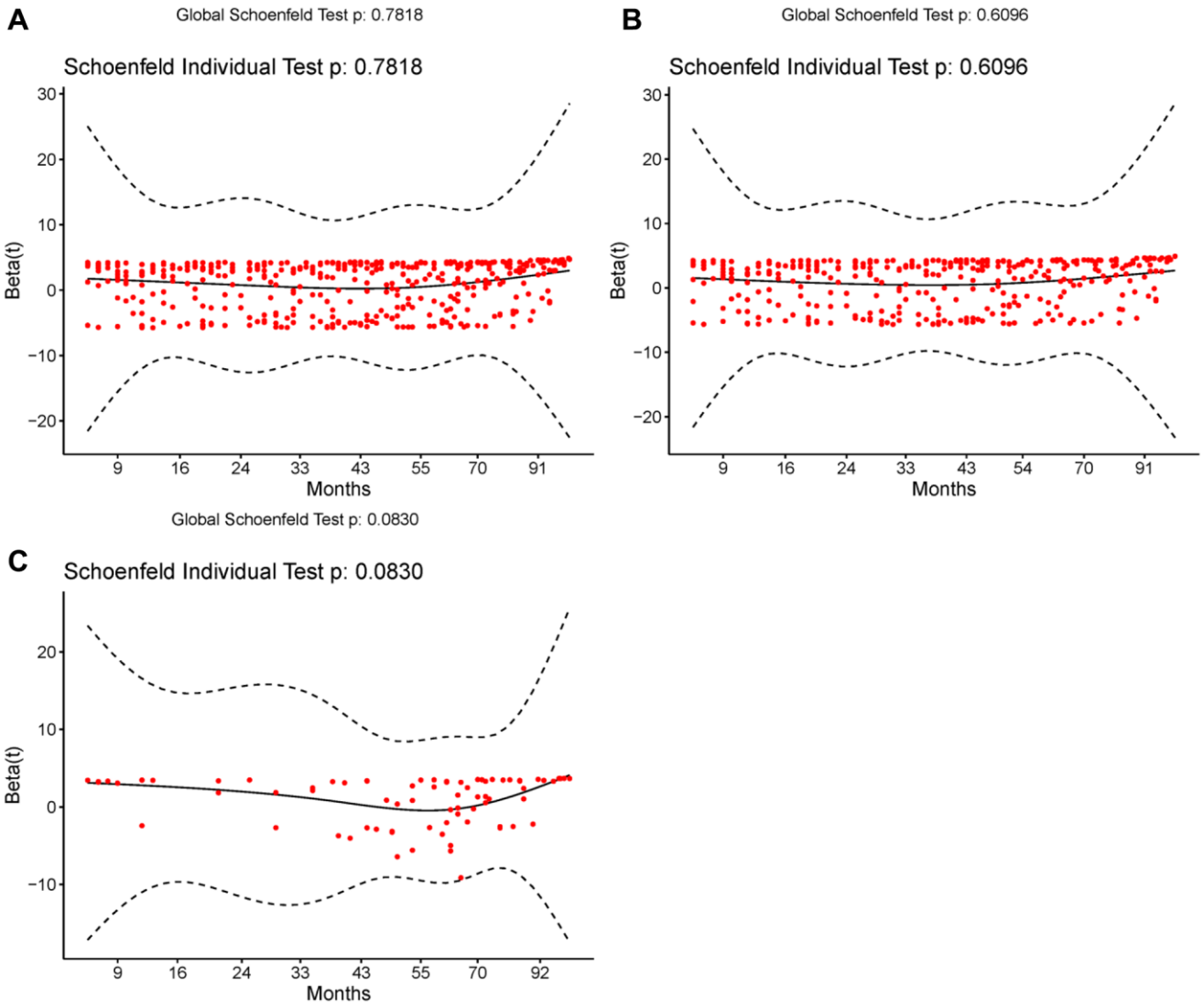
Additionally, we used C-statistics, a net reclassification index (NRI), and an integrated discrimination improvement (IDI) to evaluate the incremental predictive value of the SI beyond the conventional model. The confidence intervals for the C-statistic, NRI, and IDI were computed by bootstrapping with 1000 resamples.

All analyses were completed in R version 4.1.1 (R Foundation for Statistical Computing), and all *P* values were two-sided.

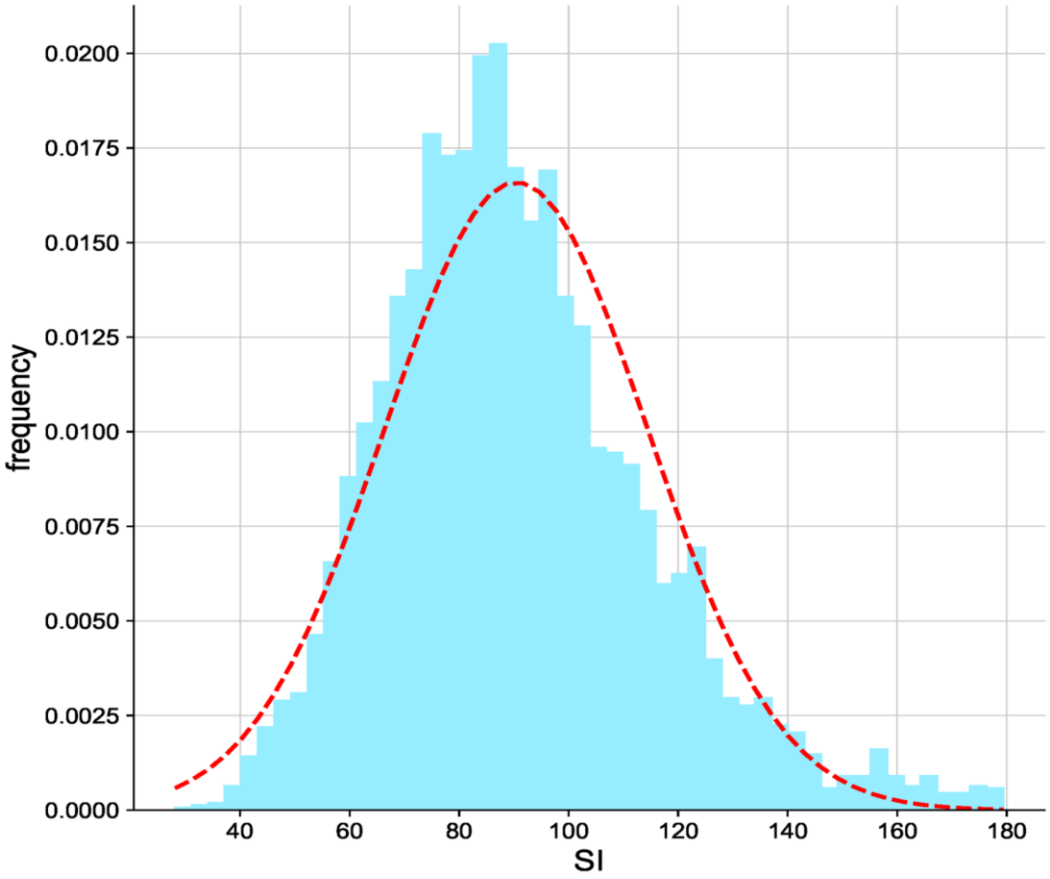
Supplementary Figures



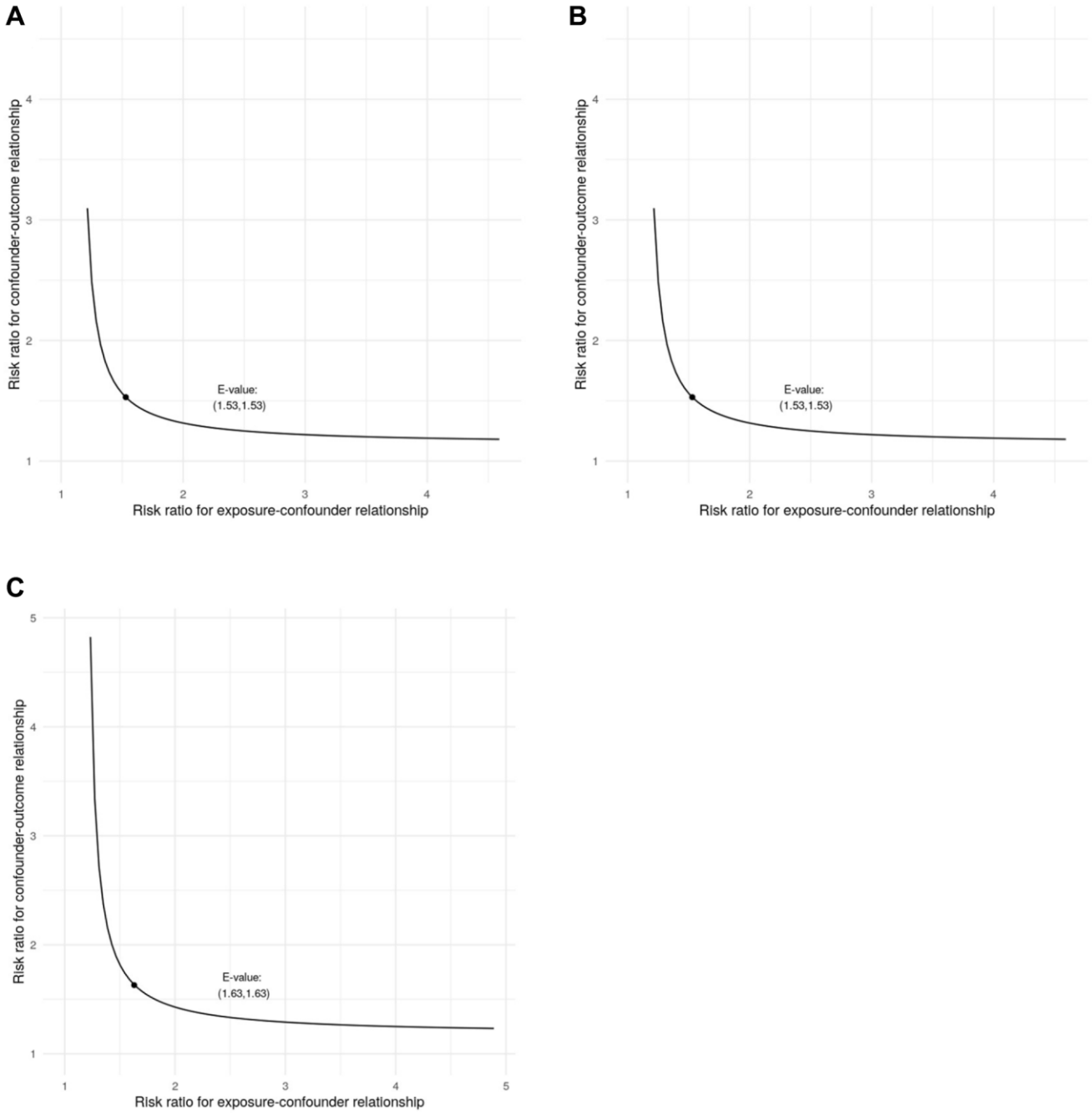
Supplementary Figure 1. Participant flow diagram.



Supplementary Figure 2. Plot of Schoenfeld residuals against time in the Cox regression model. (**A**) Total stroke; (**B**) Ischemic stroke; (**C**) Hemorrhagic stroke.



Supplementary Figure 3. Distribution of participants according to the SI.



Supplementary Figure 4. E-values for the observed associations between SI and clinical outcomes. (**A**) Total stroke; (**B**) Ischemic stroke; (**C**) Hemorrhagic stroke.

Supplementary Tables

Supplementary Table 1. List of medications included in the study.

Drug class	Drug name
Aspirin	Aspirin
Beta-blocker	Atenolol, bisoprolol, carvedilol, metoprolol, propranolol
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	Azilsartan, candestartan, captopril, enalapril, fosinopril, irbesartan, losartan, olmesartan, ramipril telmisartan, valsartan
Calcium channel blockers	Amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, verapamil
Diuretics	Acetazolamide, amiloride, benzyl hydrochlorothiazide, bumetanide, furosemide, hydrochlorothiazide, indapamide, spironolactone
Statin	Atorvastatin, fluvastatin, pitavastatin, rosuvastatin, simvastatin
Oral antidiabetic agents	Metformin, glipizide, gliclazide, glimepiride, glyburide, alogliptin, linagliptin, sitagliptin, vidagliptin, saxagliptin, acarbose, nateglinide, meglitinide, repaglinde, pioglitzone, dulaglutide, exenatide, liraglutide
Insulin	Rapid, short, intermediate and long-acting insulins

Supplementary Table 2. Counts and proportions of missing data.

Variables	Missing (%)
Heart rate	99 (1.92%)
SBP	103 (2.00%)
DBP	103 (2.00%)
BMI	84 (1.63%)
ALT	169 (3.28%)
AST	167 (3.25%)
GGT	154 (3.00%)
UA	148 (2.88%)
BUN	169 (3.28%)
TC	142 (2.76%)
TG	186 (3.62%)
HDL-C	124 (2.41%)
LDL-C	126 (2.45%)
HbA1c	245 (4.76%)
FPG	218 (4.24%)
Hcy	198 (3.85%)
Hs-CRP	398 (7.74%)

Abbreviations as presented in Table 1.

Supplementary Table 3. Collinearity diagnostics steps.

	Step 1	Step 2
SI	9.9	1.3
Sex	1.1	1.1
Age	1.0	1.0
HR	1.0	1.0
DBP	1.7	1.7
SBP	1.7	1.7
BMI	1.1	1.1
ALT	2.4	2.4
AST	2.1	2.1
GGT	1.4	1.4
Cr	**9.0**	**NA**
UA	1.5	1.5
BUN	1.1	1.1
Cystatin C	**10.5**	**NA**
eGFR	1.0	1.0
TC	4.2	4.2
TG	2.0	2.0
HDL-C	1.7	1.7
LDL-C	4.8	4.8
HbA1c	1.4	1.4
FPG	1.1	1.1
Hcy	1.1	1.1
Hs-CRP	1.0	1.0
Hypertension duration	1.0	1.0
Dyslipidemia	1.0	1.0
Atrial fibrillation	1.0	1.0
Charlson comorbidity index	1.0	1.0
Coronary heart disease	1.0	1.0
Diabetes	1.4	1.4
Current smoker	1.7	1.7
Current drinker	1.6	1.6

VIF = $1/(1-R^2)$. VIF step-by-step screening method: Calculate the VIF of each variable. If the maximum VIF value ≥5, remove the variable with the maximum VIF value. Abbreviation: VIF: variance inflation factors. Other abbreviations as presented in Table 1.

Supplementary Table 4. Sensitivity analysis excluding outcome events within the first year of follow-up.

Outcome	HR (95% CI)		
	Model 1	Model 2	Model 3
Total stroke			
Per 10-unit increment	0.91 (0.87, 0.94)	0.90 (0.87, 0.94)	0.90 (0.86, 0.93)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.86 (0.69, 1.06)	0.86 (0.69, 1.07)	0.85 (0.68, 1.06)
Q3	0.62 (0.49, 0.79)	0.63 (0.50, 0.81)	0.62 (0.49, 0.80)
Q4	0.55 (0.43, 0.70)	0.53 (0.41, 0.68)	0.50 (0.39, 0.65)
P for trend	<0.001	<0.001	<0.001
Ischemic stroke			
Per 10-unit increment	0.91 (0.87, 0.94)	0.90 (0.86, 0.94)	0.89 (0.86, 0.93)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.89 (0.70, 1.12)	0.88 (0.70, 1.12)	0.88 (0.69, 1.11)
Q3	0.61 (0.47, 0.79)	0.63 (0.48, 0.82)	0.62 (0.47, 0.81)
Q4	0.55 (0.43, 0.72)	0.53 (0.40, 0.70)	0.50 (0.38, 0.67)
P for trend	<0.001	<0.001	<0.001
Hemorrhagic stroke			
Per 10-unit increment	0.90 (0.82, 0.99)	0.89 (0.81, 0.98)	0.88 (0.80, 0.97)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.79 (0.46, 1.36)	0.79 (0.46, 1.38)	0.78 (0.44, 1.36)
Q3	0.66 (0.37, 1.17)	0.63 (0.35, 1.13)	0.60 (0.33, 1.08)
Q4	0.43 (0.22, 0.83)	0.42 (0.21, 0.82)	0.38 (0.19, 0.76)
P for trend	0.009	0.008	0.004

Model 1, adjusted for age and sex. Model 2, adjusted for variables in model 1 plus SBP, DBP, BMI, hypertension duration, heart rate, smoking status, drinking status, and comorbidities. Model 3, adjusted for variables in model 2 plus ALT, AST, GGT, UA, BUN, eGFR, TC, TG, HDL-C, LDL-C, HbA1c, FPG, Hcy, use of statins, use of aspirins, use of insulins, use of oral antidiabetic drugs, and antihypertensive drugs. Abbreviations: CI: confidence interval; HR: hazard ratio. Other abbreviations as presented in Table 1.

Supplementary Table 5. Sensitivity analysis of excluding participants with CCI ≥ 2.

Outcome	HR (95% CI)		
	Model 1	Model 2	Model 3
Total stroke			
Per 10-unit increment	0.89 (0.86, 0.93)	0.89 (0.86, 0.93)	0.89 (0.85, 0.93)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.93 (0.73, 1.18)	0.92 (0.72, 1.17)	0.92 (0.72, 1.17)
Q3	0.64 (0.49, 0.83)	0.66 (0.51, 0.87)	0.65 (0.49, 0.85)
Q4	0.49 (0.37, 0.65)	0.49 (0.36, 0.65)	0.46 (0.34, 0.62)
P for trend	<0.001	<0.001	<0.001
Ischemic stroke			
Per 10-unit increment	0.89 (0.86, 0.93)	0.90 (0.86, 0.94)	0.89 (0.85, 0.93)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.97 (0.75, 1.24)	0.96 (0.74, 1.23)	0.96 (0.74, 1.24)
Q3	0.61 (0.46, 0.81)	0.63 (0.47, 0.85)	0.62 (0.46, 0.83)
Q4	0.52 (0.39, 0.69)	0.51 (0.38, 0.69)	0.48 (0.35, 0.66)
P for trend	<0.001	<0.001	<0.001
Hemorrhagic stroke			
Per 10-unit increment	0.86 (0.77, 0.96)	0.86 (0.77, 0.97)	0.86 (0.76, 0.97)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.95 (0.51, 1.78)	0.93 (0.49, 1.76)	0.93 (0.48, 1.77)
Q3	0.80 (0.41, 1.54)	0.82 (0.42, 1.62)	0.79 (0.40, 1.58)
Q4	0.27 (0.11, 0.67)	0.27 (0.11, 0.70)	0.25 (0.10, 0.66)
P for trend	0.005	0.010	0.007

Model 1, adjusted for age and sex. Model 2, adjusted for variables in model 1 plus SBP, DBP, BMI, hypertension duration, heart rate, smoking status, and drinking status. Model 3, adjusted for variables in model 2 plus ALT, AST, GGT, UA, BUN, eGFR, TC, TG, HDL-C, LDL-C, HbA1c, FPG, Hcy, use of statins, use of aspirins, use of insulins, use of oral antidiabetic drugs, and antihypertensive drugs. Abbreviations: CI: confidence interval; HR: hazard ratio. Other abbreviations as presented in Table 1.

Supplementary Table 6. Sensitivity analysis of excluding individuals with prevalent atrial fibrillation at baseline.

Outcome	HR (95% CI)		
	Model 1	Model 2	Model 3
Total stroke			
Per 10-unit increment	0.90 (0.86, 0.93)	0.89 (0.86, 0.93)	0.89 (0.85, 0.92)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.88 (0.72, 1.09)	0.88 (0.72, 1.09)	0.88 (0.71, 1.08)
Q3	0.59 (0.47, 0.75)	0.59 (0.47, 0.75)	0.59 (0.46, 0.75)
Q4	0.51 (0.40, 0.65)	0.49 (0.38, 0.63)	0.47 (0.36, 0.61)
P for trend	<0.001	<0.001	<0.001
Ischemic stroke			
Per 10-unit increment	0.90 (0.87, 0.93)	0.89 (0.86, 0.93)	0.89 (0.85, 0.93)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.95 (0.76, 1.18)	0.94 (0.75, 1.17)	0.94 (0.75, 1.17)
Q3	0.60 (0.47, 0.77)	0.60 (0.47, 0.78)	0.60 (0.46, 0.77)
Q4	0.53 (0.41, 0.69)	0.50 (0.38, 0.65)	0.48 (0.36, 0.63)
P for trend	<0.001	<0.001	<0.001
Hemorrhagic stroke			
Per 10-unit increment	0.87 (0.79, 0.95)	0.86 (0.78, 0.95)	0.86 (0.78, 0.95)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.73 (0.44, 1.23)	0.74 (0.44, 1.25)	0.73 (0.43, 1.24)
Q3	0.57 (0.33, 0.99)	0.55 (0.31, 0.98)	0.54 (0.30, 0.97)
Q4	0.36 (0.19, 0.68)	0.36 (0.18, 0.69)	0.34 (0.17, 0.66)
P for trend	0.001	0.001	0.001

Model 1, adjusted for age and sex. Model 2, adjusted for variables in model 1 plus SBP, DBP, BMI, hypertension duration, heart rate, smoking status, drinking status, and comorbidities. Model 3, adjusted for variables in model 2 plus ALT, AST, GGT, UA, BUN, eGFR, TC, TG, HDL-C, LDL-C, HbA1c, FPG, Hcy, use of statins, use of aspirins, use of insulins, use of oral antidiabetic drugs, and antihypertensive drugs. Abbreviations: CI: confidence interval; HR: hazard ratio. Other abbreviations as presented in Table 1.

Supplementary Table 7. Sensitivity analysis was conducted using the Fine-Gray competing risk model considering non-stroke deaths as competing risk events.

Outcome	SHR (95% CI)		
	Model 1	Model 2	Model 3
Total stroke			
Per 10-unit increment	0.91 (0.87, 0.94)	0.90 (0.87, 0.94)	0.89 (0.86, 0.93)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.92 (0.75, 1.13)	0.92 (0.75, 1.13)	0.92 (0.75, 1.13)
Q3	0.67 (0.53, 0.84)	0.68 (0.54, 0.86)	0.66 (0.52, 0.84)
Q4	0.54 (0.42, 0.69)	0.51 (0.40, 0.66)	0.49 (0.38, 0.64)
P for trend	<0.001	<0.001	<0.001
Ischemic stroke			
Per 10-unit increment	0.91 (0.87, 0.94)	0.90 (0.86, 0.94)	0.89 (0.86, 0.93)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.98 (0.78, 1.22)	0.97 (0.77, 1.20)	0.97 (0.77, 1.21)
Q3	0.67 (0.52, 0.86)	0.68 (0.53, 0.88)	0.66 (0.51, 0.86)
Q4	0.55 (0.43, 0.71)	0.52 (0.40, 0.68)	0.49 (0.37, 0.65)
P for trend	<0.001	<0.001	<0.001
Hemorrhagic stroke			
Per 10-unit increment	0.89 (0.81, 0.97)	0.89 (0.81, 0.98)	0.88 (0.80, 0.97)
Quartiles			
Q1	Reference	Reference	Reference
Q2	0.78 (0.46, 1.33)	0.81 (0.47, 1.38)	0.80 (0.47, 1.38)
Q3	0.70 (0.40, 1.22)	0.70 (0.39, 1.25)	0.66 (0.37, 1.19)
Q4	0.41 (0.21, 0.78)	0.42 (0.21, 0.81)	0.38 (0.19, 0.77)
P for trend	0.007	0.010	0.006

Model 1, adjusted for age and sex. Model 2, adjusted for variables in model 1 plus SBP, DBP, BMI, hypertension duration, heart rate, smoking status, drinking status, and comorbidities. Model 3, adjusted for variables in model 2 plus ALT, AST, GGT, UA, BUN, eGFR, TC, TG, HDL-C, LDL-C, HbA1c, FPG, Hcy, use of statins, use of aspirins, use of insulins, use of oral antidiabetic drugs, and antihypertensive drugs. Abbreviations: CI: confidence interval; SHR: subdistribution hazard ratio. Other abbreviations as presented in Table 1.

Supplementary Table 8. E-values for the observed associations between SI and clinical outcomes.

	Total stroke	Ischemic stroke	Hemorrhagic stroke
Observed association* (Per 10-unit increment)	0.88 (0.85, 0.92)	0.88 (0.85, 0.92)	0.85 (0.77, 0.94)
E-value for point estimate	**1.53**	**1.53**	**1.63**
E-value for confidence interval	1.39	1.39	1.32

*The observed associations are the fully adjusted hazard ratios (95% confidence intervals) shown in Table 2 and are presented here for reference.

Supplementary Table 9. Incremental predictive value of the SI.

Models	Δ C-statistics (95% CI)	NRI (95% CI)	IDI (95% CI)
Total stroke			
Conventional model	Reference	Reference	Reference
Conventional model + SI	0.02 (0.01–0.03)	0.17 (0.10–0.23)	0.03 (0.02–0.04)
Ischemic stroke			
Conventional model	Reference	Reference	Reference
Conventional model + SI	0.02 (0.01–0.04)	0.19 (0.13–0.25)	0.02 (0.01–0.04)
Hemorrhagic stroke			
Conventional model	Reference	Reference	Reference
Conventional model + SI	0.01 (0.01–0.02)	0.14 (0.02–0.27)	0.01 (0.01–0.03)

The conventional model was adjusted for age, sex, SBP, DBP, BMI, hypertension duration, heart rate, smoking status, drinking status, comorbidities, ALT, AST, GGT, UA, BUN, eGFR, TC, TG, HDL-C, LDL-C, HbA1c, FPG, Hcy, use of statins, use of aspirins, use of insulins, use of oral antidiabetic drugs, and antihypertensive drugs. Abbreviations: CI: confidence interval; NRI: net reclassification index; IDI: integrated discrimination improvement. Other abbreviations as presented in Table 1.